http://www.e-yujm.org

eISSN 2384-0293

Vol. 37, No. 4 October 2020

Yeungnam University Journal of Medicine

YUJM

Yeungnam University College of Medicine
Yeungnam University Institute of Medical Science

Yeungnam University Journal of Medicine

Vol. 37, No. 4 October 2020

pages 251-355

Yeungnam University Journal of Medicine

YUJM

e-yujm.org

eISSN 2384-0293

Vol. 37 · No. 4 · October 2020

Aims and scope

Yeungnam University Journal of Medicine (Yeungnam Univ J Med, YUJM, eISSN 2384-0293, https://www.e-yujm.org), the official publication of the Yeungnam University College of Medicine, is an international, peer-reviewed, and open access journal in the medical field.

YUJM aims to communicate new medical information to medical personnel, and to facilitate the development of medicine and the propagation of medical knowledge by publishing high quality evidence-based articles. It covers all fields of medical science, including clinical research and basic medical science.

YUJM publishes editorials, review articles, original articles, case reports, and communications. All manuscripts should be creative, informative, and helpful for the diagnosis and treatment of medical diseases and for the communication of valuable information about all fields of medicine.

The first volume was published in December 1984. YUJM is published in English, four times a year (January 31, April 30, July 31, and October 31).

YUJM is indexed/tracked/covered by PubMed Central, PubMed, DOAJ, KoreaMed, Korea Citation Index, KoMCI, WPRIM, DOI/CrossRef, and Google Scholar.

Open access

Publisher
Yeungnam University College of Medicine

Editor-in-chief
Joon Hyuk Choi, Yeungnam University College of Medicine

Editorial office
Yeungnam University College of Medicine
170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-640-6832 Fax: +82-53-651-0394 E-mail: yujm@yu.ac.kr

Printing office
M2community Co.
8th FL, DreamTower, 66 Seongsui-ro, Seongdong-gu, Seoul 04784, Korea
Tel: +82-2-2190-7300 Fax: +82-2-2190-7333 E-mail: journal@m2community.co.kr

Published on October 31, 2020

Yeungnam University Journal of Medicine
YUJM

Editorial board

Yeungnam University Journal of Medicine
YUJM
eISSN 2384-0293

Contents

Vol. 37 · No. 4 · October 2020

Focused review

Editorial

Review articles

Review article

Original articles

Yeungnam University Journal of Medicine
YUJM
eISSN 2384-0293

Contents

Vol. 37 · No. 4 · October 2020

Case reports

Communication

Yeungnam University Journal of Medicine
YUJM

Editorial
eISSN 2384-0293
Yeungnam Univ J Med 2020;37(4):251-252
https://doi.org/10.12701/yujm.2020.00661

Advances in the science and treatment of respiratory diseases

Jin Hong Chung

Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea

Received: July 23, 2020
Revised: August 11, 2020
Accepted: August 13, 2020

Corresponding author:
Jin Hong Chung
Department of Internal Medicine, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-640-6682
Fax: +82-53-620-3849
E-mail: jhchn@med.yu.ac.kr

Respiratory research has developed and evolved over the past 30 years and it has been applied to clinical medicine. Significant progress has been achieved in identifying, treating, and preventing respiratory diseases. Looking back, the last 30 years revealed the following: (1) since the introduction of the flexible fiberoptic bronchoscope, bronchoscopy has been widely used as a diagnostic tool in the clinical field of respiratory medicine; (2) as bronchial asthma was identified as a chronic inflammatory airway disease, inhaled corticosteroids were approved for use as controller therapy. While most patients with asthma were treated effectively with this standard controller therapy, it was ineffective in those with severe asthma; (3) the pathogenesis and treatment of idiopathic pulmonary fibrosis (IPF) were poorly defined, and many patients with pulmonary fibrosis developed end-stage lung disease; (4) tuberculosis (TB) was expected to be eradicated by the development of powerful bactericidal drugs, such as isoniazid, rifampin, and pyrazinamide, but it has not been eradicated yet; and (5) with development in medicine and better hygiene, respiratory infections were expected to be managed and treated efficiently. However, there were concerns regarding the transmission of infections as global exchanges between countries gradually increased. This special review issue aims to highlight recent advances in the science and treatment of respiratory diseases through the articles in each of the following areas: (1) an update on the role of bronchoscopy in the diagnosis of pulmonary disease, (2) biological treatments for severe asthma, (3) therapeutic potential of targeting kinase inhibition in patients with IPF, (4) diagnosis and treatment of multidrug-resistant TB (MDR-TB), and (5) novel respiratory infectious disease in Korea.

Ahn [1] reviewed the advanced diagnostic role of bronchoscopy. Flexible bronchoscopy is an important diagnostic tool in the clinical field of respiratory medicine. Over the past decade, endobronchial ultrasound (EBUS) has been introduced in clinics. Convex probe-EBUS has been used to diagnose many central lung lesions and has replaced the surgical nodal staging of lung cancer, and radial probe-EBUS has been used to diagnose peripheral lung lesions. Recently, ultrathin bronchoscopy (UTB), electromagnetic navigational bronchoscopy (ENB), and transbronchial cryobiopsy have been introduced for the accurate diagnosis of respiratory diseases. Furthermore, flexible bronchoscopy in combination with new technologies, such as EBUS, UTB, and ENB has improved diagnostic yield.

Some patients with asthma, who used high-dose inhaled corticosteroid and long-acting beta-agonist compounds corresponding to steps 4 and 5 of the Global Initiative for Asthma guidelines, experience inadequately controlled symptoms, repeated asthma exacerbations, or sustained decline in lung function. Jin [2] reviewed the need for proper treatment of severe asthma and recently developed drugs, including biologics. These biologics reduce the symptoms of asthma, improve lung function, reduce the requirement for oral

corticosteroids, and improve the quality of life of the patients. Furthermore, assessment of the patient's phenotype and endotype is essential when using these biologics. Finally, the era of personalized treatment for severe asthma has arrived.

The true nature of IPF shows that pulmonary fibrosis is a particularly critical lung disease that requires effective management. Kim et al. [3], in their continued review, evaluated the therapeutic potential of targeting kinase inhibition in patients with IPF. To develop therapeutic targets for pulmonary fibrosis, it is important to understand the key factors involved in the pathogenesis of pulmonary fibrosis and the underlying signaling pathway influencing the disease. Recently, anti-fibrotic agents, such as pirfenidone and nintedanib, have been developed and are being widely used in clinical practice for IPF management. Further intensive studies using selective kinase inhibitors should be conducted to develop therapeutic agents that delay the disease progression and improve the prognosis of IPF.

TB remains a major health hazard worldwide. MDR-TB, which shows resistance to both isoniazid and rifampicin, is one of the several barriers of TB treatment. Globally, approximately 3.4% of new TB patients and 20% of those with a previous history of TB treatment are diagnosed with MDR-TB. The treatments for MDR-TB are less effective because of highly toxic second-line drugs that require long-term use (up to 20–24 months). Jang and Chung [4] reviewed the challenges in the diagnosis and treatment of MDR-TB. The technological advance in rapid molecular drug sensitivity testing and the introduction of a new agent (bedaquiline and delamanid) and repurposed drugs (linezolid, clofazimine, and cycloserine) could improve the treatment outcomes of MDR-TB.

The current coronavirus disease 2019 (COVID-19) pandemic is potentially the biggest global health issue since the influenza pandemic of 1918. Kim [5] reviewed the new epidemic of respiratory infections. Because of the development of transportation and increased global exchanges, the transmission rate of such novel respiratory infectious diseases has increased. Since respiratory infections are not specific to a region or country, they can threaten the entire world with global trends at any time. Therefore, all nations should come together to conduct research, make efforts to prevent the spread of these diseases, and develop appropriate treatments and vaccines. From the Spanish flu to the severe acute respiratory syndrome, Middle East respiratory syndrome, and COVID-19, the unmasking of the virus responsible for these epidemics stands as a testament that worldwide medical cooperation is needed to confront emerging diseases in the future.

Finally, I hope that these articles will provide clinicians and scientists a comprehensive update on the advances in the science and treatment of respiratory diseases. Moreover, I would like to express my sincere gratitude to the editorial board of *Yeungnam University Journal of Medicine* for giving me the opportunity to summarize the progress of respiratory medicine. I deeply appreciate the efforts of all the authors of the articles included in this special review issue.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

ORCID

Jin Hong Chung, https://orcid.org/0000-0003-1829-3051

References

1. Ahn JH. An update on the role of bronchoscopy in the diagnosis of pulmonary disease. Yeungnam Univ J Med 2020;37:253-61.
2. Jin HJ. Biological treatments for severe asthma. Yeungnam Univ J Med 2020;37:262-8.
3. Kim S, Lim JH, Woo SH. Therapeutic potential of targeting kinase inhibition in patients with idiopathic pulmonary fibrosis. Yeungnam Univ J Med 2020;37:269-76.
4. Jang JG, Chung JH. Diagnosis and treatment of multidrug-resistant tuberculosis. Yeungnam Univ J Med 2020;37:277-85.
5. Kim HJ. Novel respiratory infectious diseases in Korea. Yeungnam Univ J Med 2020;37:286-95.

https://doi.org/10.12701/yujm.2020.00661

Yeungnam University Journal of Medicine
YUJM

Review article
eISSN 2384-0293
Yeungnam Univ J Med 2020;37(4):253-261
https://doi.org/10.12701/yujm.2020.00584

An update on the role of bronchoscopy in the diagnosis of pulmonary disease

June Hong Ahn

Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea

Received: July 11, 2020
Revised: August 7, 2020
Accepted: August 8, 2020

Corresponding author:
June Hong Ahn
Department of Internal Medicine, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-640-6577
Fax: +82-53-620-3849
E-mail: fireajh@gmail.com

Bronchoscopy has evolved over the past few decades and has been used by respiratory physicians to diagnose various airway and lung diseases. With the popularization of medical check-ups and growing interest in health, early diagnosis of lung diseases is essential. With the development of endobronchial ultrasound, ultrathin bronchoscopy, and electromagnetic navigational bronchoscopy, bronchoscopy has been able to widen its scope in diagnosing pulmonary diseases. In this review, we have described the brief history, role, and complications of bronchoscopy used in diagnosing pulmonary lesions, from simple flexible bronchoscopy to bronchoscopy combined with several up-to-date technologies.

Keywords: Bronchoscopy; Cryobiopsy; Electromagnetic navigation bronchoscopy; Endobronchial ultrasound; Lung diseases

Introduction

Since the introduction of the flexible fiberoptic bronchoscope in 1968, it has been used as an essential tool for diagnosing lung lesions [1]. Over the past decade or so, endobronchial ultrasound (EBUS) has been widely used clinically. Convex probe EBUS (CP-EBUS) has replaced surgical mediastinal staging for lung cancer and is extensively used in diagnosing many central lung lesions [2]. Although the diagnostic yield of bronchoscopy is reasonable, CP-EBUS provides a reliable diagnosis in patients with suspected lung cancer [3]. Radial probe EBUS (RP-EBUS), along with biopsy techniques using guide sheath (GS), is widely used to diagnose peripheral pulmonary lesions [4]. Although RP-EBUS guided transbronchial lung biopsy (TBLB) showed relatively lower diagnostic yield than computed tomography (CT)-guided transthoracic needle biopsy (TTNB) in diagnosing peripheral pulmonary lesions, the procedural risks were lower [5]. Recently, ultrathin bronchoscopy (UTB), electromagnetic navigational bronchoscopy (ENB), and cryobiopsy have been introduced to help diagnose lung diseases accurately. In this review, we have described the role of bronchoscopy in diagnosing pulmonary lesions.

Flexible bronchoscopy

Since Shigeto Ikeda first introduced the flexible fiberoptic bronchoscope in 1968, it has become an essential diagnostic tool for pulmonologists [1]. Many diagnostic procedures can be performed using flexible bronchoscopy (FB), such as airway inspection, bronchoalveolar lavage (BAL), bronchial brushing, endobronchial biopsy, TBLB, and conventional transbronchial needle aspiration (TBNA).

A thorough review of chest CT anatomy determining the lesion to obtain the sample should be done before conducting bronchoscopy. The most common indications for diagnostic FB are as follows: diagnosing airway injury or the presence of a foreign body, lung cancer, interstitial lung disease, pulmonary infection, and the investigation of hemoptysis [6,7]. Bronchoscopic findings of foreign body, bronchogenic carcinoma, and endobronchial tubercu-

losis are shown in Fig. 1.

FB has diagnostic value in patients with airway injury. Concerning inhalation injury, FB is of great value in diagnosing and treating it and can be used to predict late structural complications, such as vocal cord stenosis and tracheal stenosis [8-10]. Early recognition of airway injury followed by early surgical interventions is associated with a favorable outcome in patients with acute tracheobronchial injuries by blunt or penetrating trauma [11]. In such cases, rapid diagnosis using FB is very important, and bronchoscopy is the procedure of choice.

FB is suggested as the first-line diagnostic tool in adult patients with foreign body aspiration into the lower airway [12]. The removal of a foreign body by FB was first reported in the 1970s. Since then, several studies reported the removal of foreign bodies with FB. The success rate of foreign body removal by FB is 61% to 97% [13].

FB is frequently used in diagnosing lung cancer. The diagnostic yield of bronchoscopy differs depending on the location of the lesion (central or peripheral). Concerning central lesions, the sensitivity of endobronchial forceps biopsy of a visible endobronchial lesion is 74%. A minimum of three to five biopsy specimens is recommended to increase the rate of diagnosis in an endobronchial biopsy. The sensitivity of FB in diagnosing a central tumor increases to 88% with the addition of bronchial washing, brushing, endobronchial needle aspiration, and TBNA [14,15]. In the American College of Chest Physicians' guidelines for establishing the diagnosis of lung cancer, the sensitivity of FB procedures in diagnosing peripheral tumors (78%) was lower than that of central tumors (88%) [14]. A minimum of six biopsy specimens is recommended to increase the rate of diagnosis in TBLB.

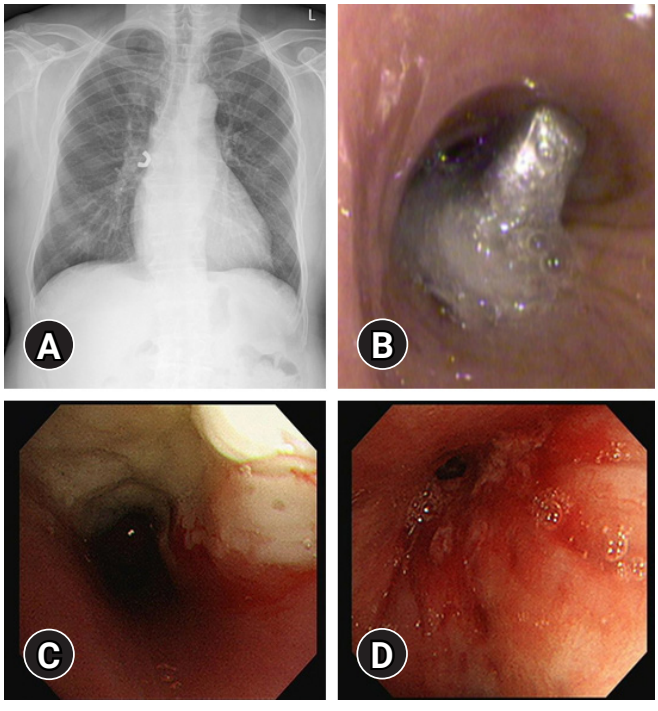


Fig. 1. Radiographic and bronchoscopic findings of foreign body (A, B), bronchogenic carcinoma (C), and endobronchial tuberculosis (D).

Since Andersen and Fontana [16] reported 450 cases undergoing TBLB in diffuse pulmonary lung disease (DPLD) in 1972, BAL and TBLB with FB are widely used in clinical practice for diagnosing DPLD. Eosinophilia and lymphocytosis with elevated CD4/CD8 ratio in BAL fluid help diagnose eosinophilic pneumonia and sarcoidosis, respectively [17]. TBLB helps diagnose sarcoidosis, eosinophilic pneumonia, hypersensitivity pneumonitis, cryptogenic organizing pneumonia, lymphangioleiomyomatosis, lymphangitic carcinomatosis, pulmonary Langerhans cell histiocytosis, and multiple lung infections [18].

In a patient with hemoptysis, it is essential to detect its cause and location. By far, studies have shown that CT is superior to FB for detecting the cause and location of hemoptysis [19-21]. However, FB can be a useful tool for performing an endoscopic treatment using cold saline, vasoconstrictive agents, topical hemostatic agents, and argon plasma coagulation. Pulmonary isolation technique using FB can also prevent blood aspiration from the bleeding lung to the intact lung, thereby securing the patients' airway and maintaining oxygenation [22].

FB can be performed safely, and most FBs are performed on an outpatient basis. A large retrospective cohort study demonstrated that the frequency of major (pneumothorax, pulmonary hemorrhage, and respiratory failure) and minor complications (laryngospasm, vomiting, vasovagal syncope, epistaxis, and bronchospasm) was 0.5% and 0.8%, respectively [23]. A multicenter study conducted in Italy also showed that bronchoscopy is a safe method with a low incidence of complications (1.08%) and mortality (0.02%) [24].

These days, with the development of new technologies, such as EBUS, UTB, and ENB, combining FB with these new technologies much improved the diagnostic yield.

Endobronchial ultrasound-transbronchial needle aspiration

CP-EBUS is integrated with a convex-shaped ultrasonic transducer at the tip of the bronchoscope. The physician can observe the airway walls and surrounding structures by placing the end of the bronchoscope directly against the airway wall or by inflating the balloon with saline solution. It can be observed in real-time that the needle passes through the bronchial wall and the lesion of interest. The physician aspirates the tissue through a needle and uses

https://doi.org/10.12701/yujm.2020.00584

it for pathological diagnosis. It is possible to avoid blood vessels through the power Doppler mode installed with ultrasound [25].

Yasufuku et al. [26] first reported experiences of CP-EBUS-TBNA for sampling mediastinal and hilar lymph nodes in 2004. In the study, the sensitivity, specificity, and accuracy of CP-EBUS-TBNA in diagnosing malignant lymph nodes were 95.7%, 100%, and 97.1%, respectively. The procedure was safe, and there were no complications. Since then, with the experience of respiratory physicians, it is now widely used as a diagnostic tool for mediastinal nodal staging of lung cancer, central lung masses, lymphoma, sarcoidosis, and tuberculosis. CP-EBUS-TBNA for the mediastinal lymph node and the central lung mass is shown in Fig. 2.

In patients with suspected mediastinal lymph node involvement (lymph node enlargement, or positron emission tomography uptake), EBUS-TBNA is recommended as the best primary diagnostic tool over surgical staging. The overall median sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 89%, 100%, 100%, and 91%, respectively. Combined with endoscopic ultrasound (EUS)-needle aspiration, the pooled median sensitivity, specificity, PPV, and NPV were 91%, 100%, 100%, and 96%, respectively [2]. The combination of EUS with bronchoscope-guided fine needle aspiration (EUS-B-FNA) and EBUS-TBNA provided additional diagnostic benefits through the sampling of inaccessible lesions by EBUS-TBNA, or when bronchoscopy was difficult due to dyspnea, or cough [27,28]. The feasibility of molecular profiling using EBUS-TBNA derived samples were acceptable, and EBUS-TBNA provided a higher amount of RNA-extraction than bronchoscopy or CT-guided core biopsy [29,30]. Rebiopsy by EBUS-TBNA was also a useful sampling method for the analysis of acquired resistance to epidermal growth factor receptor-tyrosine kinase inhibitor [31,32]. In the absence of rapid on-site evaluation, at least three needle aspirations are recommended per lymph node station, in patients with suspected lung cancer for mediastinal staging [33,34].

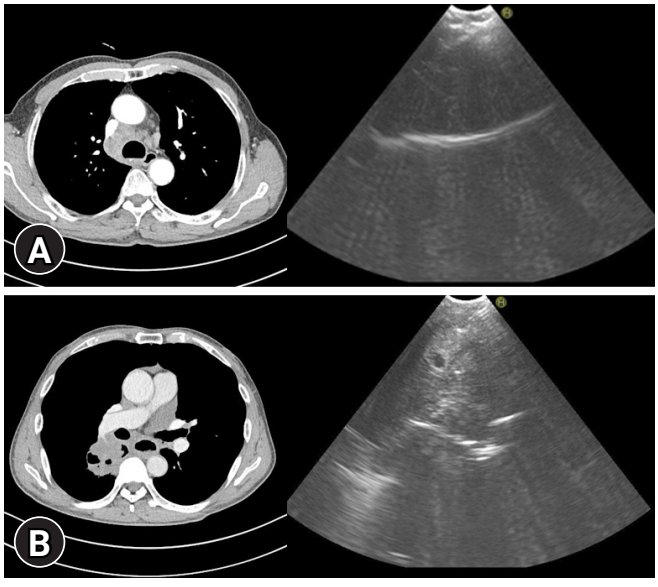


Fig. 2. Axial images of chest computed tomography and convex probe-endobronchial ultrasound-transbronchial needle aspiraton for the right paratracheal lymph node (A) and the central lung mass (B).

Most central lung tumors can be diagnosed by FB; however, some central tumors are not easily diagnosed because they are not observed by FB. If a central tumor is not accessible by FB and is in contact with the bronchus, a direct tissue examination can be carried out using CP-EBUS-TBNA. In previous studies, the sensitivity of EBUS-TBNA for diagnosing unknown lung lesions was 82% to 94%, in patients with central lung tumors not visible during FB. EBUS-related complications in diagnosing central tumors occurred in 5.4% of the cases [35-37]. However, when it comes to diagnosing lymphoma, EBUS-TBNA reported an overall sensitivity of 66.2%. Results showed a higher diagnostic sensitivity in diagnosing the recurrence of lymphoma (77.8%), than the new diagnosis of lymphoma (67.1%) [38].

In a meta-analysis of 553 patients with sarcoidosis, the pooled diagnostic accuracy of EBUS-TBNA for diagnosing sarcoidosis was 79% [39]. EBUS-TBNA was also an effective diagnostic tool for intrathoracic tuberculosis. The pooled sensitivity of EBUS-TBNA for diagnosing intrathoracic tuberculosis lymphadenopathy was 87% [40].

Complication rates in EBUS-TBNA were low (1% to 5%) [41,42]. Rarely, serious complications such as bronchogenic cyst infection, mediastinal abscess, mediastinitis, pericarditis, and sepsis have been reported [41,43].

Endobronchial ultrasound and a guide sheath

Using RP-EBUS, physicians can detect peripheral pulmonary lesions and can perform a biopsy. After peripheral pulmonary lesions are searched using an RP-EBUS inside GS, the RP is withdrawn, leaving the GS in place. Then bronchial brush and biopsy forceps are introduced into the GS, and brushings and biopsy specimens are collected [4].

In 1992, Hurter and Hanrath [44] reported the initial experience of RP-EBUS during routine FB. Following this, Kurimoto et al. [4] reported a technique using EBUS and a GS (EBUS-GS) to increase the diagnostic yield of peripheral pulmonary lesions. The overall yield of EBUS-GS was 77%, 81% for malignant lesions, and

69% for benign lesions.

Three classes of lesions were identified by RP-EBUS based on the internal structure of the lesion: type I (homogeneous pattern), type II (hyperechoic dots and linear arcs pattern), and type III (heterogeneous pattern). This endobronchial ultrasonographic information suggests the histology of the lung lesions [45].

A meta-analysis revealed that RP-EBUS had a point specificity of 1.00 (95% confidence interval [CI], 0.99–1.00) and a point sensitivity of 0.73 (95% CI, 0.70–0.76) for the detection of lung cancer. The diagnostic yield was higher for lesions >20 mm (77.7%; 95% CI, 73%–82%) than for the lesions ≤20 mm (56.3%; 95% CI, 51%–61%). The diagnostic yield was also affected by the probe location. The ultrasound image associated with the probe location of RP-EBUS is shown in Fig. 3. Advancing the probe within the pulmonary lesions yielded the highest diagnostic accuracy (87%). The yield when the probe was advanced adjacent to the lesion was lower (42%) [46]. Several studies demonstrated that the probe position within the lesion was associated with diagnostic success in patients with EBUS-GS [47-49]. Besides this, peripheral location, bronchus sign on chest tomography, and the use of forceps as the first instrument were the independent factors for diagnostic success [49-52]. The cumulative diagnostic yield reached a plateau after the fifth biopsy specimen was collected. Thus, at least five biopsy specimens are needed to increase the diagnostic yield [49].

Izumo et al. [53] reported that RP-EBUS-GS could be considered as a diagnostic method for ground-glass opacity (GGO) lesions under the guidance of fluoroscopy. The diagnostic yield was 65%, and a visible EBUS image was an independent factor affecting the diagnostic yield. The blizzard and mixed blizzard signs are useful ultrasound images to detect the correct location of GGO pulmonary lesions [54]. In our institution, RP-EBUS-GS is performed to diagnose GGO pulmonary lesions (Fig. 4). In addition to diagnosing malignant lesions, RP-EBUS-GS was a useful and safe diagnostic method for diagnosing diffuse lung lesions [55].

The complication rates were lower (0% to 7.4%) than CT-guided TTNB [56-58]. Pneumothorax occurred in 1.0% of the patients [59], and bleeding, infection, and breaking of radial probes can occur in some cases [58].

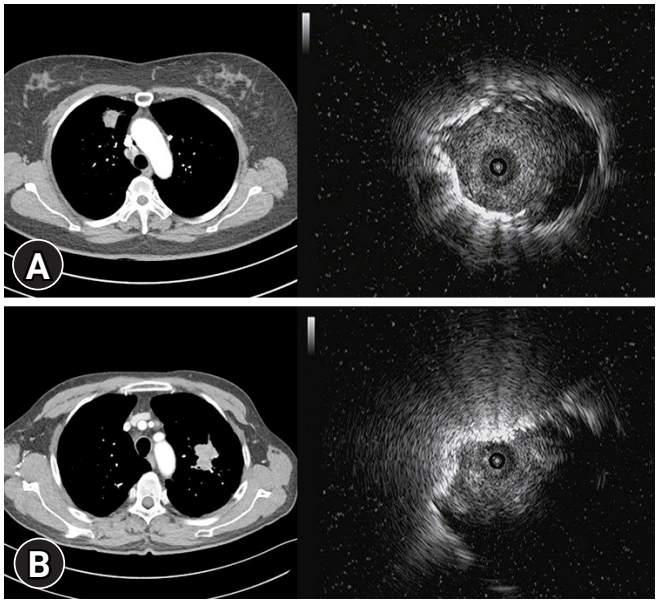


Fig. 3. Axial images of chest computed tomography and the ultrasound images associated with the probe location of radial probe-endobronchial ultrasound. (A) Within the lesion. (B) Adjacent to the lesion.

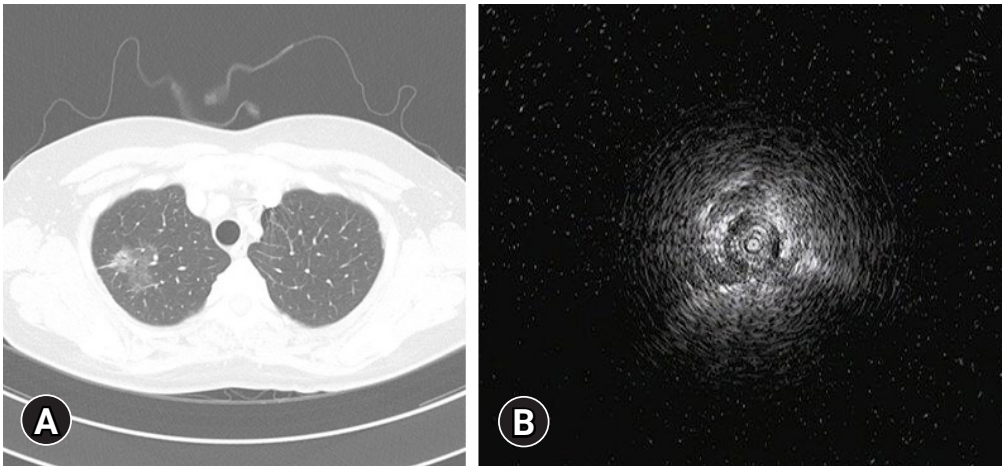


Fig. 4. Axial image of chest computed tomography (A) and the ultrasound image (B) associated with radial probe-endobronchial ultrasound-guide sheath performed to diagnose ground-glass opacity pulmonary lesions.

https://doi.org/10.12701/yujm.2020.00584

Ultrathin bronchoscopy

According to previous studies, a bronchoscope with an external diameter of 3.0 mm is considered as a UTB [60]. An ultrathin fiberscope with an external diameter of 2.7 mm and an internal diameter of 0.8 mm with a working channel was introduced in 1996. The ultrathin fiberscope was specifically used in a bronchoscope during mechanical ventilation through tracheal tubes in infants, suctioning, drug injection, and BAL [61]. The diagnostic rate of peripheral lung lesions using UTB was 60.0% to 69.4%, and the diagnostic yield was 57% in lesions less than 20 mm [62,63]. In a multicenter randomized trial conducted in Japan, the UTB with RP-EBUS group showed a superior diagnostic yield than the RP-EBUS-GS with a thin bronchoscopy group (74% vs. 59%, $p=0.044$). Complications, such as pneumothorax, bleeding, and pneumonia was similar between the two groups (3% vs. 5%, $p=0.595$) [64].

Electromagnetic navigational bronchoscopy

Despite the introduction of RP-EBUS, many peripheral pulmonary lesions are still difficult to diagnose. ENB systems were developed to overcome such limitations. Schwarz et al. [65] first reported ENB in diagnosing peripheral pulmonary lesions with an acceptable diagnostic yield (69%) and safety.

An ENB works like a car reaching its destination via the global positioning system. By far, there are two ENB systems: the SuperDimension Navigation System (Medtronic, Minneapolis, MN, USA) and the SPiN System (Veran Medical Technologies, St. Louis, MO, USA) [66]. Fig. 5 shows the ENB assisted tissue sampling for a peripheral pulmonary lesion using the SPiN System.

In a meta-analysis of the diagnostic yield of ENB for lung nodules, the pooled sensitivity, specificity, and the diagnostic odds ratio were 82%, 100%, and 97.62%, respectively [67]. One-year results of the prospective, multicenter NAVIGATE study [68] revealed that diagnostic yield was 73%. Greater nodule size, nodule visualization with RP-EBUS, presence of bronchus sign, lower registration error, and catheter suction technique were associated with an increased diagnostic yield. However, lower lobe location was correlated with a decreased diagnostic yield [67]. When ENB was combined with EBUS, the diagnostic yield was greater than ENB alone (88% vs. 59%, $p=0.02$) [69].

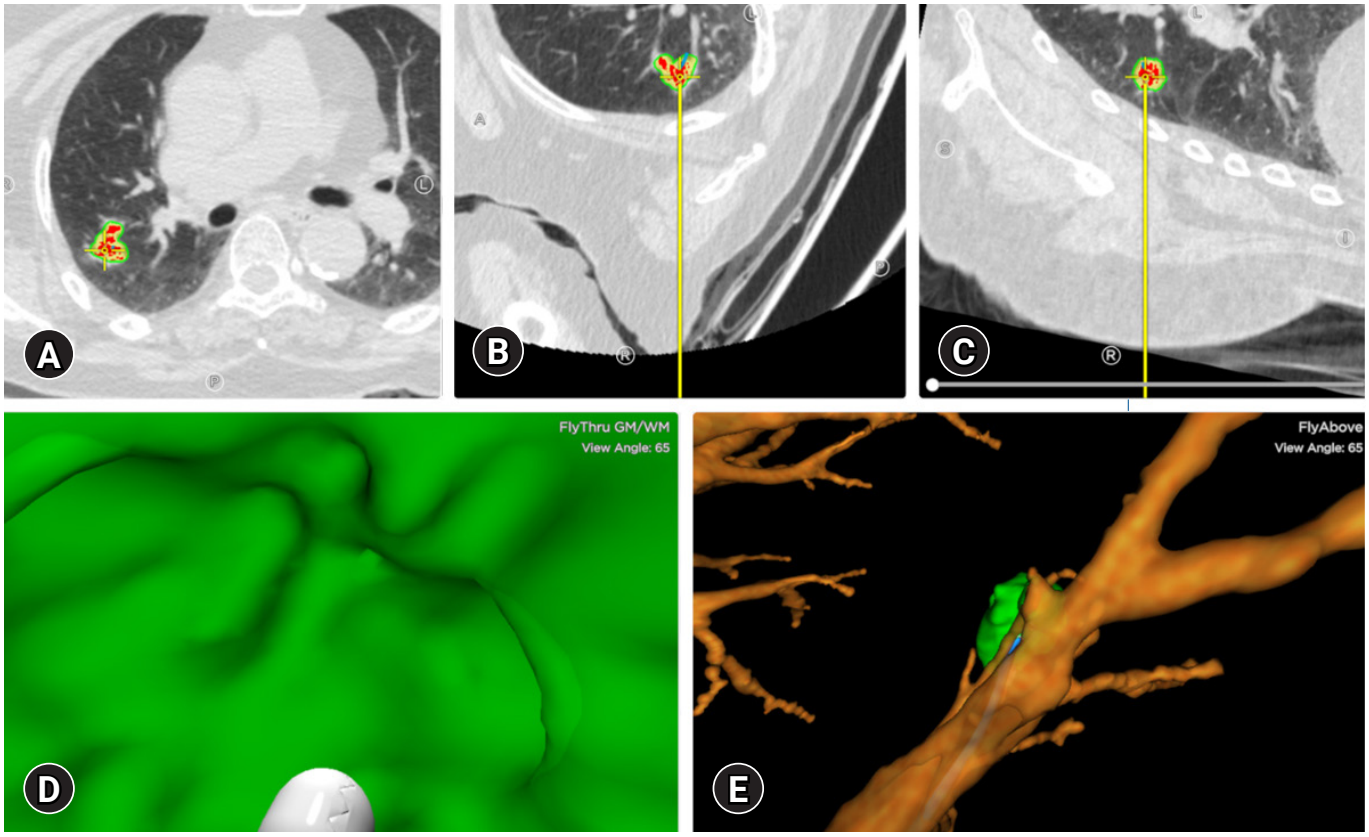


Fig. 5. (A-E) Electromagnetic navigational bronchoscopy assisted tissue sampling for a peripheral pulmonary lesion using the SPiN System (Veran Medical Technologies, St. Louis, MO, USA).

ENB related complications such as pneumothorax, bleeding, and respiratory failure are reported in about 0% to 5% of the cases in several pieces of literature [67,68]. ENB can be an effective diagnostic method for cases undetectable by FB in high-risk patients with a low complication rate [70].

Cryobiopsy

Transbronchial cryobiopsy is performed to obtain lung tissue for the diagnosis of interstitial lung diseases and lung tumors. Transbronchial cryobiopsy showed higher diagnostic yield than transbronchial forceps biopsy (91.67% vs. 73.13%, $p = 0.0002$) in diagnosing interstitial lung diseases and lung tumors [71]. Meta-analysis revealed that the diagnostic yield ranged from 74% to 98%, with a pooled estimate of 83% [72]. Quantitative assessment of samples showed that cryobiopsy samples were larger than forceps biopsy samples (11.17 mm^2 vs. 4.69 mm^2, $p < 0.001$). A qualitative difference was not observed between cryobiopsy and forceps biopsy [73]. Pneumothorax (6.8% to 12%), moderate/severe bleeding (39%), severe bleeding (0.3%), and death (0.1%) occurred after transbronchial cryobiopsy [72,74].

Conclusion

In this review, we described the role of bronchoscopy in the diagnosis of pulmonary disease. The role of bronchoscopy in the diagnostic field is further increasing as more patients visit hospitals with chest imaging abnormalities due to the popularization of health check-ups. Recent developments in EBUS have enabled safer and more accurate examinations for diagnosing lung diseases. The development and combination of a variety of new diagnostic technologies, including ENB, is expected to make the diagnosis of difficult to diagnose lung diseases more feasible in the future.

Acknowledgments

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

ORCID
June Hong Ahn, https://orcid.org/0000-0001-7104-8325

References

1. Panchabhai TS, Mehta AC. Historical perspectives of bronchoscopy: connecting the dots. Ann Am Thorac Soc 2015;12:631–41.
2. Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, et al. Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):e211S–e250S.
3. Silvestri GA, Bevill BT, Huang J, Brooks M, Choi Y, Kennedy G, et al. An evaluation of diagnostic yield from bronchoscopy: the impact of clinical/radiographic factors, procedure type, and degree of suspicion for cancer. Chest 2020;157:1656–64.
4. Kurimoto N, Miyazawa T, Okimasa S, Maeda A, Oiwa H, Miyazu Y, et al. Endobronchial ultrasonography using a guide sheath increases the ability to diagnose peripheral pulmonary lesions endoscopically. Chest 2004;126:959–65.
5. Zhan P, Zhu QQ, Miu YY, Liu YF, Wang XX, Zhou ZJ, et al. Comparison between endobronchial ultrasound-guided transbronchial biopsy and CT-guided transthoracic lung biopsy for the diagnosis of peripheral lung cancer: a systematic review and meta-analysis. Transl Lung Cancer Res 2017;6:23–34.
6. Gupta AA, Sehgal IS, Dhooria S, Singh N, Aggarwal AN, Gupta D, et al. Indications for performing flexible bronchoscopy: trends over 34 years at a tertiary care hospital. Lung India 2015;32:211–5.
7. Du Rand IA, Blaikley J, Booton R, Chaudhuri N, Gupta V, Khalid S, et al. British Thoracic Society guideline for diagnostic flexible bronchoscopy in adults: accredited by NICE. Thorax 2013;68(Suppl 1):i1–44.
8. Bai C, Huang H, Yao X, Zhu S, Li B, Hang J, et al. Application of flexible bronchoscopy in inhalation lung injury. Diagn Pathol 2013;8:174.
9. Marek K, Piotr W, Stanisław S, Stefan G, Justyna G, Mariusz N, et al. Fibreoptic bronchoscopy in routine clinical practice in confirming the diagnosis and treatment of inhalation burns. Burns 2007;33:554–60.
10. Cha SI, Kim CH, Lee JH, Park JY, Jung TH, Choi WI, et al. Isolated smoke inhalation injuries: acute respiratory dysfunction, clinical outcomes, and short-term evolution of pulmonary functions with the effects of steroids. Burns 2007;33:200–8.
11. Cassada DC, Munyikwa MP, Moniz MP, Dieter RA Jr, Schuchmann GF, Enderson BL. Acute injuries of the trachea and major bronchi: importance of early diagnosis. Ann Thorac Surg 2000;69:1563–7.
12. Chen CH, Lai CL, Tsai TT, Lee YC, Perng RP. Foreign body aspiration into the lower airway in Chinese adults. Chest 1997;112:129–33.
13. Dikensoy O, Usalan C, Filiz A. Foreign body aspiration: clinical utility of flexible bronchoscopy. Postgrad Med J 2002;78:399–

https://doi.org/10.12701/yujm.2020.00584

403.
14. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):e142S–e165S.
15. Shure D, Fedullo PF. Transbronchial needle aspiration in the diagnosis of submucosal and peribronchial bronchogenic carcinoma. Chest 1985;88:49–51.
16. Andersen HA, Fontana RS. Transbronchoscopic lung biopsy for diffuse pulmonary diseases: technique and results in 450 cases. Chest 1972;62:125–8.
17. Thomson CC, Duggal A, Bice T, Lederer DJ, Wilson KC, Raghu G. 2018 Clinical practice guideline summary for clinicians: diagnosis of idiopathic pulmonary fibrosis. Ann Am Thorac Soc 2019;16:285–90.
18. Kebbe J, Abdo T. Interstitial lung disease: the diagnostic role of bronchoscopy. J Thorac Dis 2017;9(Suppl 10):S996–1010.
19. Sakr L, Dutau H. Massive hemoptysis: an update on the role of bronchoscopy in diagnosis and management. Respiration 2010;80:38–58.
20. Revel MP, Fournier LS, Hennebicque AS, Cuenod CA, Meyer G, Reynaud P, et al. Can CT replace bronchoscopy in the detection of the site and cause of bleeding in patients with large or massive hemoptysis? AJR Am J Roentgenol 2002;179:1217–24.
21. Khalil A, Soussan M, Mangiapan G, Fartoukh M, Parrot A, Carette MF. Utility of high-resolution chest CT scan in the emergency management of haemoptysis in the intensive care unit: severity, localization and aetiology. Br J Radiol 2007;80:21–5.
22. Gagnon S, Quigley N, Dutau H, Delage A, Fortin M. Approach to hemoptysis in the modern era. Can Respir J 2017;2017:1565030.
23. Pue CA, Pacht ER. Complications of fiberoptic bronchoscopy at a university hospital. Chest 1995;107:430–2.
24. Facciolongo N, Patelli M, Gasparini S, Lazzari Agli L, Salio M, Simonassi C, et al. Incidence of complications in bronchoscopy. Multicentre prospective study of 20,986 bronchoscopies. Monaldi Arch Chest Dis 2009;71:8–14.
25. Um SW. The role of EBUS-TBNA in the diagnosis and staging of lung cancer. Hanyang Med Rev 2014;34:20–5.
26. Yasufuku K, Chiyo M, Sekine Y, Chhajed PN, Shibuya K, Iizasa T, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration of mediastinal and hilar lymph nodes. Chest 2004;126:122–8.
27. Hwangbo B, Lee HS, Lee GK, Lim KY, Lee SH, Kim HY, et al. Transoesophageal needle aspiration using a convex probe ultrasonic bronchoscope. Respirology 2009;14:843–9.
28. Hwangbo B, Lee GK, Lee HS, Lim KY, Lee SH, Kim HY, et al. Transbronchial and transesophageal fine-needle aspiration using an ultrasound bronchoscope in mediastinal staging of potentially operable lung cancer. Chest 2010;138:795–802.
29. Lee R, Cousins DJ, Ortiz-Zapater E, Breen R, McLean E, Santis G. Gene expression profiling of endobronchial ultrasound (EBUS)-derived cytological fine needle aspirates from hilar and mediastinal lymph nodes in non-small cell lung cancer. Cytopathology 2013;24:351–5.
30. Schmid-Bindert G, Wang Y, Jiang H, Sun H, Henzler T, Wang H, et al. EBUS-TBNA provides highest RNA yield for multiple biomarker testing from routinely obtained small biopsies in non-small cell lung cancer patients: a comparative study of three different minimal invasive sampling methods. PLoS One 2013;8:e77948.
31. Goag EK, Lee JM, Chung KS, Kim SY, Leem AY, Song JH, et al. Usefulness of bronchoscopic rebiopsy of non-small cell lung cancer with acquired resistance to epidermal growth factor receptor-tyrosine kinase inhibitor. J Cancer 2018;9:1113–20.
32. Izumo T, Matsumoto Y, Chavez C, Tsuchida T. Re-biopsy by endobronchial ultrasound procedures for mutation analysis of non-small cell lung cancer after EGFR tyrosine kinase inhibitor treatment. BMC Pulm Med 2016;16:106.
33. Lee HS, Lee GK, Lee HS, Kim MS, Lee JM, Kim HY, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration in mediastinal staging of non-small cell lung cancer: how many aspirations per target lymph node station? Chest 2008;134:368–74.
34. Wahidi MM, Herth F, Yasufuku K, Shepherd RW, Yarmus L, Chawla M, et al. Technical aspects of endobronchial ultrasound-guided transbronchial needle aspiration: CHEST guideline and expert panel report. Chest 2016;149:816–35.
35. Tournoy KG, Rintoul RC, van Meerbeeck JP, Carroll NR, Praet M, Buttery RC, et al. EBUS-TBNA for the diagnosis of central parenchymal lung lesions not visible at routine bronchoscopy. Lung Cancer 2009;63:45–9.
36. Nakajima T, Yasufuku K, Fujiwara T, Chiyo M, Sekine Y, Shibuya K, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis of intrapulmonary lesions. J Thorac Oncol 2008;3:985–8.
37. Kuijvenhoven JC, Leoncini F, Crombag LC, Spijker R, Bonta PI, Korevaar DA, et al. Endobronchial ultrasound for the diagnosis of centrally located lung tumors: a systematic review and meta-analysis. Respiration 2020;99:441–50.
38. Labarca G, Sierra-Ruiz M, Kheir F, Folch E, Majid A, Mehta HJ,

et al. Diagnostic accuracy of endobronchial ultrasound transbronchial needle aspiration in lymphoma: a systematic review and meta-analysis. Ann Am Thorac Soc 2019;16:1432–9.
39. Agarwal R, Srinivasan A, Aggarwal AN, Gupta D. Efficacy and safety of convex probe EBUS-TBNA in sarcoidosis: a systematic review and meta-analysis. Respir Med 2012;106:883–92.
40. Ye W, Zhang R, Xu X, Liu Y, Ying K. Diagnostic efficacy and safety of endobronchial ultrasound-guided transbronchial needle aspiration in intrathoracic tuberculosis: a meta-analysis. J Ultrasound Med 2015;34:1645–50.
41. Asano F, Aoe M, Ohsaki Y, Okada Y, Sasada S, Sato S, et al. Complications associated with endobronchial ultrasound-guided transbronchial needle aspiration: a nationwide survey by the Japan Society for Respiratory Endoscopy. Respir Res 2013;14:50.
42. Dhooria S, Sehgal IS, Gupta N, Aggarwal AN, Behera D, Agarwal R. Diagnostic yield and complications of EBUS-TBNA performed under bronchoscopist-directed conscious sedation: single center experience of 1004 subjects. J Bronchology Interv Pulmonol 2017;24:7–14.
43. Caglayan B, Yilmaz A, Bilaceroglu S, Comert SS, Demirci NY, Salepci B. Complications of convex-probe endobronchial ultrasound-guided transbronchial needle aspiration: a multi-center retrospective study. Respir Care 2016;61:243–8.
44. Hurter T, Hanrath P. Endobronchial sonography: feasibility and preliminary results. Thorax 1992;47:565–7.
45. Kurimoto N, Murayama M, Yoshioka S, Nishisaka T. Analysis of the internal structure of peripheral pulmonary lesions using endobronchial ultrasonography. Chest 2002;122:1887–94.
46. Kikuchi E, Yamazaki K, Sukoh N, Kikuchi J, Asahina H, Imura M, et al. Endobronchial ultrasonography with guide-sheath for peripheral pulmonary lesions. Eur Respir J 2004;24:533–7.
47. Chavez C, Sasada S, Izumo T, Watanabe J, Katsurada M, Matsumoto Y, et al. Endobronchial ultrasound with a guide sheath for small malignant pulmonary nodules: a retrospective comparison between central and peripheral locations. J Thorac Dis 2015;7:596–602.
48. Tamiya M, Okamoto N, Sasada S, Shiroyama T, Morishita N, Suzuki H, et al. Diagnostic yield of combined bronchoscopy and endobronchial ultrasonography, under LungPoint guidance for small peripheral pulmonary lesions. Respirology 2013;18:834–9.
49. Yamada N, Yamazaki K, Kurimoto N, Asahina H, Kikuchi E, Shinagawa N, et al. Factors related to diagnostic yield of transbronchial biopsy using endobronchial ultrasonography with a guide sheath in small peripheral pulmonary lesions. Chest 2007;132:603–8.
50. Moon SM, Choe J, Jeong BH, Um SW, Kim H, Kwon OJ, et al. Diagnostic performance of radial probe endobronchial ultrasound without a guide-sheath and the feasibility of molecular analysis. Tuberc Respir Dis (Seoul) 2019;82:319–27.
51. Yu KL, Tsai TH, Ho CC, Liao WY, Lin CK, Hsu CL, et al. The value of radial endobronchial ultrasound-guided bronchial brushing in peripheral non-squamous non-small cell lung cancer. Sci Rep 2018;8:5837.
52. Good WR, Christensen PM, Herath S, Dawkins P, Yap E. Radial-probe endobronchial ultrasound outcomes in the investigation of peripheral pulmonary lesions: a New Zealand perspective. Intern Med J 2018;48:1481–7.
53. Izumo T, Sasada S, Chavez C, Tsuchida T. The diagnostic utility of endobronchial ultrasonography with a guide sheath and tomosynthesis images for ground glass opacity pulmonary lesions. J Thorac Dis 2013;5:745–50.
54. Izumo T, Sasada S, Chavez C, Matsumoto Y, Tsuchida T. Radial endobronchial ultrasound images for ground-glass opacity pulmonary lesions. Eur Respir J 2015;45:1661–8.
55. Kim EJ, Kim KC. Utility of radial probe endobronchial ultrasound-guided transbronchial lung biopsy in diffuse lung lesions. Tuberc Respir Dis (Seoul) 2019;82:201–10.
56. Han Y, Kim HJ, Kong KA, Kim SJ, Lee SH, Ryu YJ, et al. Diagnosis of small pulmonary lesions by transbronchial lung biopsy with radial endobronchial ultrasound and virtual bronchoscopic navigation versus CT-guided transthoracic needle biopsy: a systematic review and meta-analysis. PLoS One 2018;13:e0191590.
57. Ahn JH, Jang JG. Initial experience in CT-guided percutaneous transthoracic needle biopsy of lung lesions performed by a pulmonologist. J Clin Med 2019;8:821.
58. Zhang L, Wu H, Wang G. Endobronchial ultrasonography using a guide sheath technique for diagnosis of peripheral pulmonary lesions. Endosc Ultrasound 2017;6:292–9.
59. Steinfort DP, Khor YH, Manser RL, Irving LB. Radial probe endobronchial ultrasound for the diagnosis of peripheral lung cancer: systematic review and meta-analysis. Eur Respir J 2011;37:902–10.
60. Shinagawa N. A review of existing and new methods of bronchoscopic diagnosis of lung cancer. Respir Investig 2019;57:3–8.
61. Hasegawa S, Hitomi S, Murakawa M, Mori K. Development of an ultrathin fiberscope with a built-in channel for bronchoscopy in infants. Chest 1996;110:1543–6.
62. Oki M, Saka H, Kitagawa C, Tanaka S, Shimokata T, Mori K, et al. Novel thin bronchoscope with a 1.7-mm working channel for peripheral pulmonary lesions. Eur Respir J 2008;32:465–71.

https://doi.org/10.12701/yujm.2020.00584

63. Yamamoto S, Ueno K, Imamura F, Matsuoka H, Nagatomo I, Omiya Y, et al. Usefulness of ultrathin bronchoscopy in diagnosis of lung cancer. Lung Cancer 2004;46:43–8.
64. Oki M, Saka H, Ando M, Asano F, Kurimoto N, Morita K, et al. Ultrathin bronchoscopy with multimodal devices for peripheral pulmonary lesions: a randomized trial. Am J Respir Crit Care Med 2015;192:468–76.
65. Schwarz Y, Greif J, Becker HD, Ernst A, Mehta A. Real-time electromagnetic navigation bronchoscopy to peripheral lung lesions using overlaid CT images: the first human study. Chest 2006;129:988–94.
66. Dhillon SS, Harris K. Bronchoscopy for the diagnosis of peripheral lung lesions. J Thorac Dis 2017;9(Suppl 10):S1047–58.
67. Zhang W, Chen S, Dong X, Lei P. Meta-analysis of the diagnostic yield and safety of electromagnetic navigation bronchoscopy for lung nodules. J Thorac Dis 2015;7:799–809.
68. Folch EE, Pritchett MA, Nead MA, Bowling MR, Murgu SD, Krimsky WS, et al. Electromagnetic navigation bronchoscopy for peripheral pulmonary lesions: one-year results of the prospective, multicenter NAVIGATE study. J Thorac Oncol 2019;14:445–58.
69. Eberhardt R, Anantham D, Ernst A, Feller-Kopman D, Herth F. Multimodality bronchoscopic diagnosis of peripheral lung lesions: a randomized controlled trial. Am J Respir Crit Care Med 2007;176:36–41.
70. Mahajan AK, Patel S, Hogarth DK, Wightman R. Electromagnetic navigational bronchoscopy: an effective and safe approach to diagnose peripheral lung lesions unreachable by conventional bronchoscopy in high-risk patients. J Bronchology Interv Pulmonol 2011;18:133–7.
71. Ganganah O, Guo SL, Chiniah M, Li YS. Efficacy and safety of cryobiopsy versus forceps biopsy for interstitial lung diseases and lung tumours: a systematic review and meta-analysis. Respirology 2016;21:834–41.
72. Johannson KA, Marcoux VS, Ronksley PE, Ryerson CJ. Diagnostic yield and complications of transbronchial lung cryobiopsy for interstitial lung disease: a systematic review and metaanalysis. Ann Am Thorac Soc 2016;13:1828–38.
73. Schuhmann M, Bostanci K, Bugalho A, Warth A, Schnabel PA, Herth FJ, et al. Endobronchial ultrasound-guided cryobiopsies in peripheral pulmonary lesions: a feasibility study. Eur Respir J 2014;43:233–9.
74. Dhooria S, Sehgal IS, Aggarwal AN, Behera D, Agarwal R. Diagnostic yield and safety of cryoprobe transbronchial lung biopsy in diffuse parenchymal lung diseases: systematic review and meta-analysis. Respir Care 2016;61:700–12.

Yeungnam University Journal of Medicine
YUJM

Review article
eISSN 2384-0293
Yeungnam Univ J Med 2020;37(4):262-268
https://doi.org/10.12701/yujm.2020.00647

Biological treatments for severe asthma

Hyun Jung Jin

Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea

Received: July 16, 2020
Revised: August 20, 2020
Accepted: August 24, 2020

Corresponding author:
Hyun Jung Jin
Department of Internal Medicine, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-620-3830
Fax: +82-53-620-3849
Email: jhj0619@yu.ac.kr

Severe asthma patients comprise about 3% to 13% of all asthma patients, but they have higher hospital utilization rates and higher medical costs than those of nonsevere asthma patients. Treatment methods for severe asthma patients are still lacking; however, the recent development of biologics is expected to have a positive effect. The biological therapies developed so far are mainly aimed at treating asthma patients with type 2 inflammation. These biologics have been found to reduce symptoms of asthma, improve lung function, reduce the use of oral corticosteroids, and improve quality of life of patients. This article reviews the mechanism of action and indications for approved biologics and discusses what should be considered when choosing biologics.

Keywords: Biological products; Eosinophils; Monoclonal antibodies; Severe asthma

Introduction

Asthma is a chronic airway disease characterized by airway inflammation, bronchial hypersensitivity, and variable airway obstruction, and more than 300 million people are affected by it worldwide. Most asthmatic patients are effectively treated with standard controller therapy. However, some patients who use high-dose inhaled corticosteroid (ICS) and long-acting beta-agonist compounds endure inadequately controlled symptoms, repeated asthma exacerbations (AEs), or continuous lung function decline. Such patients can be categorized as having severe asthma (SA) [1].

While the definition of SA has changed over time, the definition of the European Respiratory Society/American Thoracic Society guidelines of 2014 has become the most widely used ones in recent years. According to this definition, patients with uncontrolled SA are those who need to use systemic steroids for asthma symptom control, despite the implementation of high-intensity treatments corresponding to the stages 4 to 5 of the Global Initiative for Asthma guideline, excluding all other diagnostic possibilities, comorbidities, deterioration factors, compliance, and so on that correspond to SA [2].

The prevalence of SA is less than 3.5% to 13% of the total asthmatic population [3,4]; however, SA patients use more than 50% of the treatment cost for asthma due to increased use of drugs, frequent outpatient and emergency room visits, and frequent hospitalizations [5]. In addition, unregulated asthma symptoms can lead to significant social overhead costs, such as reduced quality of life of the patients and family members and adverse effects on academic and work life, resulting in reduced productivity [6].

For these reasons, proper treatment for SA is required, and recently, many new drugs have been developed. This article reviews the mechanism of action, indications for approved biologics and discusses what should be considered when choosing biologics.

Type-2 high and low airway inflammation

Recently, many studies have been conducted on asthma endotypes. Several attempts are being made to classify SA into various clusters according to clinical characteristics and pathophysiology. Wenzel et al. [7] reported that SA can be divided into two inflammatory reactions: type 2 (T2)-high expression and T2-low expression, with the high and low eosinophils, respectively. In the Belgian

Severe Asthma Registry study, the prevalence of T2-high expression was 57%, based on ≥ 3% sputum eosinophil or ≥ 27 ppb of fractional exhaled nitric oxide (FeNO) and ≥ 188 cells/μL of peripheral blood eosinophil in SA patients [8].

1. Type 2-high asthma

T2-high asthma includes both allergic and nonallergic eosinophilic asthma. Immunoglobulin E (IgE)-dependent processes play an important role in allergic asthma, but T2 cytokine inflammation could play a dominant role in nonallergic asthma [9]. In the T2-high asthma, inhaled allergens, microorganisms, and pollutants interact with the airway epithelium, resulting in the activation of mediators such as thymine stromal lymphopoietin, interleukin (IL)-25, and IL-33. This process leads to activation of IL-4, IL-5, and IL-13. IL-5 is an important cytokine for the recruitment, maturity, and survival of eosinophils, while IL-4 and IL-13 increase the number of attachment receptors in the vascular endothelium, helping the eosinophil penetrate the tissue. Eosinophil is recruited by the lung mucous membrane due to the effect of chemokines, via the activation of the prostaglandin D2 type 2 receptor, which is expressed in T2 lymphocytes, type 2 innate lymphoid cells (ILC2) cells, and mast cells. The recruited eosinophil damages the bronchial epithelium and causes bronchial obstruction with leukotriene secretion. Additionally, IL-4 allows IgE to be produced in B cells, and IgE combines with mast cells to induce cell degeneration, and this secures eicosanoids and cytokines and activates airway inflammation, epithelial cells, mucous glands, and airway smoothing muscles. IL-13 is also involved in airway smooth muscle hypersensitivity and mucus hypersecretion [10-12]. Serum IgE, sputum, and blood eosinophil count, FeNO, and serum periostin are all important biomarkers of T2 inflammation that predict response to biologics [13].

2. Type 2-low asthma

T2-low asthma includes neutrophilic, paucigranulocytic, or mixed asthma, whose pathophysiologies are not as well understood as those of T2-high asthma. T2-low asthma activates both T helper (Th) 1 cells and Th17 cells, and high IL-17A mRNA levels were found in patients with moderate-to-severe asthma [14-16]. These patients are generally less responsive to corticosteroids, less prone to allergies, and older at diagnosis than patients of other endotypes. The development of treatment drugs for T2-low asthma has not made significant progress and no biologics have been approved yet. Some studies have reported the effects of bronchial thermoplasty and azithromycin treatment [17,18].

Biologics for treatment of severe asthma

So far, there are five biologics approved in South Korea as treatment for SA, all of which are drugs for T2-high asthma. The characteristics of these biologics are summarized in Tables 1 and 2.

Anti-immunoglobulin E

Omalizumab

As an anti-IgE treatment, omalizumab (Xolair, Genentech/Novartis, South San Francisco, CA, USA) was approved in 2002, becoming the first biological drug for the treatment of severe allergic asthma. It was approved for use in South Korea by the Ministry of Food and Drug Safety (MFDS) in 2007. IgE is produced by B cells in response to allergen activation. Omalizumab is a monoclonal antibody that binds to IgE to prevent it from combining with the high-affinity IgE receptors on mast cells and basophils and also reduces the expression of the IgE receptor on mast cells. This prevents mast cell activation and the generation of its inflammatory mediators when IgE is activated by allergens [19,20].

Table 1. Summary of the biologics currently approved for severe asthma in Korea

Biologics (trade name)	Mechanism of action	Indication	Dose and route
Omalizumab (Xolair)	Anti-IgE; prevents IgE from binding to its receptor on mast cells and basophils	≥ 6 yr old; positive allergy testing (allergic asthma); IgE, 30–700 IU/mL	0.016 mg/kg per IU of IgE SC every 2–4 wk
Mepolizumab (Nucala)	Anti–IL-5; binds to IL-5 ligand; prevents IL-5 from binding to its receptor	≥ 18 yr old; AEC ≥ 150 cells/μL or ≥ 300 cells/μL at least once a year	100 mg SC every 4 wk
Reslizumab (Cinqair)	Anti–IL-5; binds to IL-5 ligand; prevents IL-5 from binding to its receptor	≥ 18 yr old; AEC ≥ 400 cells/μL	Weight-based dosing of 3 mg/kg IV every 4 wk
Benralizumab (Fasenra)	Anti–IL-5; binds to IL-5 receptor α; causes apoptosis of eosinophils and basophils	≥ 18 yr old; severe eosinophilic asthma	30 mg SC every 4 wk for three doses; followed by every 8 wk subsequently
Dupilumab (Dupixent)	Anti–IL-4R; binds to IL-4 receptor α; blocks signaling of IL-4 and IL-13	≥ 12 yr old; AEC ≥ 150 cells/μL or FeNO ≥ 25 ppb with OCS-dependent	400–600 mg SC loading dose followed by 200 or 300 mg SC every 2 wk

IgE, immunoglobulin E; SC, subcutaneous; IL, interleukin; AEC, absolute blood eosinophil count; IV, intravenous; FeNO, fractional exhaled nitric oxide; OCS, oral corticosteroids.
Xolair, Genentech/Novartis, South San Francisco, CA, USA; Nucala, GlaxoSmithKline, Research Triangle Park, NC, USA; Cinqair, Teva Repatriation, Frazer, PA, USA; Fasenra, MedImmune, Gaithersburg, MD, USA; Dupixent, Regeneron, Tarrytown, NY, USA/Sanofi, Paris, France.

Table 2. Efficacy of the biologics currently approved for severe asthma in Korea

Biologics (trade name)	Asthma exacerbation	Lung function improvement	Corticosteroid weaning
Omalizumab (Xolair)	Reduces by 25%–50%	Minimal or equivocal improvement	Decreases use of ICS, but no clear data that it facilitates with OCS weaning
Mepolizumab (Nucala)	Reduces by 50%	Some, but not all, studies showed some improvement	Decreases total use of OCS
			Facilitate discontinuation of chronic OCS (14%)
Reslizumab (Cinqair)	Reduces by 50%–60%	Improved	OCS weaning has not been evaluated for this indication
Benralizumab (Fasenra)	Reduces by 25%–60%	Improved	Decreases total use of OCS
			Facilitate discontinuation of chronic OCS (50%)
Dupilumab (Dupixent)	Reduces by 50%–70%	Improved	Decreases total use of OCS
			Facilitate discontinuation of chronic OCS (50%)

ICS, inhaled corticosteroid; OCS, oral corticosteroid.
Xolair, Genentech/Novartis, South San Francisco, CA, USA; Nucala, GlaxoSmithKline, Research Triangle Park, NC, USA; Cinqair, Teva Repatriation, Frazer, PA, USA; Fasenra, MedImmune, Gaithersburg, MD, USA; Dupixent, Regeneron, Tarrytown, NY, USA/Sanofi, Paris, France.

Omalizumab reduces the number of AEs, doses of ICSs, asthma symptoms, and frequency of the use of emergency relief drugs [21-23]. In addition, some studies have reported some improvement in lung function [24,25]. However, there have been no data on its contribution to oral corticosteroid (OCS) weaning. IgE levels could not predict therapeutic reactions, but the T2 biomarkers, FeNO, peripheral blood eosinophil, and periostin, were related to therapeutic reactions [26].

Previous studies have shown that omalizumab works in only about 60% to 70% of SA patients. In most patients, the response to omalizumab at 16 weeks is an effective predictor of persistent response [27]. Stopping omalizumab treatment may be considered for patients with well-controlled asthma under medium-dose ICS treatment and those who are no longer exposed to previously well-documented allergic triggers, with at least 12 months of good posttreatment response [28].

Omalizumab is well tolerated with a risk of anaphylaxis of 0.1% [29]. It has been recommended that patients should be observed for 2 hours after the first three injections of omalizumab and for 30 minutes after subsequent injections. It should not be self-administered or administered outside of a medical setting given the risk of anaphylaxis [28].

Anti–interleukin-5

IL-5 is the cytokine involved in the recruitment, activation, and survival of eosinophils, and by inhibiting this pathway, anti–IL-5 biologics reduce eosinophilic airway inflammation [10,30].

1. Mepolizumab

Mepolizumab (Nucala, GlaxoSmithKline, Research Triangle Park, NC, USA) is a monoclonal anti–IL-5 IgG1κ antibody that prevents IL-5 from binding to the α-subunit of the IL-5 receptor on the surface of the eosinophil. It was approved for use in South Korea by the MFDS in 2016. In clinical trials, mepolizumab reduced the number of AEs and doses of ICSs or OCSs and improved lung function, asthma symptoms, and quality of life [31-34]. It was relatively safe, but there were warnings of hypersensitivity and herpes zoster and parasite infections [35].

2. Reslizumab

Reslizumab (Cinqair, Teva Repatriation, Frazer, PA, USA) is a monoclonal anti–IL-5 IgG1κ antibody with a similar mechanism to mepolizumab. It was approved for use in South Korea by the MFDS in 2017. In a previous study, intravenous reslizumab (3.0 mg/kg) reduced the number of AEs and sputum eosinophils and improved lung function, asthma symptoms, and quality of life in patients who had blood eosinophil levels of ≥ 400 cells/μL and ≥ 1 AE [36-38]. It was relatively safe, but there are warnings of hypersensitivity. Blood eosinophil levels appear to return to previous levels after cessation, in approximately 4 months after the last dose [39].

3. Benralizumab

Benralizumab (Fasenra, MedImmune, Gaithersburg, MD, USA) is a monoclonal anti–IL-5 IgG1κ antibody that binds to the α-subunit of the IL-5 receptor. Unlike other anti–IL-5 antibodies, it inhibits the proliferation and activation of eosinophils. It can also be combined with natural-killer cells Fc receptor FcγRIIIα to induce apoptosis with antibody-dependent cell-mediated cytotoxicity, which effectively depletes eosinophils. It was approved for use in South Korea by the MFDS in 2019. In a previous study, benrali-

https://doi.org/10.12701/yujm.2020.00647

zumab reduced the number of AEs and frequency of OCS use, and it improved lung function and asthma symptoms in patients who had blood eosinophil levels of ≥ 300 cells/μL and ≥ 2 AE [40-43]. Another study showed that the therapeutic effect of benralizumab was maintained for up to 2 years [44]. It was relatively safe but there were warnings of hypersensitivity.

Anti–interleukin-4/interleukin-13

Dupilumab

Dupilumab (Dupixent, Regeneron, Tarrytown, NY, USA/Sanofi, Paris, France) is a monoclonal antibody to the IL-4 receptor α (IL-4Rα) subunit that is a part of the type 2 receptor activated by IL-4 and IL-13. IL-4 and IL-13 are mainly produced by CD4+ Th2 cells and ILC2 cells, and they promote the production of IgE and recruitment of inflammatory cells [45]. Dupilumab has been approved by the MFDS for treatment of atopic dermatitis and was recently approved for treatment of asthma. Dupilumab significantly reduced the number of AEs, frequency of OCS use, and levels of T2 inflammation markers such as FeNO, thymus- and activation-regulated chemokines, eotaxin-3, and IgE; it also rapidly improved lung function in cases of moderate-to-severe asthma. Peripheral blood eosinophils and FeNO are effective biomarkers that predict treatment response [46-48]. Dupilumab has a favorable safety profile, with common side effects including injection site reaction and transient blood eosinophilia [12].

Selection of biologics for severe asthma

It is difficult to select the most appropriate biologics in patients with SA. Since there has been no direct comparison between biologics, the argument for the superiority of one biologics over another by indirect treatment comparisons using meta-analysis and matching-adjusted strategies may be unreasonable and misleading. There is no useful biomarker for predicting or monitoring treatment response. The mechanism of a drug's action, blood/sputum eosinophil levels, serum IgE levels, FeNO levels, atopic status, comorbidities, and drug cost should be considered when selecting specific biologics. For allergic asthma patients, omalizumab is recommended first. In eosinophilic asthmatic patients with a history of exacerbation, anti–IL-5/5R therapy can be considered as first-line treatment [28]. Some researchers suggest an algorithm approach for selecting the appropriate biologics. Papaioannou et al. [49] defined patients with sputum eosinophil level of 3%, blood eosinophil count of 300 cells/μL, and FeNO level of 25 ppb as eosinophilic types and suggested a drug selection algorithm according to eosinophilic inflammatory markers, the onset of asthma, and allergic tendencies. Fitzpatrick and Moore [50] suggested drug selection according to airway obstruction, symptom onset, exacerbation, and the presence of biomarkers. We need to develop an algorithm that can be easily applied in clinical settings. In addition, the algorithm needs to be modified continuously, considering further research results on outcome predictors and new drug development.

Assessment of treatment response to biologics

Assessment of therapeutic response to biologics is essential. In general, it is recommended to evaluate treatment response 3 to 4 months after treatment [28]. Unfortunately, to date, there are no clear criteria or biomarkers to evaluate responses. Exacerbations, symptom control, lung function, and OCS dose should be considered comprehensively in order to determine the response. If patients show a good response to biologics, consider reducing OCS carefully and then stopping other add-on medications by evaluating asthma control. It is recommended to maintain a medium dose of ICS. If patients show a poor response, clinicians may consider changing to different type-2-targeted biologics or using a combination of different biologics. However, the rationale for such use is still lacking [28].

Conclusion

Currently, the use of biologics for treating SA is gaining popularity, and the development of new drugs is actively taking place. These drugs are beneficial for SA patients who have been suffering despite the use of standard inhalation medications. In order to use biological agents, assessment of the patient's phenotype and endotype is an essential step. The era of personalized treatment of SA has arrived, and novel tests are needed to determine each patient's phenotype and endotype. However, the biomarkers for predicting the efficacy of biologics are not yet clear. In addition, these expensive biological agents are accompanied by healthcare costs, and there is currently no consensus on the duration of treatment with biologicals. Moreover, although biological preparations are based on the mechanism of asthma, it is only one path and it does not prevent the entire mechanism of asthma. Therefore, it is still questionable whether the natural course of asthma can be changed. There are many drug treatment options for T2-high asthma, but very few fort T2-low asthma. In the future, we expect to develop innovative treatments for T2-low asthma.

Acknowledgments

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

ORCID
Hyun Jung Jin, https://orcid.org/0000-0003-2888-420X

References

1. Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. J Allergy Clin Immunol 2007;119:405–13.
2. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343–73.
3. Lee E, Kim A, Ye YM, Choi SE, Park HS. Increasing prevalence and mortality of asthma with age in Korea, 2002-2015: a nationwide, population-based study. Allergy Asthma Immunol Res 2020;12:467–84.
4. Kim SH, Moon JY, Lee JH, Ban GY, Kim S, Kim MA, et al. Perceptions of severe asthma and asthma-COPD overlap syndrome among specialists: a questionnaire survey. Allergy Asthma Immunol Res 2018;10:225–35.
5. Ivanova JI, Bergman R, Birnbaum HG, Colice GL, Silverman RA, McLaurin K. Effect of asthma exacerbations on health care costs among asthmatic patients with moderate and severe persistent asthma. J Allergy Clin Immunol 2012;129:1229–35.
6. Kim JH. Diagnosis of severe asthma: definition and identification. Korean J Med 2018;93:153–8.
7. Wenzel SE, Schwartz LB, Langmack EL, Halliday JL, Trudeau JB, Gibbs RL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. Am J Respir Crit Care Med 1999;160:1001–8.
8. Schleich F, Brusselle G, Louis R, Vandenplas O, Michils A, Pilette C, et al. Heterogeneity of phenotypes in severe asthmatics. The Belgian Severe Asthma Registry (BSAR). Respir Med 2014;108:1723–32.
9. Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? Thorax 1999;54:268–72.
10. Russell RJ, Brightling C. Pathogenesis of asthma: implications for precision medicine. Clin Sci (Lond) 2017;131:1723–35.
11. Diver S, Russell RJ, Brightling CE. New and emerging drug treatments for severe asthma. Clin Exp Allergy 2018;48:241–52.
12. McGregor MC, Krings JG, Nair P, Castro M. Role of biologics in asthma. Am J Respir Crit Care Med 2019;199:433–45.
13. Pavord ID, Afzalnia S, Menzies-Gow A, Heaney LG. The current and future role of biomarkers in type 2 cytokine-mediated asthma management. Clin Exp Allergy 2017;47:148–60.
14. Bullens DM, Truyen E, Coteur L, Dilissen E, Hellings PW, Dupont LJ, et al. IL-17 mRNA in sputum of asthmatic patients: linking T cell driven inflammation and granulocytic influx? Respir Res 2006;7:135.
15. Green RH, Brightling CE, Woltmann G, Parker D, Wardlaw AJ, Pavord ID. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. Thorax 2002;57:875–9.
16. Choy DF, Hart KM, Borthwick LA, Shikotra A, Nagarkar DR, Siddiqui S, et al. TH2 and TH17 inflammatory pathways are reciprocally regulated in asthma. Sci Transl Med 2015;7:301ra129.
17. Godar M, Blanchetot C, de Haard H, Lambrecht BN, Brusselle G. Personalized medicine with biologics for severe type 2 asthma: current status and future prospects. MAbs 2018;10:34–45.
18. Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. Lancet 2017;390:659–68.
19. Busse WW. Biological treatments for severe asthma: a major advance in asthma care. Allergol Int 2019;68:158–66.
20. Strunk RC, Bloomberg GR. Omalizumab for asthma. N Engl J Med 2006;354:2689–95.
21. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol 2001;108:184–90.
22. Solèr M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. Eur Respir J 2001;18:254–61.
23. Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. Ann Intern Med 2011;154:573–82.
24. Pillai P, Chan YC, Wu SY, Ohm-Laursen L, Thomas C, Durham SR, et al. Omalizumab reduces bronchial mucosal IgE and im-

https://doi.org/10.12701/yujm.2020.00647

proves lung function in non-atopic asthma. Eur Respir J 2016;48:1593–601.
25. Humbert M, Beasley R, Ayres J, Slavin R, Hébert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy 2005;60:309–16.
26. Hanania NA, Wenzel S, Rosén K, Hsieh HJ, Mosesova S, Choy DF, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med 2013;187:804–11.
27. Bousquet J, Siergiejko Z, Swiebocka E, Humbert M, Rabe KF, Smith N, et al. Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma. Allergy 2011;66:671–8.
28. Kim BK, Park SY, Ban GY, Kim MA, Lee JH, An J, et al. Evaluation and management of difficult-to-treat and severe asthma: an expert opinion from the Korean Academy of Asthma, Allergy and Clinical Immunology, the Working Group on Severe Asthma. Allergy Asthma Immunol Res 2020;12:e61.
29. Cox L, Lieberman P, Wallace D, Simons FE, Finegold I, Platts-Mills T, et al. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology Omalizumab-Associated Anaphylaxis Joint Task Force follow-up report. J Allergy Clin Immunol 2011;128:210–2.
30. Walsh GM. An update on biologic-based therapy in asthma. Immunotherapy 2013;5:1255–64.
31. Chupp GL, Bradford ES, Albers FC, Bratton DJ, Wang-Jairaj J, Nelsen LM, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. Lancet Respir Med 2017;5:390–400.
32. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med 2014;371:1198–207.
33. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 2012;380:651–9.
34. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 2014;371:1189–97.
35. Katial RK, Bensch GW, Busse WW, Chipps BE, Denson JL, Gerber AN, et al. Changing paradigms in the treatment of severe asthma: the role of biologic therapies. J Allergy Clin Immunol Pract 2017;5(2 Suppl):S1–14.
36. Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. Chest 2016;150:789–98.
37. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med 2011;184:1125–32.
38. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 2015;3:355–66.
39. Murphy K, Jacobs J, Bjermer L, Fahrenholz JM, Shalit Y, Garin M, et al. Long-term safety and efficacy of reslizumab in patients with eosinophilic asthma. J Allergy Clin Immunol Pract 2017;5:1572–81.
40. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet 2016;388:2115–27.
41. Park HS, Lee SH, Lee SY, Kim MK, Lee BJ, Werkström V, et al. Efficacy and safety of benralizumab for Korean patients with severe, uncontrolled eosinophilic asthma. Allergy Asthma Immunol Res 2019;11:508–18.
42. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. N Engl J Med 2017;376:2448–58.
43. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2016;388:2128–41.
44. Busse WW, Bleecker ER, FitzGerald JM, Ferguson GT, Barker P, Sproule S, et al. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. Lancet Respir Med 2019;7:46–59.
45. Pepper AN, Renz H, Casale TB, Garn H. Biologic therapy and novel molecular targets of severe asthma. J Allergy Clin Immunol Pract 2017;5:909–16.
46. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe un-

controlled asthma. N Engl J Med 2018;378:2486–96.
47. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med 2018;378:2475–85.
48. Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet 2016;388:31–44.
49. Papaioannou AI, Diamant Z, Bakakos P, Loukides S. Towards precision medicine in severe asthma: treatment algorithms based on treatable traits. Respir Med 2018;142:15–22.
50. Fitzpatrick AM, Moore WC. Severe asthma phenotypes - how should they guide evaluation and treatment? J Allergy Clin Immunol Pract 2017;5:901–8.

https://doi.org/10.12701/yujm.2020.00647

Yeungnam University Journal of Medicine
YUJM

Review article
eISSN 2384-0293
Yeungnam Univ J Med 2020;37(4):269-276
https://doi.org/10.12701/yujm.2020.00458

Therapeutic potential of targeting kinase inhibition in patients with idiopathic pulmonary fibrosis

Suji Kim[1,2], Jae Hyang Lim[3], Chang-Hoon Woo[1,2]

[1]Smart-Ageing Convergence Research Center, Yeungnam University College of Medicine, Daegu, Korea
[2]Department of Pharmacology, Yeungnam University College of Medicine, Daegu, Korea
[3]Department of Microbiology, Ewha Womans University College of Medicine, Seoul, Korea

Received: June 8, 2020
Revised: July 1, 2020
Accepted: July 2, 2020

Corresponding authors:
Chang-Hoon Woo
Department of Pharmacology, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-640-6973
Fax: +82-53-656-7995
E-mail: changhoon_woo@yu.ac.kr

Jae Hyang Lim
Department of Microbiology, Ewha Womans University College of Medicine, 25 Magokdong-ro 2-gil, Gangseo-gu, Seoul 07804, Korea
Tel: +82-2-6986-6277
Fax: +82-2-6986-7012
E-mail: jlim19@ewha.ac.kr

Fibrosis is characterized by excessive accumulation of extracellular matrix components. The fibrotic process ultimately leads to organ dysfunction and failure in chronic inflammatory and metabolic diseases such as pulmonary fibrosis, advanced kidney disease, and liver cirrhosis. Idiopathic pulmonary fibrosis (IPF) is a common form of progressive and chronic interstitial lung disease of unknown etiology. Pathophysiologically, the parenchyma of the lung alveoli, interstitium, and capillary endothelium becomes scarred and stiff, which makes breathing difficult because the lungs have to work harder to transfer oxygen and carbon dioxide between the alveolar space and bloodstream. The transforming growth factor beta (TGF-β) signaling pathway plays an important role in the pathogenesis of pulmonary fibrosis and scarring of the lung tissue. Recent clinical trials focused on the development of pharmacological agents that either directly or indirectly target kinases for the treatment of IPF. Therefore, to develop therapeutic targets for pulmonary fibrosis, it is essential to understand the key factors involved in the pathogenesis of pulmonary fibrosis and the underlying signaling pathway. The objective of this review is to discuss the role of kinase signaling cascades in the regulation of either TGF-β-dependent or other signaling pathways, including Rho-associated coiled-coil kinase, *c-jun* N-terminal kinase, extracellular signal-regulated kinase 5, and p90 ribosomal S6 kinase pathways, and potential therapeutic targets in IPF.

Keywords: Fibrosis; Idiopathic pulmonary fibrosis; Kinase; Transforming growth factor beta

Introduction

Fibrosis is an excessive deposition of extracellular matrix (ECM) components, particularly fibrillar type I and III collagen [1,2]. Fibrosis is mainly driven by profibrogenic and proinflammatory cytokines, including the transforming growth factor beta (TGF-β) superfamily, tumor necrosis factor alpha (TNF-α), various interleukins, oxidative stress, and inflammation [3,4]. As a result, fibrosis can lead to failure of vital organs, including the lung, liver, heart, kidney, skin, and eye [5]. Pulmonary fibrosis is the final outcome of various parenchymal lung disorders, known as interstitial lung disease (ILD) [6]. One of the most common subtypes of ILD is idiopathic pulmonary fibrosis (IPF), which is a chronic, progressive, and generally fatal parenchymal lung disorder of unknown cause, with an approximate median survival of 2 to 5 years from diagnosis [7]. The clinical characteristics of IPF are heterogeneous and unpredictable, mainly including chronic cough, exertional dyspnea, declining lung function, and poor quality of life [8]. Epidemiological studies indicate that IPF is an age-related disease, and the majority of cases are diagnosed in patients over

60 years of age [9].

The pathogenic mechanism in IPF is not clearly defined, but the disease is characterized by epithelial injury and activation, epithelial-mesenchymal transition (EMT), sustained fibroblast activation, and excessive ECM accumulation, which result in progressive and irrevocable distortion of the histological lung structure [10,11]. Previous studies have revealed the complex and vital role of TGF-β/Smad signaling in lung fibrosis [12-15]. Enhanced TGF-β1 signaling with excessive ECM accumulation has been reported in experimental models of pulmonary fibrosis as well as in human lung fibrotic tissue [16,17]. The inhibition of TGF-β by neutralizing anti-TGF-β antibody, decorin, RNA interference, or antisense oligonucleotides alleviates fibrosis [18-21]. Moreover, in a mouse model of bleomycin-induced pulmonary fibrosis, Smad3 deficiency attenuated pulmonary fibrosis [22]. TGF-β signaling can initiate both canonical Smad-dependent and Smad-independent signaling pathways [23]. In Smad-independent pathways, TGF-β activates the phosphoinositide 3-kinase (PI3K)/Akt pathway and mitogen-activated protein kinases (MAPKs) such as extracellular signal-regulated kinase (ERK) 1/2, p38, and *c-jun* N-terminal kinase (JNK) 1/2/3 [24].

It has long been assumed that acute and chronic alveolitis lead to a fibrogenic response and play a critical role in the disease progression of IPF [25]. There are two different mechanisms involved in the pathogenesis of IPF. One of these is the 'inflammatory pathway,' which represents the major etiological pathway for IPF, associated with a marked collapse in the integrity of alveolar epithelial cells and subsequent fibrotic stage [25]. The other is the 'epithelial/fibroblastic pathway,' revealed by IPF [26]. These pathological changes, along with the disruption of the epithelial basement membrane enhance the migration of fibroblasts/myofibroblasts into the alveolar spaces and their subsequent deposition into the intra-alveolar ECM [26,27]. Many studies have shown that injured/activated alveolar epithelial cells in lungs from patients with IPF produce a variety of growth factors and pro-fibrotic cytokines [27,28].

Clinical treatment for pulmonary fibrosis

Pirfenidone and nintedanib have been recently approved for the treatment of IPF [29-31]. Pirfenidone is a small molecule that inhibits inflammatory responses and the progression of fibrosis in experimental models and patients with IPF [32-34]. It downregulates the proliferation of fibroblasts and TGF-β1-induced collagen synthesis and reduces the production of the inflammatory cytokine TNF-α and interleukin-1β both *in vitro* and *in vivo* [35]. In a phase 3 study comparing pirfenidone with placebo in patients with IPF, pirfenidone treatment for 52 weeks significantly prolonged progression-free survival, compared with placebo [36]. In addition, with pirfenidone, there was a relative reduction of 47.9% in the proportion of patients who had a decline in predicted forced vital capacity or who died [36]. Pirfenidone is frequently associated with gastrointestinal adverse effects such as dyspepsia, nausea, and gastritis [37].

Nintedanib is a small-molecule tyrosine kinase inhibitor targeting fibroblast growth factor receptor (FGFR) 1–3, vascular endothelial growth factor receptor (VEGFR) 1–3, and platelet-derived growth factor receptor (PDGFR) αβ, which are potentially involved in the progression of pulmonary fibrosis [38]. Nintedanib inhibits FGFR and PDGFR autophosphorylation and subsequent activation of downstream signaling via the Ras/Raf/MAPK, ERK1/2, and PI3K/Akt pathways [38]. Vascular endothelial growth factor (VEGF) stimulates angiogenesis through VEGFR and also binds to PDGFR in fibroblasts, subsequently stimulating cellular proliferation [38]. Nintedanib reduces migration, proliferation, and survival of fibroblasts, and ultimately attenuates angiogenesis in the lung [39]. In addition, administration of nintedanib attenuated the histopathological features of pulmonary fibrosis and expression of profibrogenic genes in experimental models of lung fibrosis [40]. In the two replicate phase 3 trials, nintedanib was shown to slow disease progression in patients with IPF by decreasing the annual rate of decline in forced vital capacity [41].

Other recommendations for the pharmacological treatment of pulmonary fibrosis are warfarin, N-acetyl cysteine, imatinib, and endothelin receptor antagonists [9]. However, most clinical trials did not show significant differences between placebo and treatment effects in patients with IPF [9]. Therefore, there is still a need to develop new therapeutic targets and agents to inhibit the progression of pulmonary fibrosis and improve mortality rates.

Clinical trials with kinase inhibitors for idiopathic pulmonary fibrosis

1. Receptor kinases

In recent years, growth factors and receptor kinases have attracted attention as potential drug targets for pulmonary fibrosis. Several therapies targeting receptor kinases, including growth factor receptors, are currently in clinical trials for IPF (Table 1). Aberrantly activated lung epithelial cells are the primary source of TGF-β, fibroblast growth factor (FGF)-2, PDGF, connective tissue growth factor (CTGF), and endothelin-1, key factors in the development of IPF. Based on this evidence, clinical trials of nintedanib targeting multiple growth factor receptors could be successful. Additionally, several clinical trials of cytokine receptors, including

https://doi.org/10.12701/yujm.2020.00458

TNF-α, interferon-γ, and interleukin-13, have been conducted with no significant impact in patients with IPF (NCT 02277145, NCT00532233, and NCT00075998).

TGF-β mediates tissue fibrosis via recruitment and activation of monocytes and fibroblasts, and production of ECM through activation of serine/threonine kinase receptors [42,43]. In addition, TGF-β1 regulates the proliferation, differentiation, apoptosis, adhesion and migration, immunity, and even embryonic development, which ultimately contribute to fibrogenesis [44]. TGF-β has been shown to drive fibroblast-to-myofibroblast differentiation and directly promote pulmonary fibrosis in a mouse model of IPF [45]. Although TGF-β1 causes tissue fibrosis mainly by stimulating its downstream Smad signal transduction pathway, it is also known to activate Smad-independent signaling pathways, including MAPKs, focal adhesion kinase, and PI3K-Akt cascades in the pathogenesis of pulmonary fibrosis [46-48]. Both pharmacological and genetic inhibition of PI3K reduced pulmonary fibrosis in experimental rodent models, whereas overexpression of PI3K was observed in lung tissues from patients with IPF. A phase 1 clinical trial with a pharmacological inhibitor of PI3K is being conducted in healthy male and female subjects (NCT03502902).

Drug development has been challenged by the problem of identifying selective pharmacological inhibitors of the TGF-β1 signaling pathway that function by inactivating either the ligand or receptor of TGF-β1. Since TGF-β family members are secreted in the form of inactive complexes with latency-associated peptide (LAP), which binds to integrin αVβ6, inhibition of the binding between αVβ6 and the LAP region of TGF-β1 has been considered as a potential strategy for drug development in IPF [49]. A couple of phase 2 clinical trials of an immunoglobulin G monoclonal antibody and a small-molecule inhibitor of integrin αVβ6 are being conducted in patients with IPF (NCT01371305 and NCT04396756). In addition, an inhalation formulation of a nucleic acid medicine that selectively suppresses the expression of TGF-β1 has been tested in a phase 1 clinical trial in patients with IPF (NCT03727802). In contrast to those of TGF-β ligand inhibition, there are no active clinical trials of direct inhibitors of TGF-β1 receptor in patients with IPF. There is, however, an ongoing phase 2 clinical trial of a galectin-3 inhibitor that indirectly suppresses TGF-β signaling via reduced cell surface expression of TGF-β receptors (NCT03832946) [50].

CTGF, also known as cellular communication network factor 2, is a multifunctional growth factor that has been implicated in cell migration, proliferation, differentiation, and angiogenesis [51-54]. Since CTGF is an immediate early gene induced by TGF-β, PDGF, FGF-2, VEGF, and hypoxia, CTGF could regulate ECM deposition, tissue remodeling, and neovascularization, leading to the development of tissue fibrosis [55-58]. CTGF binds to integrin receptor α5β1 and induces the transactivation of FGFR2, PDGFR, and TGF-β receptor [59]. The fact that CTGF was elevated in lung fibrosis model and also in patients with IPF suggests its potential role in the treatment of IPF [60]. The neutralizing monoclonal antibody for CTGF has been shown to reduce lung fibrosis in experimental models [61,62]. A phase 3 clinical trial of a monoclonal antibody for CTGF is progressing in patients with IPF (NCT03955146).

2. Intracellular kinases

Intracellular kinases are attractive targets for the treatment of IPF. There are a couple of clinical trials of inhibitors of the Rho-associated coiled-coil kinase (ROCK) and JNK (Table 1). The regulation of the actin cytoskeleton is a major feature of chronic fibrotic diseases implicating the wound healing process against tissue injury [63,64]. The ROCK family of serine/threonine kinases are key

Table 1. Featured clinical trials targeting kinases in patients with idiopathic pulmonary fibrosis

Target molecule	Compound (type)	Mode of action	NCT ID (phase)
Multiple receptor kinases	Nintedanib[a] (small-molecule)	Inhibit receptor kinases including PDGFR, FGFR, and VEGFR	Completed
TGF-β	BG00011 (IgG antibody)	Inhibit the activation of latent TGF-β via targeting integrin αVβ6	NCT01371305 (2)
TGF-β	PLN-74809 (small-molecule)	Inhibit the activation of latent TGF-β via targeting αVβ1 and αVβ6	NCT04396756 (2)
TGF-β	TRK-250 (nucleic acid)	Interfere the expression of TGF-β mRNA	NCT03727802 (1)
TGF-β receptor	TD139 (small-molecule)	Suppress the expression of TGFR via targeting galectin-3	NCT03832946 (2)
CTGF	Pamrevlumab (IgG antibody)	Interfere CTGF bioavailability and subsequent receptor signaling	NCT03955146 (3)
ROCK	KD025 (small-molecule)	Inhibit ROCK	NCT02688647 (2)
JNK	CC-90001 (small-molecule)	Inhibit JNK	NCT03142191 (2)

NCT ID, national clinical trial identifier number from ClinicalTrials.gov; PDGFR, platelet-derived growth factor receptor; FGFR, fibroblast growth factor receptor; VEGFR, vascular endothelial growth factor receptor; TGF-β, transforming growth factor beta; mRNA, messenger RNA; TGFR, transforming growth factor receptor; CTGF, connective tissue growth factor; IgG, immunoglobulin G; ROCK, Rho-associated coiled-coil protein kinase; JNK, *c-jun* N-terminal kinase.
[a]U.S. Food and Drug Administration approved.

regulators of profibrotic processes and reasonable targets for a new therapeutic strategy for pulmonary fibrosis [65]. ROCK activation has been observed both in patients with IPF and in a mouse model of lung fibrosis, and pharmacological inhibition of ROCK protected mice from experimental lung fibrosis [66]. A phase 2 clinical trial of a pharmacological inhibitor of ROCK is ongoing in patients with IPF (NCT02688647) [67].

It has been suggested that JNK activation in multiple cell types involved in lung fibrosis is positively correlated with the degree of fibrosis [68]. JNK1-deficient mice showed improved lung function in experimental models of lung fibrosis [69,70]. In a house dust mite model of lung fibrosis, a pharmacological JNK inhibitor decreased ECM accumulation and fibrosis [71,72]. A phase 2 clinical trial with a small-molecule inhibitor of JNK is being conducted in patients with IPF (NCT03142191).

ERK5 and p90 ribosomal S6 kinase (p90RSK) in the fibrotic response

A multitude of profibrotic mediators, including TGF-β, CTGF, PDGF, and FGF, and their signaling cascades, play an important role in the pathogenesis of fibrotic lung diseases. Collectively these signs of progress imply that kinase can be a good therapeutic target for pulmonary fibrosis. It has been shown that MAPK kinase (MEK) 1/2-ERK1/2-p90RSK inhibition reduces PDGF-AA-induced cellular migration [73]. FGF-2, a potent mitogen for fibroblasts, induces the synthesis of collagen in lung fibroblasts and myofibroblasts. Inhibition of ERK1/2 suppresses FGF-induced DNA synthesis, phosphorylation of ERK1/2, and p90RSK [74]. VEGF also causes rapid activation of Raf-1, MAPK, p90RSK in cardiac myocytes, and fibroblasts [75]. In addition, ERK5 modulates PDGF-induced proliferation and migration of hepatic stellate cells [76]. Many studies have revealed that ERK5 activation is induced by growth factors such as epidermal growth factor (EGF), FGF-2, and VEGF [77]. Thus, it is interesting that ERK5 is a common combined target for the treatment of pulmonary fibrosis through the regulation of growth factor signaling (Fig. 1A).

ERK5 is an atypical member of the MAPK family and plays a critical role in hypertrophic cardiac remodeling via regulating fibrotic genes and ECM expression [78]. ERK5 is also involved in the enhancement of cell viability and ECM accumulation in chronic glomerulonephritis [79]. Since ERK5 could be activated by various growth factors affecting pulmonary fibrosis, it has been investigated whether ERK5 regulates TGF-β1-induced profibrotic responses and the pathogenesis of pulmonary fibrosis. Kim et al. [80] reported that pharmacological inhibition of MEK5/ERK5 with BIX02189 and depletion of ERK5 using small inter-

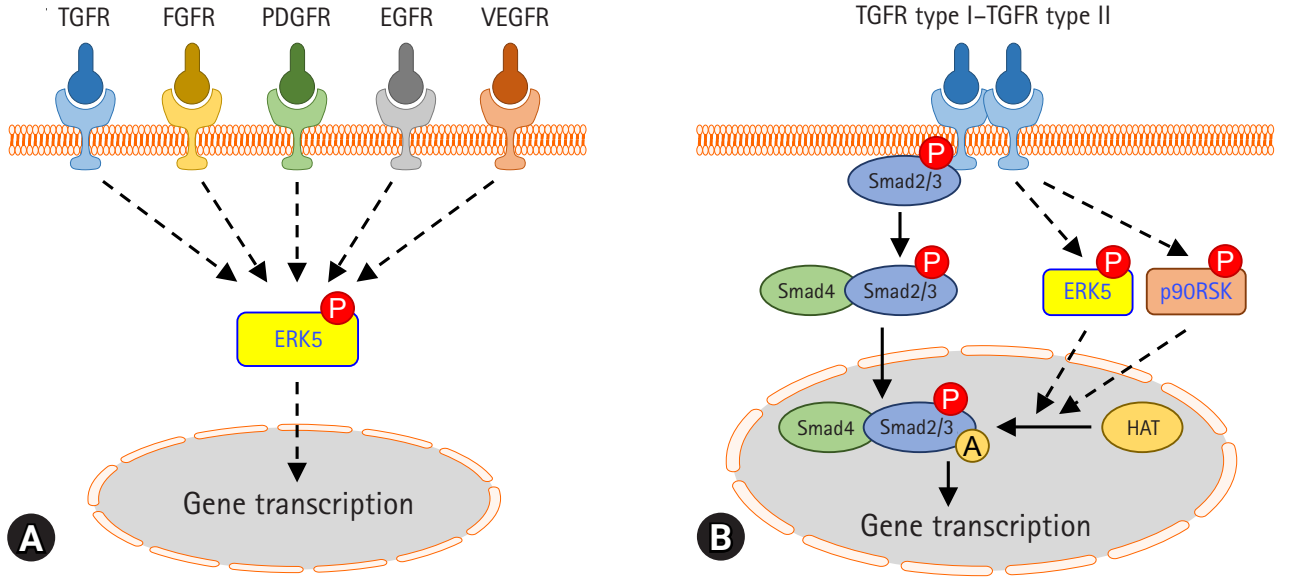


Fig. 1. Roles of extracellular signal-regulated kinase 5 (ERK5) and p90 ribosomal S6 kinase (p90RSK) in pulmonary fibrosis. (A) ERK5 may be activated by multiple receptors involved in pulmonary fibrosis. (B) Transforming growth factor beta (TGF-β) activates ERK5 and p90RSK in lung alveolar epithelial cells and lung fibroblasts. Activation of ERK5 or p90RSK regulates Smad3 transcriptional activity via acetylation modification. The pharmacological inhibitors of ERK5 or p90RSK reduce TGF-β-induced fibrogenic gene expression and experimental lung fibrosis. TGFR, transforming growth factor receptor; FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; EGFR, epidermal growth factor receptor; VEGFR, vascular endothelial growth factor receptor; P, phosphorylation; A, acetylation; HAT, histone acetyltransferase.

https://doi.org/10.12701/yujm.2020.00458

fering RNA against ERK5 inhibited TGF-β1-induced ECM production and Smad3 transcriptional activity, but not Smad3 phosphorylation and nuclear translocation. Notably, it has been shown that ERK5 plays a vital role in TGF-β1-induced fibrogenic signaling via enhancing Smad3 acetylation [80]. Moreover, the pharmacological inhibition of ERK5 ameliorated lung fibrosis and improved survival rate in a mouse model of bleomycin-induced lung fibrosis [80]. This suggests that ERK5 may provide a potential therapeutic strategy to prevent the progression of pulmonary fibrosis (Fig. 1B).

p90RSK is a family of serine/threonine kinases that is activated by the extracellular signal-regulated kinase signaling pathway. p90RSK is involved in numerous signal transduction and regulation of diverse cellular processes, including cell proliferation, growth, apoptosis, and transformation [81]. A recent study proposed that p90RSK is involved in the development and progression of liver fibrosis and hepatocellular injury in chronically damaged livers [82]. In addition, it has been reported that pharmacological inhibition of p90RSK using kaempferol inhibits TGF-β1-induced EMT and migration of A549 lung cancer cells [83]. A recent report showed that pharmacological inhibition of p90RSK by fluoromethyl ketone (FMK) or genetic inhibition of p90RSK significantly inhibited TGF-β1-induced Smad3 transcriptional activity, but not Smad3 phosphorylation and nuclear translocation [84]. In an experimental mouse model of bleomycin-induced lung fibrosis, p90RSK inhibitor FMK reduced pulmonary fibrosis, which suggests that it may be a novel therapeutic target for the treatment of lung fibrosis (Fig. 1B).

Conclusion

Pulmonary fibrosis is a dreadful condition that demands urgent attention. Although TGF-β1 is known to play a critical role in the pathogenesis of pulmonary fibrosis, clinical trials of therapies targeting TGF-β are progressing through repeated failures. According to recent data, kinase inhibitors have been identified as reliable targets for developing therapeutic drugs to treat IPF through regulation of not only TGF-β signaling but also multiple kinase cascades. A couple of receptor kinases are progressing for clinical trials in patients with IPF. In addition to clinical trials, recent preclinical studies with an experimental mouse model of bleomycin-induced lung fibrosis in our group have suggested that pharmacological inhibition of ERK5 or p90RSK could be a potential target of pharmacological treatment of pulmonary fibrosis through inhibition of TGF-β-induced Smad3 transcriptional activation. Further intensive studies using selective kinase inhibitors are needed to develop therapeutic agents that might slow the progression of the disease and improve the prognosis of IPF.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Funding

This study was supported by the Basic Science Research Program (NRF-2018R1A2B6004664 to CHW, NRF-2018R1D-1A1B07048399 to JHL) through the Korean National Research Foundation (NRF) funded by the Ministry of Science, ICT, and Future Planning, and by the Basic Science Research Program through the NRF funded by the Ministry of Education (NRF-2019R1I1A1A01060129 to SK).

Author contributions

Conceptualization, Investigation, Funding acquisition: all authors; Writing-original draft: SK; Writing-review & editing: JHL, CHW.

ORCID

Suji Kim, https://orcid.org/0000-0002-4212-0129
Jae Hyang Lim, https://orcid.org/0000-0003-0972-9271
Chang-Hoon Woo, https://orcid.org/0000-0002-2023-8636

References

1. Bonnans C, Chou J, Werb Z. Remodelling the extracellular matrix in development and disease. Nat Rev Mol Cell Biol 2014;15:786–801.
2. Iredale JP, Thompson A, Henderson NC. Extracellular matrix degradation in liver fibrosis: biochemistry and regulation. Biochim Biophys Acta 2013;1832:876–83.
3. Borthwick LA, Wynn TA, Fisher AJ. Cytokine mediated tissue fibrosis. Biochim Biophys Acta 2013;1832:1049–60.
4. Liu RM, Gaston Pravia KA. Oxidative stress and glutathione in TGF-beta-mediated fibrogenesis. Free Radic Biol Med 2010;48:1–15.
5. Rockey DC, Bell PD, Hill JA. Fibrosis: a common pathway to organ injury and failure. N Engl J Med 2015;372:1138–49.
6. King TE Jr. Clinical advances in the diagnosis and therapy of the interstitial lung diseases. Am J Respir Crit Care Med 2005;172:268–79.
7. Strongman H, Kausar I, Maher TM. Incidence, prevalence, and survival of patients with idiopathic pulmonary fibrosis in the

UK. Adv Ther 2018;35:724–36.
8. Hopkins RB, Burke N, Fell C, Dion G, Kolb M. Epidemiology and survival of idiopathic pulmonary fibrosis from national data in Canada. Eur Respir J 2016;48:187–95.
9. Raghu G. Idiopathic pulmonary fibrosis: lessons from clinical trials over the past 25 years. Eur Respir J 2017;50:1701209.
10. Noble PW, Homer RJ. Idiopathic pulmonary fibrosis: new insights into pathogenesis. Clin Chest Med 2004;25:749–58.
11. Thannickal VJ, Toews GB, White ES, Lynch JP 3rd, Martinez FJ. Mechanisms of pulmonary fibrosis. Annu Rev Med 2004;55:395–417.
12. Saito A, Horie M, Nagase T. TGF-β signaling in lung health and disease. Int J Mol Sci 2018;19:2460.
13. Flanders KC. Smad3 as a mediator of the fibrotic response. Int J Exp Pathol 2004;85:47–64.
14. Nakerakanti S, Trojanowska M. The role of TGF-β receptors in fibrosis. Open Rheumatol J 2012;6:156–62.
15. Gordon KJ, Blobe GC. Role of transforming growth factor-beta superfamily signaling pathways in human disease. Biochim Biophys Acta 2008;1782:197–228.
16. Hoyt DG, Lazo JS. Alterations in pulmonary mRNA encoding procollagens, fibronectin and transforming growth factor-beta precede bleomycin-induced pulmonary fibrosis in mice. J Pharmacol Exp Ther 1988;246:765–71.
17. Broekelmann TJ, Limper AH, Colby TV, McDonald JA. Transforming growth factor beta 1 is present at sites of extracellular matrix gene expression in human pulmonary fibrosis. Proc Natl Acad Sci U S A 1991;88:6642–6.
18. Wu CF, Chiang WC, Lai CF, Chang FC, Chen YT, Chou YH, et al. Transforming growth factor β-1 stimulates profibrotic epithelial signaling to activate pericyte-myofibroblast transition in obstructive kidney fibrosis. Am J Pathol 2013;182:118–31.
19. Border WA, Noble NA, Yamamoto T, Harper JR, Yamaguchi Yu, Pierschbacher MD, et al. Natural inhibitor of transforming growth factor-beta protects against scarring in experimental kidney disease. Nature 1992;360:361–4.
20. Isaka Y, Tsujie M, Ando Y, Nakamura H, Kaneda Y, Imai E, et al. Transforming growth factor-beta 1 antisense oligodeoxynucleotides block interstitial fibrosis in unilateral ureteral obstruction. Kidney Int 2000;58:1885–92.
21. Takabatake Y, Isaka Y, Mizui M, Kawachi H, Shimizu F, Ito T, et al. Exploring RNA interference as a therapeutic strategy for renal disease. Gene Ther 2005;12:965–73.
22. Zhao J, Shi W, Wang YL, Chen H, Bringas P Jr, Datto MB, et al. Smad3 deficiency attenuates bleomycin-induced pulmonary fibrosis in mice. Am J Physiol Lung Cell Mol Physiol 2002;282:L585–93.
23. Zi Z, Chapnick DA, Liu X. Dynamics of TGF-β/Smad signaling. FEBS Lett 2012;586:1921–8.
24. Zhang YE. Non-Smad pathways in TGF-beta signaling. Cell Res 2009;19:128–39.
25. Bringardner BD, Baran CP, Eubank TD, Marsh CB. The role of inflammation in the pathogenesis of idiopathic pulmonary fibrosis. Antioxid Redox Signal 2008;10:287–301.
26. Selman M, Pardo A. Idiopathic pulmonary fibrosis: an epithelial/fibroblastic cross-talk disorder. Respir Res 2002;3:3.
27. Sakai N, Tager AM. Fibrosis of two: epithelial cell-fibroblast interactions in pulmonary fibrosis. Biochim Biophys Acta 2013;1832:911–21.
28. Camelo A, Dunmore R, Sleeman MA, Clarke DL. The epithelium in idiopathic pulmonary fibrosis: breaking the barrier. Front Pharmacol 2014;4:173.
29. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2071–82.
30. Ogura T, Taniguchi H, Azuma A, Inoue Y, Kondoh Y, Hasegawa Y, et al. Safety and pharmacokinetics of nintedanib and pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 2015;45:1382–92.
31. Taniguchi H, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga M, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 2010;35:821–9.
32. Gurujeyalakshmi G, Hollinger MA, Giri SN. Pirfenidone inhibits PDGF isoforms in bleomycin hamster model of lung fibrosis at the translational level. Am J Physiol 1999;276:L311–8.
33. Iyer SN, Gurujeyalakshmi G, Giri SN. Effects of pirfenidone on transforming growth factor-beta gene expression at the transcriptional level in bleomycin hamster model of lung fibrosis. J Pharmacol Exp Ther 1999;291:367–73.
34. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 2011;377:1760–9.
35. Lopez-de la Mora DA, Sanchez-Roque C, Montoya-Buelna M, Sanchez-Enriquez S, Lucano-Landeros S, Macias-Barragan J, et al. Role and new insights of pirfenidone in fibrotic diseases. Int J Med Sci 2015;12:840–7.
36. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2083–92.
37. Jiang C, Huang H, Liu J, Wang Y, Lu Z, Xu Z. Adverse events of pirfenidone for the treatment of pulmonary fibrosis: a meta-analysis of randomized controlled trials. PLoS One 2012;

https://doi.org/10.12701/yujm.2020.00458

7:e47024.
38. Wollin L, Wex E, Pautsch A, Schnapp G, Hostettler KE, Stowasser S, et al. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. Eur Respir J 2015;45:1434–45.
39. Hostettler KE, Zhong J, Papakonstantinou E, Karakiulakis G, Tamm M, Seidel P, et al. Anti-fibrotic effects of nintedanib in lung fibroblasts derived from patients with idiopathic pulmonary fibrosis. Respir Res 2014;15:157.
40. Wollin L, Maillet I, Quesniaux V, Holweg A, Ryffel B. Antifibrotic and anti-inflammatory activity of the tyrosine kinase inhibitor nintedanib in experimental models of lung fibrosis. J Pharmacol Exp Ther 2014;349:209–20.
41. Richeldi L, Cottin V, Flaherty KR, Kolb M, Inoue Y, Raghu G, et al. Design of the INPULSIS™ trials: two phase 3 trials of nintedanib in patients with idiopathic pulmonary fibrosis. Respir Med 2014;108:1023–30.
42. Meng XM, Nikolic-Paterson DJ, Lan HY. TGF-β: the master regulator of fibrosis. Nat Rev Nephrol 2016;12:325–38.
43. Choi ME. Mechanism of transforming growth factor-β1 signaling: role of the mitogen-activated protein kinase. Kidney Int 2000;58(Suppl 77):S53–8.
44. Leask A, Abraham DJ. All in the CCN family: essential matricellular signaling modulators emerge from the bunker. J Cell Sci 2006;119(Pt 23):4803–10.
45. Yue X, Shan B, Lasky JA. TGF-β: titan of lung fibrogenesis. Curr Enzym Inhib 2010;6:10.2174/10067.
46. Varga J, Abraham D. Systemic sclerosis: a prototypic multisystem fibrotic disorder. J Clin Invest 2007;117:557–67.
47. Derynck R, Zhang YE. Smad-dependent and Smad-independent pathways in TGF-beta family signalling. Nature 2003;425:577–84.
48. Das F, Ghosh-Choudhury N, Venkatesan B, Li X, Mahimainathan L, Choudhury GG. Akt kinase targets association of CBP with SMAD 3 to regulate TGFbeta-induced expression of plasminogen activator inhibitor-1. J Cell Physiol 2008;214:513–27.
49. Munger JS, Huang X, Kawakatsu H, Griffiths MJD, Dalton SL, Wu J, et al. The integrin αvβ6 binds and activates latent TGFβ1: a mechanism for regulating pulmonary inflammation and fibrosis. Cell 1999;96:319–28.
50. Mackinnon AC, Gibbons MA, Farnworth SL, Leffler H, Nilsson UJ, Delaine T, et al. Regulation of transforming growth factor-β1-driven lung fibrosis by galectin-3. Am J Respir Crit Care Med 2012;185:537–46.
51. Brigstock DR. The connective tissue growth factor/cysteine-rich 61/nephroblastoma overexpressed (CCN) family. Endocr Rev 1999;20:189–206.
52. Kondo S, Kubota S, Shimo T, Nishida T, Yosimichi G, Eguchi T, et al. Connective tissue growth factor increased by hypoxia may initiate angiogenesis in collaboration with matrix metalloproteinases. Carcinogenesis 2002;23:769–76.
53. Shimo T, Nakanishi T, Nishida T, Asano M, Sasaki A, Kanyama M, et al. Involvement of CTGF, a hypertrophic chondrocyte-specific gene product, in tumor angiogenesis. Oncology 2001;61:315–22.
54. Takigawa M. CTGF/Hcs24 as a multifunctional growth factor for fibroblasts, chondrocytes and vascular endothelial cells. Drug News Perspect 2003;16:11–21.
55. Igarashi A, Okochi H, Bradham DM, Grotendorst GR. Regulation of connective tissue growth factor gene expression in human skin fibroblasts and during wound repair. Mol Biol Cell 1993;4:637–45.
56. Grotendorst GR, Okochi H, Hayashi N. A novel transforming growth factor beta response element controls the expression of the connective tissue growth factor gene. Cell Growth Differ 1996;7:469–80.
57. Shimo T, Kubota S, Kondo S, Nakanishi T, Sasaki A, Mese H, et al. Connective tissue growth factor as a major angiogenic agent that is induced by hypoxia in a human breast cancer cell line. Cancer Lett 2001;174:57–64.
58. Suzuma K, Naruse K, Suzuma I, Takahara N, Ueki K, Aiello LP, et al. Vascular endothelial growth factor induces expression of connective tissue growth factor via KDR, Flt1, and phosphatidylinositol 3-kinase-akt-dependent pathways in retinal vascular cells. J Biol Chem 2000;275:40725–31.
59. Lau LF. Cell surface receptors for CCN proteins. J Cell Commun Signal 2016;10:121–7.
60. Wang Q, Usinger W, Nichols B, Gray J, Xu L, Seeley TW, et al. Cooperative interaction of CTGF and TGF-β in animal models of fibrotic disease. Fibrogenesis Tissue Repair 2011;4:4.
61. Kono M, Nakamura Y, Suda T, Kato M, Kaida Y, Hashimoto D, et al. Plasma CCN2 (connective tissue growth factor; CTGF) is a potential biomarker in idiopathic pulmonary fibrosis (IPF). Clin Chim Acta 2011;412:2211–5.
62. Pan LH, Yamauchi K, Uzuki M, Nakanishi T, Takigawa M, Inoue H, et al. Type II alveolar epithelial cells and interstitial fibroblasts express connective tissue growth factor in IPF. Eur Respir J 2001;17:1220–7.
63. Gabbiani G. Modulation of fibroblastic cytoskeletal features during wound healing and fibrosis. Pathol Res Pract 1994;190:851–3.
64. Sandbo N, Dulin N. Actin cytoskeleton in myofibroblast differentiation: ultrastructure defining form and driving function. Transl Res 2011;158:181–96.
65. Knipe RS, Tager AM, Liao JK. The Rho kinases: critical media-

tors of multiple profibrotic processes and rational targets for new therapies for pulmonary fibrosis. Pharmacol Rev 2015;67:103–17.
66. Zhou Y, Huang X, Hecker L, Kurundkar D, Kurundkar A, Liu H, et al. Inhibition of mechanosensitive signaling in myofibroblasts ameliorates experimental pulmonary fibrosis. J Clin Invest 2013;123:1096–108.
67. Griffith DE, Eagle G, Thomson R, Aksamit TR, Hasegawa N, Morimoto K, et al. Amikacin liposome inhalation suspension for treatment-refractory lung disease caused by Mycobacterium avium complex (CONVERT): a prospective, open- label, randomized study. Am J Respir Crit Care Med 2018;198:1559–69.
68. Yoshida K, Kuwano K, Hagimoto N, Watanabe K, Matsuba T, Fujita M, et al. MAP kinase activation and apoptosis in lung tissues from patients with idiopathic pulmonary fibrosis. J Pathol 2002;198:388–96.
69. Alcorn JF, van der Velden J, Brown AL, McElhinney B, Irvin CG, Janssen-Heininger YM. c-Jun N-terminal kinase 1 is required for the development of pulmonary fibrosis. Am J Respir Cell Mol Biol 2009;40:422–32.
70. Van der Velden JL, Alcorn JF, Chapman DG, Lundblad LK, Irvin CG, Davis RJ, et al. Airway epithelial specific deletion of Jun-N-terminal kinase 1 attenuates pulmonary fibrosis in two independent mouse models. PLoS One 2020;15:e0226904.
71. Bennett B, Blease K, Ye Y, Azaryan A, Ramirez-Valle F, Ceres R, et al. CC-90001, a second generation Jun N-terminal kinase (JNK) inhibitor for the treatment of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2017;195:A5409.
72. Van der Velden JL, Ye Y, Nolin JD, Hoffman SM, Chapman DG, Lahue KG, et al. JNK inhibition reduces lung remodeling and pulmonary fibrotic systemic markers. Clin Transl Med 2016;5:36.
73. Clement DL, Mally S, Stock C, Lethan M, Satir P, Schwab A, et al. PDGFRα signaling in the primary cilium regulates NHE1-dependent fibroblast migration via coordinated differential activity of MEK1/2-ERK1/2-p90RSK and AKT signaling pathways. J Cell Sci 2013;126(Pt 4):953–65.
74. Delehedde M, Seve M, Sergeant N, Wartelle I, Lyon M, Rudland PS, et al. Fibroblast growth factor-2 stimulation of p42/44MAPK phosphorylation and IkappaB degradation is regulated by heparan sulfate/heparin in rat mammary fibroblasts. J Biol Chem 2000;275:33905–10.
75. Seko Y, Takahashi N, Tobe K, Ueki K, Kadowaki T, Yazaki Y. Vascular endothelial growth factor (VEGF) activates Raf-1, mitogen-activated protein (MAP) kinases, and S6 kinase (p90rsk) in cultured rat cardiac myocytes. J Cell Physiol 1998;175:239–46.
76. Rovida E, Navari N, Caligiuri A, Dello Sbarba P, Marra F. ERK5 differentially regulates PDGF-induced proliferation and migration of hepatic stellate cells. J Hepatol 2008;48:107–15.
77. Roberts OL, Holmes K, Muller J, Cross DA, Cross MJ. ERK5 and the regulation of endothelial cell function. Biochem Soc Trans 2009;37(Pt 6):1254–9.
78. Kimura TE, Jin J, Zi M, Prehar S, Liu W, Oceandy D, et al. Targeted deletion of the extracellular signal-regulated protein kinase 5 attenuates hypertrophic response and promotes pressure overload-induced apoptosis in the heart. Circ Res 2010;106:961–70.
79. Urushihara M, Takamatsu M, Shimizu M, Kondo S, Kinoshita Y, Suga K, et al. ERK5 activation enhances mesangial cell viability and collagen matrix accumulation in rat progressive glomerulonephritis. Am J Physiol Renal Physiol 2010;298:F167–76.
80. Kim S, Lim JH, Woo CH. ERK5 inhibition ameliorates pulmonary fibrosis via regulating Smad3 acetylation. Am J Pathol 2013;183:1758–68.
81. Frodin M, Gammeltoft S. Role and regulation of 90 kDa ribosomal S6 kinase (RSK) in signal transduction. Mol Cell Endocrinol 1999;151:65–77.
82. Morales-Ibanez O, Affo S, Rodrigo-Torres D, Blaya D, Millan C, Coll M, et al. Kinase analysis in alcoholic hepatitis identifies p90RSK as a potential mediator of liver fibrogenesis. Gut 2016;65:840–51.
83. Jo E, Park SJ, Choi YS, Jeon WK, Kim BC. Kaempferol suppresses transforming growth factor-β1-induced epithelial-to-mesenchymal transition and migration of A549 lung cancer cells by inhibiting akt1-mediated phosphorylation of Smad3 at threonine-179. Neoplasia 2015;17:525–37.
84. Kim S, Han JH, Kim S, Lee H, Kim JR, Lim JH, et al. p90RSK inhibition ameliorates TGF-β1 signaling and pulmonary fibrosis by inhibiting Smad3 transcriptional activity. Cell Physiol Biochem 2020;54:195–210.

https://doi.org/10.12701/yujm.2020.00458

Yeungnam University Journal of Medicine
YUJM

Review article
eISSN 2384-0293
Yeungnam Univ J Med 2020;37(4):277-285
https://doi.org/10.12701/yujm.2020.00626

Diagnosis and treatment of multidrug-resistant tuberculosis

Jong Geol Jang, Jin Hong Chung

Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea

Received: July 14, 2020
Revised: August 21, 2020
Accepted: August 25, 2020

Corresponding author:
Jin Hong Chung
Department of Internal Medicine, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-640-6682
Fax: +82-53-620-3849
E-mail: jhchn@med.yu.ac.kr

Tuberculosis (TB) is still a major health problem worldwide. Especially, multidrug-resistant TB (MDR-TB), which is defined as TB that shows resistance to both isoniazid and rifampicin, is a barrier in the treatment of TB. Globally, approximately 3.4% of new TB patients and 20% of the patients with a history of previous treatment for TB were diagnosed with MDR-TB. The treatment of MDR-TB requires medications for a long duration (up to 20–24 months) with less effective and toxic second-line drugs and has unfavorable outcomes. However, treatment outcomes are expected to improve due to the introduction of a new agent (bedaquiline), repurposed drugs (linezolid, clofazimine, and cycloserine), and technological advancement in rapid drug sensitivity testing. The World Health Organization (WHO) released a rapid communication in 2018, followed by consolidated guidelines for the treatment of MDR-TB in 2019 based on clinical trials and an individual patient data meta-analysis. In these guidelines, the WHO suggested reclassification of second-line anti-TB drugs and recommended oral treatment regimens that included the new and repurposed agents. The aims of this article are to review the treatment strategies of MDR-TB based on the 2019 WHO guidelines regarding the management of MDR-TB and the diagnostic techniques for detecting resistance, including phenotypic and molecular drug sensitivity tests.

Keywords: Diagnosis; Multidrug-resistant tuberculosis; Treatment

Introduction

Tuberculosis (TB) is the tenth leading cause of death worldwide and a major global health problem [1]. The World Health Organization (WHO) reported that 10.4 million patients developed TB and 1.6 million patients died from TB worldwide in 2017 [2]. Drug resistance is one of the major threats to the treatment of TB. The WHO has defined multidrug-resistant TB (MDR-TB) as TB that shows resistance to isoniazid as well as rifampicin, the most effective anti-TB drugs [3]. In 2018, a total of 186,772 cases were diagnosed with MDR-TB and rifampicin-resistant TB, and 156,071 patients began treatment worldwide [4]. Approximately 3.4% of the new TB patients and 20% of the patients with a history of previous treatment for TB were diagnosed with MDR-TB worldwide [4]. Treatment of MDR-TB lasts for a long duration of approximately 2 years and consists of a combination of multiple second-line drugs, which are more expensive, less effective, and more toxic than the first-line drugs. Therefore, treatment outcomes for MDR-TB are poor, with a success rate of approximately 54% [2]. WHO published new guidelines for MDR-TB treatment in 2019. This article reviews the treatment of MDR-TB according to the most recent updated WHO guidelines and diagnosis of MDR-TB [2].

Definitions of tuberculosis drug resistance

- Mono-resistant TB is defined as TB caused by an isolate that shows resistance to a single first-line anti-TB drug (isoniazid, rifampicin, ethambutol, or pyrazinamide) [5].

- Isoniazid-resistant TB is defined as TB caused by an isolate that shows resistance to isoniazid, but is susceptible to rifampicin.
- Rifampicin-resistant TB is defined as TB caused by an isolate that shows resistance to rifampicin, but is susceptible to isoniazid.
- Poly-resistant TB is defined as TB caused by an isolate that is resistant to more than one anti-TB drug, but not resistant to both isoniazid and rifampicin simultaneously.
- MDR-TB is defined as TB caused by an isolate that shows resistance to at least isoniazid and rifampicin.
- Pre-extensively drug-resistant TB is defined as TB caused by an isolate that shows resistance to isoniazid, rifampicin, and either fluoroquinolones or injectable agents (amikacin, kanamycin, or capreomycin), but not both.
- Extensively drug-resistant TB is a rare type of MDR-TB that is resistant to isoniazid and rifampicin as well as to any fluoroquinolone and at least one out of the three injectable agents (amikacin, kanamycin, or capreomycin). Approximately 9% of the MDR-TB patients have extensively drug-resistant TB.

Mechanism of drug resistance

Drug resistance to *Mycobacterium tuberculosis* (MTB) results from spontaneous and random chromosomal mutations that result in reduced susceptibility to specific agents [6]. The mechanism leading to the development of drug resistance includes activation of the efflux pump at the surface of the bacteria, drug target alteration, production of drug inactivating enzymes, and disruption of drug activation [7]. The incidence of MDR-TB is low, as the rate of mutation is 10^{-5} for isoniazid and 10^{-7} for rifampicin [8]. Drug resistance can occur in two ways (primary or secondary resistance). Primary resistance develops when patients are exposed to and infected with an already drug-resistant strain. Secondary resistance or acquired resistance develops due to poor adherence to medication, drug malabsorption, and inadequate regimen among patients taking TB medication. Although most cases of MDR-TB arise from acquired resistance, a previous study reported that most of the incidences of MDR-TB resulted from transmission rather than acquisition of resistance during treatment in most high-burden settings [9].

Diagnosis of multidrug-resistant tuberculosis

Successful diagnosis and treatment of MDR-TB are based on a rapid and precise drug sensitivity test (DST), which provides evidence for selecting an effective drug [4]. DST is divided into phenotypic tests that observe growth or metabolic inhibition in anti-TB drug-free and drug-containing media and molecular tests that detect genes related to drug resistance [7]. Conventional phenotypic DST is a solid culture-based method that uses egg-based or agar-based media. There are three different methods, namely: the proportion method, the resistance ratio method, and the absolute concentration method [10,11]. The proportion method is the most commonly used method. It is the reference method for phenotypic testing, which provides a measure of the susceptibility of the bacteria to a drug [11,12]. The absolute concentration method is also commonly used due to its technical convenience [7]. These methods are sensitive, have good clinical correlation, and enable the determination of minimal inhibitory concentration. However, it takes a relatively long time as long as 2 to 3 months to confirm the DST results due to the long turnaround time for MTB culture [13]. Liquid culture and DST have a higher rate of MTB isolation and require less time for detection than solid culture and DST. However, it is more expensive and carries a risk of increased bacterial contamination and cross infection by nontuberculous mycobacterial isolation [14]. In order to shorten the turnaround time for mycobacterial culture and DST, a variable rapid culture technique has been developed that usually utilizes liquid media (BACTEC 460, Becton Dickinson, Sparks, MD, USA; Mycobacteria Growth Indicator Tube [MGIT], Becton Dickinson; Septi-Check, Becton Dickinson; Myco-ESP Culture System II, Trek Diagnostic Systems, Westlake, OH, USA; BacT/ALERT MB susceptibility kit, bioMérieux Inc., Durham, NC, USA). This technique can provide DST results within a month [15]. Among the liquid-based culture systems, the most commonly used systems are BACTEC 460 that detects carbon dioxide production and MGIT that detects oxygen consumption [14].

Molecular DSTs have been developed to offer an advantage over conventional phenotypic tests that are more time-consuming. These tests can be used to diagnose TB through amplification of nucleic acids. They detect drug resistance by identifying genetic mutations in specific genes. These genotypic tests are more rapid and accurate than the phenotypic DSTs [16]. Molecular DSTs are divided broadly into two types; probe-based assays and sequence-based assays.

The probe-based DSTs include line probe assays (LPA) and GeneXpert (Cepheid Inc., Sunnyvale, CA, USA). In 2008, WHO approved the use of commercial LPAs (the INNO-LiPA Rif.TB assay [Innogenetics, Ghent, Belgium] and the GenoType MTBDR*plus* version 1 [MTBDRplus; Hain Lifescience GmbH, Nehren, Germany]) for detecting MTB and drug resistance [17]. In 2015, WHO performed a systemic review of the accuracy of commercial LPAs (MTBDR*plus* version 1, version 2, and Nipro NTM+MTBDR [NIPRO Corp., Osaka, Japan]) for detecting MTB

https://doi.org/10.12701/yujm.2020.00626

and resistance to isoniazid and rifampicin, and later in 2016, WHO recommended the use of LPAs in patients with culture-positive (direct testing) or a sputum smear-positive specimens (indirect testing) [18,19]. The MTBDR*plus* is a semi-automated genotypic method that consists of three steps, namely DNA extraction, multiplex polymerase chain reaction (PCR) amplification, and reverse hybridization. This method can detect mutations in the *rpo*B gene for rifampicin resistance and in the *kat*G gene and the *inh*A promoter region for isoniazid resistance [20,21]. Although MTBDR*plus* has shown high accuracy for rifampicin resistance (98.7%), its accuracy for isoniazid is variable and has relatively low sensitivity (84.3%) [22]. Recently, the WHO recommended the GenoType MTBDR*sl* (Hain Lifescience GmbH) that was developed to detect resistance to ethambutol (mutation in *emb*B), fluoroquinolones (mutations in *gyr*A and *gyr*B), and injectable agents (mutation in *rrs*, leading to resistance to kanamycin, amikacin, and capreomycin) [23].

In 2020, the updated WHO guidelines recommended the use of molecular assays (Xpert MTB/RIF and Xpert MTB/RIF [Xpert Ultra]; GeneXpert) as the initial test for the diagnosis of pulmonary and extrapulmonary TB and rifampicin resistance in adults and children [19,24]. The Xpert MTB/RIF is a fully automated real-time PCR based molecular assay for detecting MTB and resistance to rifampicin [25], which provides results within 2 hours. In a large clinical trial, the Xpert MTB/RIF showed an MTB detection accuracy of 98.2% in smear-positive and culture-positive patients, but the accuracy was 72.5% in smear-negative and culture-positive patients. The specificity of the Xpert MTB/RIF was 99.2%. In the same study, the Xpert MTB/RIF showed 97.6% sensitivity for detecting rifampicin resistance [22]. The WHO also recommends Xpert MTB/RIF for the diagnosis of extrapulmonary TB (e.g., tuberculous lymphadenitis and tuberculous meningitis) based on a systematic review [26]. The Xpert Ultra was developed to improve the sensitivity of TB diagnosis (especially in smear-negative, human immunodeficiency virus [HIV]-infected patients and in case of extrapulmonary TB such as tuberculous meningitis and tuberculous lymphadenitis) and rifampicin resistance identification. For TB detection, the sensitivity of Xpert Ultra was higher than that of Xpert in smear-negative patients and in patients with HIV, but the specificity was lower than that of Xpert in all patients [27]. A recent study reported that Xpert Ultra was not superior to Xpert in diagnosing tuberculous meningitis [26]. Further evaluation of the diagnostic accuracy of Xpert Ultra is required. To date, there have been no fully automated molecular assays that can detect resistance to second-line agents. In Korea, rapid DST using LPA and Xpert can be used.

Probe-based DSTs are not able to detect resistance profiles when mutations occur outside the target genetic region [28]. Next-generation sequencing (NGS) is a technique that can compensate for this weakness. NGS provides rapid and detailed sequence information of a part of the genome (targeted NGS) or the whole genome (whole genome sequencing). It can identify genotypes that predict drug-resistant phenotypes. It can also provide genetic information that can detect transmission in potential outbreak situation [29]. This technique can provide drug susceptibility profiles not only for the first-line drugs but also for many second-line drugs [30]. Whole genome sequencing was well correlated with phenotypic DST as well as with culture conversion rate and treatment outcome [31]. However, NGS has several disadvantages, such as poor sensitivity while using sputum rather than culture isolate as a specimen and the need for specialized staff [32].

Treatment of multidrug-resistant tuberculosis

The goal of treatment for MDR-TB is to cure the individual patient and to avoid the transmission of MDR-TB to other people. The WHO developed guidelines for the programmatic management of drug-resistant TB in 2006 and updated these guidelines in 2011. These updated guidelines recommend the use of rapid diagnosis of rifampicin resistance and a combination of four effective drugs, including pyrazinamide, an injectable agent, and a later generation fluoroquinolone for the treatment of patients with MDR-TB [33]. In the updated guidelines of 2016, the WHO suggested MDR-TB regimens with at least five effective TB drugs, including pyrazinamide and four second-line TB drugs [5]. Drugs to be included in the regimen are fluoroquinolone, an injectable agent, ethionamide or prothionamide, pyrazinamide, and either cycloserine or *para*-aminosalicylic acid (Table 1). Rapid DST for isoniazid and rifampicin or rifampicin alone is recommended. The WHO released a rapid communication in 2018 [34] and updated the consolidated guidelines in 2019 [2]. These guidelines include a new drug classification, guidelines for building regimens, enhanced monitoring strategies, and a feasible implementation plan based on clinical trials and individual patient data meta-analysis (IPD-MA) [2,35,36]. A recent IPD-MA including 12,030 patients from 25 countries involved analysis of anti-MDR-TB drugs associated with favorable outcomes. Treatment success was positively associated with the use of linezolid, levofloxacin, carbapenems, moxifloxacin, bedaquiline, and clofazimine. Reduced mortality was significantly associated with the use of linezolid, levofloxacin, moxifloxacin, and bedaquiline.

Streptomycin and amikacin provided modest benefits when compared with regimens without injectable agents [35]. Accord-

Table 1. Classification of medication for multidrug-resistant tuberculosis in 2016

Group	Classification	Medicine
A	Fluoroquinolones	Levofloxacin
		Moxifloxacin
		Gatifloxacin
B	Second-line injectable agents	Amikacin
		Capreomycin
		Kanamycin
		Streptomycin
C	Other core second-line agents	Ethionamide or prothionamide
		Cycloserine or terizidone
		Linezolid
		Clofazimine
D	Add-on agents	
D1		Pyrazinamide
		Ethabutol
		High-dose isoniazid
D2		Bedaquiline
		Delamanid
D3		*Para*-aminosalicylic acid
		Imipenem/cilastatin
		Meropenem
		Amoxicillin/clavulanate

Modified from World Health Organization treatment guidelines for drug-resistant tuberculosis [5].

Table 2. Classification of medication for multidrug-resistant tuberculosis in 2019

Group	Medicine	Step
A	Levofloxacin or moxifloxacin	Include all three medicines (unless they cannot be used)
	Bedaquiline	
	Linezolid	
B	Clofazimine	Add one or both medicines (unless they cannot be used)
	Cycloserine or terizidone	
C	Ethambutol	Add to complete a four- to five drug regimen when medicines from groups A and B cannot be used
	Delamanid	
	Pyrazinamide	
	Imipenem-cilastatin or meropenem	
	Amikacin or streptomycin	
	Ethionamide or prothionamide	
	Para-aminosalicylic acid	

Modified from World Health Organization consolidated guidelines on drug-resistant tuberculosis treatment [2].

ing to the results of this IPD-MA, the updated guidelines have developed a new drug classification that divided drugs for MDR-TB into three groups (A, B, and C) after prioritizing their effectiveness and toxicities (Table 2). Oral regimens are preferred for almost all patients. Fluoroquinolones (levofloxacin or moxifloxacin), bedaquiline, and linezolid are strongly recommended for a longer MDR-TB regimen. These three drugs should be included in the initial therapy unless there is an evidence of drug resistance or a risk of toxicity. In IPD-MA, when compared with injectable-free regimen, regimen including streptomycin or amikacin was associated with increased treatment success, while regimen including kanamycin or capreomycin showed poorer outcomes. Kanamycin treatment was associated with lower treatment success, and capreomycin was associated with lower success and higher mortality [35]. Injectable agents have critical toxicities (including hearing loss and nephrotoxicity) and poor adherence to drug. Considering the benefits and harms of injectable agents, they are not recommended in the initial MDR-TB regimen and have been downgraded to group C [35]. WHO recommended that amikacin and streptomycin be considered only when the patient's isolate is susceptible to these drugs and high-quality monitoring of hearing loss is possible. However, the poorer outcomes of injectable agents could be attributed to several confounding factors, such as drug changes during the treatment, misclassification of treatment outcomes, and their selective use in severe clinical cases [35]. Although Korean guidelines also excluded kanamycin in classification of MDR-TB drug, they recommended that kanamycin can be used as a substitute for amikacin until additional data are available [37].

1. Classification of drugs

In 2018, the WHO rapid communication classified the drugs for the longer MDR-TB regimen into three groups (Table 2) [34]. Agents in group A include fluoroquinolones, bedaquiline, and linezolid, which are highly effective and strongly recommended in the MDR-TB regimen unless contraindicated. Clofazimine and either cycloserine or terizidone are included in group B. These drugs are conditionally recommended as the second choice. Group C drugs can be used when an adequate regimen cannot be formulated with agents from group A or group B. Agents in group C are ranked by the balance of benefits to toxicities. It includes all other drugs except high-dose isoniazid, amoxicillin-clavulanate, kanamycin, and capreomycin.

Fluoroquinolones are effective against growing as well as non-growing tuberculous bacilli and are well tolerated over the long treatment period. Fluoroquinolones inhibit DNA transcription and bacterial replication of MTB by interfering with DNA gyrase, which is a tetramer composed of two α and two β subunits encoded by *gyr*A and *gyr*B genes [38]. Fluoroquinolone resistance in MTB is usually caused by mutations in the *gyr*A gene [39]. Fluoroquinolones have become a mainstay of regimens used to treat MDR-TB, as their mechanism of action is distinct from both isoniazid and rifampicin [40].

https://doi.org/10.12701/yujm.2020.00626

Levofloxacin and moxifloxacin are the two most frequently recommended agents, and the WHO has recommended the use of these drugs for the treatment of MDR-TB. The optimal dose of levofloxacin is 750 mg once daily and that of moxifloxacin is 400 mg once daily. The study from South Korea reported that levofloxacin and moxifloxacin have similar effectiveness and side effects [41]. Adverse effects of fluoroquinolones include gastrointestinal trouble, problems related to the central nervous system, and QT interval prolongation. However permanent discontinuation of fluoroquinolones due to side effects was uncommon [42].

Linezolid is an oxazolidinone antibiotic that inhibits bacterial protein synthesis by preventing the fusion of 30S and 50S ribosomal subunits [43]. Linezolid was categorized as a "group 5" drug in the 2011 WHO guidelines for drug-resistant TB. Agents in group 5 were not recommended for use as core drugs, as there was insufficient evidence regarding their efficacy and safety [33]. However, the 2016 WHO update reclassified linezolid into group C, which includes other core second-line agents [5]. In 2018, in the rapid communication released by the WHO regarding treatment of MDR-TB, linezolid was further elevated to group A. The effectiveness of linezolid in the treatment of drug-resistant TB has been confirmed in clinical trial and meta-analysis [35,43]. The optimal duration of linezolid use has not been established, but its long-term administration (at least 6 months) was associated with treatment success [34]. Concerns have been raised about safety and toxicity of linezolid. Critical adverse effects of linezolid include peripheral neuropathy, myelosuppression with consequent anemia and thrombocytopenia, and optic neuropathy leading to disability and blindness [44]. In a recent IPD-MA, the incidence of permanent discontinuation due to adverse effects of linezolid was 16.3% [44]. The optimal dose of linezolid is unclear. A variety of dosing strategies have been used for drug-resistant TB, which range from 300 to 1,200 mg daily, with once-daily or twice-daily administration [45,46]. The 600-mg daily dose was reported to be safer than the 1,200-mg dose without lowering its effectiveness [46]. The WHO also recommends a daily dose of 600 mg. Although some studies report that a daily dose of 300 mg is effective and reduces toxicities [45], it is associated with a risk for development of drug resistance. Moreover, there is no sufficient evidence for initiating treatment with a 300-mg daily dose.

Bedaquiline is a diarylquinoline compound that specifically inhibits the adenosine triphosphate synthase by blocking the flow of mycobacterial proton pump [47]. Bedaquiline has a concentration-dependent bactericidal effect by causing cell death in both replicating and non-replicating mycobacteria [48]. The standard regimens including bedaquiline showed a reduction in time to culture conversion and a higher cure rate at 120 weeks when compared with a placebo [49,50]. Common adverse events include QT prolongation, nausea/vomiting, and arthralgia/myalgia. Severe adverse events were reported in 2.8% of the patients [44]. Bedaquiline is well absorbed, and its absorption increases with food. According to the clinical data for safety, tolerability, and efficacy, the U.S. Food and Drug Administration approved the dose of 400 mg daily for 14 days followed by 200 mg three times weekly for 22 weeks [51].

Delamanid is a new anti-TB agent derived from the nitro-dihydro-imidazooxazole class of compounds that inhibits mycolic acid synthesis of bacterial cell wall. It has shown potent *in vitro* and *in vivo* activity against both drug-susceptible and drug-resistant strains of MTB in early clinical development [52,53]. Due to the lack of data in the 2018 IPD-MA, delamanid was classified in group C, and WHO recommended conditionally that delamanid may be included in the treatment of patients with MDR-TB aged 3 years or more on the longer regimen [2,35]. However, several studies reported that delamanid-containing regimen was as effective and safe as bedaquiline [54-56]. Thus, Korean guidelines classified delamanid in group C2, and recommend that delamanid can be used as a substitute for bedaquiline (Table 3) [37].

2. Building of regimen

This review will focus on building of longer MDR-TB regimens according to the WHO guidelines [2], since the shorter MDR-TB regimens are fixed. The regimens should include all three drugs from group A and at least one drug from group B. Thus, the regimens should include at least four effective drugs (ideally five

Table 3. Classification of medication for multidrug-resistant tuberculosis in updated Korean guidelines

Group	Medicine
A	Levofloxacin or moxifloxacin
	Bedaquiline
	Linezolid
B	Clofazimine
	Cycloserine
C	
C1[a]	Amikacin (streptomycin)[b]
	Ethambutol
	Imipenem or meropenem
	Para-aminosalicylic acid
	Prothionamide
	Pyrazinamide
C2	Delamanid[c]

Modified from Korean guidelines for tuberculosis, 4th ed. [37].
[a]The order of drug in group C1 does not mean the ranking of drug selection. [b]Amikacin is preferred over streptomycin. Kanamycin can be used as a substitute for amikacin. [c]Delamanid can be used as a substitute for bedaquiline.

drugs) at the initiation of the treatment. If regimens cannot be built based on the optimal regimen involving drugs from groups A and B due to drug resistance and toxicity, drugs from group C can be used. If the regimen cannot include all three agents from group A, initial treatment should be started with five agents, including all available agents in groups A and B. Injectable agents (amikacin or streptomycin), delamanid, pyrazinamide, or ethambutol can be chosen preferably. Susceptibility testing for fluoroquinolones should be performed prior to initiating MDR-TB treatment. Among the group A agents, fluoroquinolones have a high rate of resistance (up to 33%) [57], and it is the only drug class for which rapid molecular tests are available. Resistance to fluoroquinolones was associated with poor outcomes (failure of treatment or relapse) in MDR-TB treatment [58]. Delamanid and second-line injectable drugs could be useful alternatives in fluoroquinolone-resistant MDR-TB. The possibility of treatment success in MDR-TB depends on patient factors (HIV infection, diabetes mellitus, low weight, large disease burden on chest radiography, genetic factors, and alcohol abuse), mycobacterial factors (resistance patterns, mycobacterial load), and optimal management (building of effective regimen and management of adverse effects and toxicities) [2,35]. American Thoracic Society, Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America (ATS/CDC/ERS/IDSA) published new guidelines for the treatment of drug-resistant-TB (including MDR-TB and isoniazid-resistant TB) in 2019. The WHO and ATS/CDC/ERS/IDSA guidelines were largely consistent, but there were some differences between two guidelines. ATS/CDC/ERS/IDSA recommended larger number of drugs in building regimen and focused less on shorter regimen and injectable agents. ATS/CDC/ERS/IDSA guidelines recommended that the regimens should include at least five drugs at the initiation of the treatment and four drugs in the continuation phase [42]. These guidelines recommended six steps for building regimen: step 1, choose later generation of fluoroquinolone (levofloxacin or moxifloxacin); step 2, choose both of the prioritized drugs (bedaquiline and linezolid); step 3, choose both of the two effective drugs (clofazimine and cycloserine); step 4, if a regimen cannot be built with five effective oral drugs, and the isolate is susceptible, use one of injectables (amikacin or streptomycin); step 5, if needed or if oral agents are preferred over injectable agents in step 4, injectables can be replaced by delamanid, pyrazinamide, or ethambutol; and step 6, if the options are limited, and a regimen of five effective drugs cannot be assembled, consider use of ethionamide/prothionamide, imipenem/meropenem plus clavulanate, *para*-aminosalicylic acid, or high-dose isoniazid [42].

3. Duration of treatment

The optimal duration of therapy for MDR-TB is unclear. The WHO recommends two types of standardized MDR-TB treatment regimens (longer and shorter regimens) [2]. They differ in drug combination as well as in duration. Treatment with the longer regimen is suggested for 18 to 20 months (at least 15 to 17 months after culture conversion), and oral regimens are preferred. The intensive phase, which lasts for 6 to 7 months and includes at least four drugs, is recommended until bedaquiline is stopped. The recommended duration of treatment may be modified depending on the culture conversion status and the patient's response to treatment [2]. The continuation phase of the treatment should include at least three drugs [2]. ATS/CDC/ERS/IDSA guidelines recommended the duration of intensive phase to be between 5 and 7 months after culture conversion [42].

The shorter regimen was originally based on the so-called Bangladesh regimen [59]. It was later tested in an international, randomized controlled trial (STREAM stage 1 trial) [60]. The recommended duration of this regimen is 9 to 11 months. The short regimen can be an alternative to the longer regimen in simple MDR-TB cases under specific conditions. This regimen includes an intensive phase lasting 4 to 6 months, which includes seven drugs (kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol). It is followed by a 5-month course with moxifloxacin, clofazimine, pyrazinamide, and ethambutol. Exclusion criteria for the shorter regimen are (1) resistance to or suspected ineffectiveness of a medicine from the shorter regimen (except isoniazid resistance); (2) exposure to one or more second-line medicines from the shorter MDR-TB regimen for greater than 1 month; (3) intolerance to medicines from the shorter MDR-TB regimen or risk of toxicity (e.g., drug-drug interactions); (4) pregnancy; (5) disseminated, meningeal, or central nervous system TB; (6) any extrapulmonary disease in patients with HIV infection; and (7) unavailability of at least one medicine from the shorter MDR-TB regimen. ATS/CDC/ERS/IDSA did not make a recommendation either for or against the standardized short-course regimen [42]. Korean guidelines also did not recommend shorter MDR-TB regimen because of the high incidence of resistance to quinolone, injectable agent, and pyrazinamide, and a lack of evidence on the effectiveness and safety of the shorter regimen when compared with the newly developed longer regimen [37].

Conclusion

MDR-TB remains a major concern in TB control. A rapid diagnosis of drug resistance and optimal treatment with effective and less toxic regimens is important in the management of MDR-TB. Re-

https://doi.org/10.12701/yujm.2020.00626

cently, the WHO published updated guidelines regarding the programmatic management of MDR-TB, which focused on rapid diagnosis and effective treatment via advanced rapid molecular tests and oral regimens with new and repurposed anti-TB drugs. Using these current recommendations might be helpful in the management of MDR-TB. However, well-designed clinical trials and studies for further assessment of new agents and shorter regimens are needed.

Acknowledgments

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Author contributions
Conceptualization, Formal analysis, and Validation: JJG, CJH; Data curation, Methodology, Project administration, Visualization, Investigation, and Resources: JJG; Supervision: CJH; Writing-original draft: JJG, CJH; Writing-review & editing: JJG, CJH.

ORCID
Jong Geol Jang, https://orcid.org/0000-0001-8040-5363
Jin Hong Chung, https://orcid.org/0000-0003-1829-3051

References

1. World Health Organization. Global health estimates 2016: deaths by cause, age, sex, by country and by region, 2000-2016 [Internet]. Geneva: World Health Organization; 2018 [cited 2020 Jul 14]. https://www.who.int/healthinfo/global_burden_disease/estimates/en/.
2. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment [Internet]. Geneva: World Health Organization; 2019 [cited 2020 Jul 14]. https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/.
3. World Health Organization. Global tuberculosis report 2015 [Internet]. 20th ed. Geneva: World Health Organization; 2015 [cited 2020 Jul 14]. https://apps.who.int/iris/handle/10665/191102.
4. World Health Organization. Global tuberculosis report 2019 [Internet]. Geneva: World Health Organization; 2019 [cited 2020 Jul 14]. https://www.who.int/tb/publications/global_report/en/.
5. World Health Organization. Treatment guidelines for drug-resistant tuberculosis, 2016 update [Internet]. Geneva: World Health Organization; 2016 [cited 2020 Jul 14]. https://www.who.int/publications/i/item/9789241549639.
6. David HL. Probability distribution of drug-resistant mutants in unselected populations of Mycobacterium tuberculosis. Appl Microbiol 1970;20:810–4.
7. Kim SJ. Drug-susceptibility testing in tuberculosis: methods and reliability of results. Eur Respir J 2005;25:564–9.
8. Zhang Y, Yew WW. Mechanisms of drug resistance in Mycobacterium tuberculosis: update 2015. Int J Tuberc Lung Dis 2015;19:1276–89.
9. Kendall EA, Fofana MO, Dowdy DW. Burden of transmitted multidrug resistance in epidemics of tuberculosis: a transmission modelling analysis. Lancet Respir Med 2015;3:963–72.
10. Canetti G, Froman S, Grosset J, Hauduroy P, Langerova M, Mahler HT, et al. Mycobacteria: laboratory methods for testing drug sensitivity and resistance. Bull World Health Organ 1963;29:565–78.
11. World Health Oraganization. Guidelines for surveillance of drug resistance in tuberculosis [Internet]. 4th ed. Geneva: World Health Oraganization; 2009 [cited 2020 Jul 14]. https://www.who.int/tb/publications/surveillance_guidelines/en/.
12. CanettI G, Rist N, Grosset J. Measurement of sensitivity of the tuberculous bacillus to antibacillary drugs by the method of proportions. Methodology, resistance criteria, results and interpretation. Rev Tuberc Pneumol (Paris) 1963;27:217–72.
13. Schaberg T, Reichert B, Schülin T, Lode H, Mauch H. Rapid drug susceptibility testing of Mycobacterium tuberculosis using conventional solid media. Eur Respir J 1995;8:1688–93.
14. World Health Organization. Use of liquid TB culture and drug susceptibility testing (DST) in low and medium income setting. Summary report of the Expert Group Meeting on the use of liquid culture media [Internet]. Geneva: World Health Organization; 2007 [cited 2018 Dec 18]. https://www.who.int/tb/laboratory/use_of_liquid_tb_culture_summary_report.pdf?ua=1.
15. Koh WJ, Ko Y, Kim CK, Park KS, Lee NY. Rapid diagnosis of tuberculosis and multidrug resistance using a MGIT 960 system. Ann Lab Med 2012;32:264–9.
16. Coll F, McNerney R, Preston MD, Guerra-Assunção JA, Warry A, Hill-Cawthorne G, et al. Rapid determination of anti-tuberculosis drug resistance from whole-genome sequences. Genome Med 2015;7:51.
17. World Health Organization. Molecular line probe assays for rapid screening of patients at risk of multidrug-resistant tuberculosis (MDR-TB) [Internet]. Geneva: World Health Organization; 2008 [cited 2020 Jul 14]. https://www.who.int/tb/laboratory/line_probe_assays/en/.
18. World Health Organization. The use of molecular line probe as-

says for the detection of resistance to isoniazid and rifampicin [Internet]. Geneva: World Health Organization; 2016 [cited 2020 Jul 14]. https://www.who.int/tb/publications/molecular-test-resistance/en/.
19. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 3: diagnosis–rapid diagnostics for tuberculosis detection [Internet]. Geneva: World Health Organization; 2020 [cited 2020 Jul 14]. https://www.who.int/publications/i/item/who-consolidated-guidelines-on-tuberculosis-module-3-diagnosis---rapid-diagnostics-for-tuberculosis-detection.
20. Hillemann D, Rüsch-Gerdes S, Richter E. Evaluation of the GenoType MTBDRplus assay for rifampin and isoniazid susceptibility testing of Mycobacterium tuberculosis strains and clinical specimens. J Clin Microbiol 2007;45:2635–40.
21. Hain Lifescience GmbH. GenoType MTBDRplus, ver. 2.0. Instructions for use (IFU-304A-06) [Internet]. Nehren: Hain Lifescience GmbH; 2008 [cited 2020 Jul 14]. https://www.hain-lifescience.de/include_datei/kundenmodule/packungsbeilage/download.php?id=936.
22. Ling DI, Zwerling AA, Pai M. GenoType MTBDR assays for the diagnosis of multidrug-resistant tuberculosis: a meta-analysis. Eur Respir J 2008;32:1165–74.
23. Theron G, Peter J, Richardson M, Barnard M, Donegan S, Warren R, et al. The diagnostic accuracy of the GenoType(®) MTBDRsl assay for the detection of resistance to second-line anti-tuberculosis drugs. Cochrane Database Syst Rev 2014;(10):CD010705.
24. World Health Organization. Molecular assays intended as initial tests for the diagnosis of pulmonary and extrapulmonary TB and rifampicin resistance in adults and children: rapid communication [Internet]. Geneva: World Health Organization; 2020 [cited 2020 Jun 5]. https://apps.who.int/iris/handle/10665/330395.
25. El-Hajj HH, Marras SA, Tyagi S, Kramer FR, Alland D. Detection of rifampin resistance in Mycobacterium tuberculosis in a single tube with molecular beacons. J Clin Microbiol 2001;39:4131–7.
26. Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M, Steingart KR. Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. Eur Respir J 2014;44:435–46.
27. Dorman SE, Schumacher SG, Alland D, Nabeta P, Armstrong DT, King B, et al. Xpert MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study. Lancet Infect Dis 2018;18:76–84.
28. Feliciano CS, Namburete EI, Rodrigues Plaça J, Peronni K, Dippenaar A, Warren RM, et al. Accuracy of whole genome sequencing versus phenotypic (MGIT) and commercial molecular tests for detection of drug-resistant Mycobacterium tuberculosis isolated from patients in Brazil and Mozambique. Tuberculosis (Edinb) 2018;110:59–67.
29. Witney AA, Cosgrove CA, Arnold A, Hinds J, Stoker NG, Butcher PD. Clinical use of whole genome sequencing for Mycobacterium tuberculosis. BMC Med 2016;14:46.
30. CRyPTIC Consortium and the 100,000 Genomes Project; Allix-Béguec C, Arandjelovic I, Bi L, Beckert P, Bonnet M, et al. Prediction of susceptibility to first-line tuberculosis drugs by DNA sequencing. N Engl J Med 2018;379:1403–15.
31. Katale BZ, Mbelele PM, Lema NA, Campino S, Mshana SE, Rweyemamu MM, et al. Whole genome sequencing of Mycobacterium tuberculosis isolates and clinical outcomes of patients treated for multidrug-resistant tuberculosis in Tanzania. BMC Genomics 2020;21:174.
32. World Health Organization. The use of next-generation sequencing technologies for the detection of mutations associated with drug resistance in Mycobacterium tuberculosis complex: technical guide [Internet]. Geneva: World Health Organization; 2018 [cited 2020 Jul 14]. https://apps.who.int/iris/handle/10665/274443.
33. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis-2011 update [Internet]. Geneva: World Health Organization; 2011 [cited 2020 Jul 14]. https://apps.who.int/iris/bitstream/handle/10665/44597/9789241501583_eng.pdf?sequence=1.
34. World Health Organization. Rapid communication: key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) [Internet]. Geneva: World Health Organization; 2011 [cited 2020 Jul 14]. https://www.who.int/tb/publications/2018/rapid_communications_MDR/en/.
35. Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017; Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JC, Anderson LF, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018;392:821–34.
36. Bastos ML, Lan Z, Menzies D. An updated systematic review and meta-analysis for treatment of multidrug-resistant tuberculosis. Eur Respir J 2017;49:1600803.
37. Joint Committee for the Revision of Korean Guidelines for Tuberculosis; Korean Centers for Disease Control and Prevention. Korean guidelines for tuberculosis. 4th ed. Cheongju: Korea Centers for Disease Control and Prevention; 2020.

https://doi.org/10.12701/yujm.2020.00626

38. Moadebi S, Harder CK, Fitzgerald MJ, Elwood KR, Marra F. Fluoroquinolones for the treatment of pulmonary tuberculosis. Drugs 2007;67:2077–99.
39. Sirgel FA, Warren RM, Streicher EM, Victor TC, van Helden PD, Böttger EC. gyrA mutations and phenotypic susceptibility levels to ofloxacin and moxifloxacin in clinical isolates of Mycobacterium tuberculosis. J Antimicrob Chemother 2012;67:1088–93.
40. Migliori GB, Langendam MW, D'Ambrosio L, Centis R, Blasi F, Huitric E, et al. Protecting the tuberculosis drug pipeline: stating the case for the rational use of fluoroquinolones. Eur Respir J 2012;40:814–22.
41. Kang YA, Shim TS, Koh WJ, Lee SH, Lee CH, Choi JC, et al. Choice between levofloxacin and moxifloxacin and multidrug-resistant tuberculosis treatment outcomes. Ann Am Thorac Soc 2016;13:364–70.
42. Nahid P, Mase SR, Migliori GB, Sotgiu G, Bothamley GH, Brozek JL, et al. Treatment of drug-resistant tuberculosis. An official ATS/CDC/ERS/IDSA clinical practice guideline. Am J Respir Crit Care Med 2019;200:e93–142.
43. Livermore DM. Linezolid in vitro: mechanism and antibacterial spectrum. J Antimicrob Chemother 2013;51(Suppl 2):ii9–16.
44. Lan Z, Ahmad N, Baghaei P, Barkane L, Benedetti A, Brode SK, et al. Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet Respir Med 2020;8:383–94.
45. Koh WJ, Kang YR, Jeon K, Kwon OJ, Lyu J, Kim WS, et al. Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients. J Antimicrob Chemother 2012;67:1503–7.
46. Sotgiu G, Centis R, D'Ambrosio L, Alffenaar JW, Anger HA, Caminero JA, et al. Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. Eur Respir J 2012;40:1430–42.
47. Koul A, Dendouga N, Vergauwen K, Molenberghs B, Vranckx L, Willebrords R, et al. Diarylquinolines target subunit c of mycobacterial ATP synthase. Nat Chem Biol 2007;3:323–4.
48. Rouan MC, Lounis N, Gevers T, Dillen L, Gilissen R, Raoof A, et al. Pharmacokinetics and pharmacodynamics of TMC207 and its N-desmethyl metabolite in a murine model of tuberculosis. Antimicrob Agents Chemother 2012;56:1444–51.
49. Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med 2014;371:723–32.
50. Diacon AH, Pym A, Grobusch M, Patientia R, Rustomjee R, Page-Shipp L, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med 2009;360:2397–405.
51. Centers for Disease Control and Prevention. Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis. MMWR Recomm Rep 2013;62(RR-09):1–12.
52. Matsumoto M, Hashizume H, Tomishige T, Kawasaki M, Tsubouchi H, Sasaki H, et al. OPC-67683, a nitro-dihydro-imidazooxazole derivative with promising action against tuberculosis in vitro and in mice. PLoS Med 2006;3:e466.
53. Barry PJ, O'Connor TM. Novel agents in the management of Mycobacterium tuberculosis disease. Curr Med Chem 2007;14:2000–8.
54. Kim CT, Kim TO, Shin HJ, Ko YC, Choe YH, Kim HR, et al. Bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis: a multicentre cohort study in Korea. Eur Respir J 2018;51:1702467.
55. Mok J, Kang H, Koh WJ, Jhun BW, Yim JJ, Kwak N, et al. Final treatment outcomes of delamanid-containing regimens in patients with MDR-/XDR-TB in South Korea. Eur Respir J 2019;54:1900811.
56. Ferlazzo G, Mohr E, Laxmeshwar C, Hewison C, Hughes J, Jonckheere S, et al. Early safety and efficacy of the combination of bedaquiline and delamanid for the treatment of patients with drug-resistant tuberculosis in Armenia, India, and South Africa: a retrospective cohort study. Lancet Infect Dis 2018;18:536–44.
57. Lange C, Duarte R, Fréchet-Jachym M, Guenther G, Guglielmetti L, Olaru ID, et al. Limited benefit of the new shorter multidrug-resistant tuberculosis regimen in Europe. Am J Respir Crit Care Med 2016;194:1029–31.
58. Cegielski JP, Kurbatova E, van der Walt M, Brand J, Ershova J, Tupasi T, et al. Multidrug-resistant tuberculosis treatment outcomes in relation to treatment and initial versus acquired second-line drug resistance. Clin Infect Dis 2016;62:418–30.
59. Van Deun A, Maug AK, Salim MA, Das PK, Sarker MR, Daru P, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med 2010;182:684–92.
60. Nunn AJ, Phillips PP, Meredith SK, Chiang CY, Conradie F, Dalai D, et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. N Engl J Med 2019;380:1201–13.

Yeungnam University Journal of Medicine
YUJM

Review article
eISSN 2384-0293
Yeungnam Univ J Med 2020;37(4):286-295
https://doi.org/10.12701/yujm.2020.00633

Novel respiratory infectious diseases in Korea

Hyun Jung Kim

Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Keimyung University Dongsan Hospital, Keimyung University School of Medicine, Daegu, Korea

Received: July 16, 2020
Revised: September 2, 2020
Accepted: September 6, 2020

Corresponding author:
Hyun Jung Kim
Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Keimyung University Dongsan Hospital, Keimyung University School of Medicine, 1095 Dalgubeol-daero, Dalseo-gu, Daegu 42601, Korea
Tel: +82-53-258-4988
Fax: +82-53-258-4990
E-mail: khj82827@kmu.ac.kr

Respiratory infections are very common and highly contagious. Respiratory infectious diseases affect not only the person infected but also the family members and the society. As medical sciences advance, several diseases have been conquered; however, the impact of novel infectious diseases on the society is enormous. As the clinical presentation of respiratory infections is similar regardless of the pathogen, the causative agent is not distinguishable by symptoms alone. Moreover, it is difficult to develop a cure because of the various viral mutations. Various respiratory infectious diseases ranging from influenza, which threaten the health of mankind globally, to the coronavirus disease 2019, which resulted in a pandemic, exist. Contrary to human expectations that development in health care and improvement in hygiene will conquer infectious diseases, humankind's health and social systems are threatened by novel infectious diseases. Owing to the development of transport and trading activity, the rate of spread of new infectious diseases is increasing. As respiratory infections can threaten the members of the global community at any time, investigations on preventing the transmission of these diseases as well as development of effective antivirals and vaccines are of utmost importance and require a worldwide effort.

Keywords: Coronavirus infections; COVID-19; Human influenza; Middle East respiratory syndrome; SARS virus; Severe acute respiratory syndrome coronavirus 2

Introduction

As medical sciences advanced and sanitation improved, infectious diseases were perceived to occur in underdeveloped countries. However, an increase in the number of travelers and increased trading activity led to the influx of foreign infectious diseases and novel infectious diseases caused by varying strains. Respiratory viral infections are very common and highly contagious and can lead to big trends in a short time. As respiratory viral infections present similar signs and symptoms, the causative agent cannot be distinguished by clinical manifestations alone. Therefore, early diagnoses and proper establishment of infection control strategies are important. Respiratory infectious diseases affect not only an individual's health but also limit travel, paralyze the medical system, and affect the socialization and daily life of the affected patients and medical staff, thus hampering the social system.

Influenza, historically referred to as the Spanish flu, had infected 500 million people of the 1.6 billion people worldwide and 50 million people died. The mortality rate was approximately 10%, and 3% of the world's population had succumbed to this disease [1]. From Spanish flu to severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) to coronavirus disease 2019 (COVID-19), which is currently a major problem globally, respiratory infections have had a huge impact on human health and healthcare systems; thus, a worldwide effort is required to combat this conundrum [2]. To implement future measures, we would like to summarize the respiratory infectious diseases that have recently affected human health and the society. Here, we review the current state of epidemiology, clinical manifestations, diagnosis, treatment, and prevention of novel respiratory infectious diseases.

Influenza

1. Introduction and epidemiology

Globally, influenza is an important infectious disease, causing big and small epidemics annually [3]. Approximately 20% of the children and 5% of the adults suffer from influenza A or B worldwide each year [4]. The largest influenza pandemic was in 1918, when influenza A (H1N1), known as the "Spanish flu," resulted in 20 million deaths worldwide. Thereafter, there have been two major global outbreaks of influenza A: in 1957, influenza A (H2N2), namely, "Asian" influenza; and in 1967, influenza A (H3N2), namely, "Hong Kong" influenza [5]. The first case of swine-origin influenza A (H1N1) infection was reported in Mexico and the United States in April 2009, after which the novel influenza (H1N1) virus spread globally [6,7]. It mainly affected children and young adults and had no significant impact on the elderly. A similar pattern was also observed in Korea. The influenza A (H3N2) virus had the largest contribution to influenza-associated mortality in all age groups from 2009 to 2016; however, influenza A (H1N1) virus-associated influenza or pneumonia deaths were more common in those under 65 years old [8]. This is thought to be due to the cross-reactive effect of antibodies from past immunizations or infections to novel influenza A (H1N1) infections [6].

2. Clinical manifestation and transmission

Three mechanisms of person-to-person transmission have been identified, namely, small-particle aerosols, large droplets, and contact transmission [9]. The basic reproduction number (the mean number of secondary cases of infection transmitted by a single primary case in a susceptible population) is estimated to be approximately 1.3 to 1.7 but may rise up to 3.6 in crowded areas such as schools [7]. The clinical presentation of influenza ranges from afebrile upper respiratory illness to acute respiratory distress syndrome (ARDS) requiring mechanical ventilator support. Common symptoms of influenza include fever, chills, myalgia, cough, headache, etc. In 2009, a characteristic of the influenza H1N1 pandemic was to present as diffuse viral pneumonia associated with severe hypoxemia, ARDS, and shock in young adults. This phenomenon led to the promulgation of extracorporeal membrane oxygenation (ECMO) for ARDS treatment worldwide [10,11]. In Korea, mortality in intensive care units varied widely among hospitals, with the need for specialists of intensive care thus emerging [12].

3. Diagnosis

To confirm an influenza infection, real-time polymerase chain reaction (RT-PCR) or a viral culture is performed. As it takes about 3 days to culture the virus using rapid cell culture, RT-PCR with an upper airway specimen taking less than a day is widely used in clinical practice [13]. Detection using rapid antigen testing is fast; however, its sensitivity for H1N1 is low at 9.6% to 51% [14].

4. Treatment

Influenza is usually a self-limiting disease in a healthy person. Thus, while only supportive care is needed for healthy people, antiviral treatment is considered for high-risk patients including persons of any age hospitalized with influenza, children aged <2 years and adults aged ≥ 65 years, outpatients at a high risk of complications from influenza, pregnant women and those within 2 weeks postpartum, etc. [15].

1) Neuraminidase inhibitors (oseltamivir and zanamivir)

Antiviral treatment using neuraminidase inhibitors is recommended mainly for patients hospitalized with influenza H1N1 or for high-risk patients who are likely to develop complications from the seasonal influenza. It has been recognized as a prophylactic for influenza A and B in patients aged >13 years [9].

2) Baloxavir marboxil

Baloxavir marboxil (trade name Xofluza; Genentech Inc., San Francisco, CA, USA) is a selective inhibitor of the cap-dependent endonuclease. A significant reduction in viral load was observed a day after taking the drug compared with placebo or oseltamivir administration [16]. In addition, a single oral dose of baloxavir marboxil had a similar effect as oseltamivir in relieving influenza symptoms in high-risk outpatients and children [17,18].

5. Prevention

Vaccination is the most effective way of preventing influenza and controlling the disease [19]. Oseltamivir, zanamivir, and baloxavir showed a high efficacy for postexposure prophylaxis in their contacts [20-22]. Influenza vaccinations are updated annually based on the annual surveillance data World Health Organization (WHO) to predict the influenza strain that will be prevalent next year [9]. The effect of vaccination is maximized in high-risk groups such as young children, immunocompromised patients, and adults aged 65 years and older [23]. Compliance with contact precaution and isolation guidelines is required to prevent person-to-person spread.

Severe acute respiratory syndrome

1. Introduction and epidemiology

SARS, a new coronavirus that causes severe viral pneumonia, was

first reported in November 2002, in Guangdong, a province in southern China [24,25]. This new coronavirus variant was termed SARS coronavirus (SARS-CoV) [25,26]. The intermediate host of SARS-CoV was found to be a masked palm civet cat [27]. Researchers have found a virus genetically similar to this strain of coronavirus in masked palm civets sold in the animal market of Guangdong Province. Numerous studies have shown large number of SARS-related coronaviruses circulating in China's horseshoe bats, suggesting that the deadly strain probably originated in bats and, subsequently, transmitted the virus to civets before infecting humans [28]. SARS resulted in 8,273 cases in a year and 774 deaths with a fatality rate of 9.5% in 2002. The national surveillance system for SARS was implemented on March 16, 2003, in Korea, and there were three probable cases of SARS diagnosed with clinical, laboratory, and radiological features. No patient was confirmed serologically in Korea, and all three probable cases were imported and showed improvement after provision of supportive care [29]. Both SARS and MERS are caused by coronaviruses; however, SARS propagated more in humans and had a relatively low mortality rate [30]. SARS appeared in 2002 and disappeared in the summer of 2003.

2. Clinical manifestation and transmission

Most patients (85% to 99%) with SARS initially complained of fever and chills. Other symptoms included nonproductive cough (69%), myalgia (49%), and dyspnea (42%) [31,32]. Initially, chest examination results were usually normal, but as the disease progressed, signs of consolidation, crackles, and dullness were observed [33]. Blood tests showed lymphopenia and elevated transaminase, lactate dehydrogenase, and creatinine kinase levels [34]. The radiographic findings of SARS are similar to pneumonia caused by other causes; they show airspace consolidation, mainly invading the peripheral and lower zone of the lungs. However, cavitation, hilar lymphadenopathy, and pleural effusion are rare [35].

SARS-CoV spreads quickly by close contact through droplet transmission or fomites. The highly infectious nature of the this viral disease is well illustrated by the fact that 158 patients were hospitalized with SARS in 2 weeks owing to their exposure to one patient in a general ward in Hong Kong [36].

3. Diagnosis

As molecular assays currently available for the detection of SARS-CoV have low sensitivity and specificity during the early stages of the illness, additional serological tests indicating a significant increase in specific antibody titers or a positive viral culture is necessary to diagnose SARS [37,38]. This diagnostic process is usually based on the careful review of the clinical manifestations and epidemiological and radiological findings.

4. Treatment

Antiviral treatments such as interferons, ribavirin, and lopinavir/ritonavir have been used in many patients; however, there is no clear conclusion regarding the effectiveness of these treatments [39].

5. Prevention

In the hospitals in Hong Kong, when 254 medical staff members who had contacted 11 index patients were divided into infected and noninfected groups and a survey was conducted about the use of masks, gloves, and gowns and hand washing while caring for the index patients with SARS, the infection rate was high in those who omitted at least one measure. Adopting precautionary measures to prevent droplet and contact transmission is of utmost importance [40].

Middle East respiratory syndrome

1. Introduction and epidemiology

A decade after SARS appeared, a new coronavirus causing severe viral pneumonia was reported in the Arabian Peninsula [41]. The clinical manifestations of MERS, caused by β-coronavirus of the C lineage (MERS-CoV), can range from no symptoms to respiratory failure. During the first outbreak of MERS-CoV in June 2012 in Saudi Arabia, 688 people were confirmed to be infected, with a fatality rate of 35.7%, i.e., 282 deaths in 27 countries [42]. In Korea, the large outbreak of MERS was mainly related to in-hospital infections. A total of 186 patients had been diagnosed with MERS-CoV in Korea, with 36 deaths [43]. MERS has a weaker human-to-human transmission than SARS; however, it has a higher mortality rate. The zoonotic vector and possible reservoir of MERS-CoV have been found to be dromedary camels, with bats as another possible vector for transmission to humans [44].

2. Clinical manifestation and transmission

Approximately 90% of patients with MERS complain of dyspnea, and 83% of patients show the symptom of coughing [45,46]. Fever and upper respiratory symptoms such as cough present first, followed by shortness of breath and lymphopenia 1 week later [46]. Serious complications usually occur in those with comorbidities such as diabetes, renal failure, and underlying immunosuppression. However, in patients without comorbidities, the infection may be asymptomatic or may show mild symptoms.

Imaging findings include nonspecific chest radiographs and ground-glass opacities in early chest tomographic scans followed by interlobular septal and intralobular interstitial thickening with

https://doi.org/10.12701/yujm.2020.00633

peripheral and lower lobe involvement [47,48].

Primary cases were found to show various mild to severe clinical symptoms after direct or indirect patient contact with dromedary camels. Secondary cases were due to human-to-human transmission via close contact and occurred among people with laboratory-confirmed MERS-CoV in household settings [42,49]. Contact and droplet transmission is suggested; however, the possibility of airborne or fomite transmission cannot be ruled out.

3. Diagnosis

MERS-CoV testing is performed by skilled technicians in appropriately equipped biosafety laboratories following the relevant technical and safety procedures [50]. MERS-CoV could be detected in a short time using a reverse transcription loop-mediated isothermal amplification technique and a vertical flow visualization strip assay [51]. Several serological assays, including enzyme-linked immunosorbent assay, recombinant spike immunofluorescent assay, and spike pseudoparticle neutralization and microneutralization assay, are available for the detection of MERS-CoV [52].

4. Treatment

Although the role of antiviral treatment in MERS has not been clearly established, considering the high mortality rate, antiviral treatment could be considered in addition to supportive care in the patients with an older age, underlying diseases, breathing difficulties, and bilateral pneumonia [53]. Empirical treatments with convalescent plasma, interferon with or without ribavirin, and lopinavir/ritonavir have been studied in severely ill patients and are most likely to be beneficial, but evidence is weak and controlled trials are warranted [44,54].

5. Prevention

MERS-CoV transmission in healthcare facilities mainly results from lapses in infection control measures and late isolation of suggested cases. Although currently, no human vaccine is available, the use of personnel protective equipment, early identification and isolation of patients, disinfection of environmental surfaces, and sanitization are required to minimize transmission [55].

Coronavirus disease 2019

1. Introduction and epidemiology

SARS-CoV-2 spread beyond China to the world within a few months. The COVID-19 outbreak that emerged in China in December 2019 spread globally, and in January 2020, the WHO declared that COVID-19 is an important issue threatening human health worldwide. SARS-CoV-2 is closely related to two bat-derived SARS-like (SL) coronaviruses: bat-SL-CoVAC45 and bat-SL-CoVZXC21 [56,57]. Current evidence indicates that SARS-CoV-2 spread to humans via transmission from wild animals illegally sold in Huanan's seafood wholesale market. Phylogenetic analysis shows that SARS-CoV-2 is a new member of the *Coronaviridae* family but is distinct from SARS-CoV (identity of approximately 79%) and MERS-CoV (identity of approximately 50%) [58]. Clinical characteristics comparing SARS, MERS and COVID-19 are seen in Table 1.

As of July 15, 2020, Korea reported a total of 13,551 confirmed cases and 289 deaths. Globally, approximately 13 million confirmed cases and 570,000 death were reported by the WHO [59]. In Korea, sporadic infections continue owing to community spread and globalization.

Table 1. Clinical features of human coronavirus pneumonia

Feature	SARS [24,32,34]	MERS [42,44,49]	COVID-19 [56,57,68]
Year first recognized	2002	2012	2019
Causative virus	SARS-CoV	MERS-CoV	SARS-CoV-2
Intermediate host	Palm civets	Dromedary camels	Pangolins
Nosocomial infection	Yes	Yes	Yes
Healthcare worker infection (%)	21.0	18.6	3.8
Incubation period (day)	2–11	2–13	3–6
Treatment	Supportive care	Supportive care	Supportive care
Vaccination	-	-	-
Total case (global)	8,096	2,229	12,964,809+
Total death (global)	774	791	570,288+
CFR (%)	9.6	34.4	3.5
CFR with comorbidities (%)	46.0	60.0	73.3

SARS, severe acute respiratory syndrome; MERS, Middle East respiratory syndrome; COVID-19, coronavirus disease 2019; CoV, coronavirus; CFR, case-fatality rate.

2. Clinical manifestation and transmission

SARS-CoV-2 is highly contagious; when compared with SARS and MERS, the fatality rate of MERS was higher than that of SARS and COVID-19; however, within a short time, COVID-19 affected a larger number of people worldwide than SARS and MERS [56]. Current evidence suggests that human-to-human transmission of SARS-CoV-2 is via droplets expelled from the infected individual when in close contact while talking, coughing, or sneezing [57]. However, transmission via aerosols outside a laboratory setting has inconclusive evidence [60,61]. One of the biggest hurdles encountered while preventing spread of the disease is that the infection can be spread by asymptomatic as well as presymptomatic carriers [62].

The mean incubation period of the virus is 2 to 14 days, and the basic reproduction number is estimated at 2.24 to 3.58. The major clinical manifestations include cough, fever, chills, dyspnea, myalgia, diarrhea, confusion, and pneumonia. Extrapulmonary symptoms include myocarditis, loss of taste and smell, and venous thrombosis [63-66]. These coronavirus infections cause more severe diseases among older individuals and people with comorbid conditions [67]. In Korea, the mortality rate is 2.36%, wherein it is 1% in individuals aged < 50 years; however, it is higher in older individuals. Therefore, as a higher mortality rate has been reported in individuals aged > 65 years and having underlying diseases, appropriate precautionary measures are warranted [68].

3. Diagnosis

The genomic sequence of SARS-CoV-2 was released immediately on public databases in January 2020 after the start of the outbreak in Wuhan, China [69]. In Korea, infections were confirmed on the basis of a positive result for SARS-CoV-2 viral RNA in an RT-PCR assay or by virus isolation, irrespective of the clinical manifestations [70]. With an exponentially increasing number of patients, drive-through screening centers were introduced in Korea, considering patient and medical staff safety while obtaining samples, which required equipment that could perform large-scale testing in a short duration [71].

4. Treatment

A specific treatment modality has not been developed yet [69]. To date, early detection and quarantine are considered optimum to minimize the spread of the disease. There are several ongoing clinical trials for COVID-19 treatment.

1) Remdesivir

Remdesivir, a nucleotide analog prodrug that inhibits viral RNA polymerase, is administered intravenously. Previously, it has been tested against Ebola virus and two coronaviruses, SARS and MERS [72]. It was first administered to a patient with COVID-19 in the USA [73]. The preliminary data indicated that on comparing 521 patients with placebo and 538 patients with a 10-day remdesivir regimen, the time to recovery was shorter in the remdesivir group (11 days) than in the placebo group (15 days) [74]. For patients with pneumonia and hypoxemia ($SpO_2 \leq 94\%$) caused by SARS-CoV-2, therapeutic effects of the 5-day and 10-day remdesivir regimen were similar [75]. Further, the compassionate use of remdesivir in patients hospitalized for severe COVID-19 showed clinical improvement in 68% of the patients [76]. In Korea, remdesivir permitted to be used for COVID-19 from July 2020. It was administered to 10 patients, including a patient on mechanical ventilation, and all patients showed clinical and laboratory signs of improvement without serious adverse events [77]. Large-scale clinical trials to ensure the safety and effectiveness of remdesivir in the treatment of COVID-19 are warranted [78]. Remdesivir is the most promising COVID-19 treatment candidate so far.

2) Chloroquine/hydroxychloroquine

Chloroquine is used for the treatment of malaria, and it demonstrated potential broad-spectrum antiviral activities by inhibiting endosomal acidification required for virus–host cell fusion [79]. The result of a multinational registry analysis of the use of chloroquine/hydroxychloroquine with or without a macrolide for treatment of COVID-19 showed that chloroquine/hydroxychloroquine was associated with a decreased in-hospital survival and an increased risk of arrhythmia when used for the treatment of COVID-19 [80]. In contrast, studies have shown that early (within 5 days from diagnosis) use of hydroxychloroquine inhibits SARS-CoV-2 shedding [81]. The role of hydroxychloroquine in the treatment and prophylaxis of COVID-19 is inconclusive.

3) Lopinavir/ritonavir

Lopinavir/ritonavir is a combination of human immunodeficiency virus protease inhibitors, with a modest antiviral activity against SARS-CoV-2 and nucleoside analogs, which increase drug bioavailability. Some studies have reported lopinavir/ritonavir to be a more effective agent for rapid viral clearance than hydroxychloroquine in mild to moderate cases of COVID-19 [82-84]. In contrast, some studies have reported that lopinavir/ritonavir did not shorten the duration of SARS-CoV-2 shedding in the patients with COVID-19 and a meta-analysis concluded that treatment with lopinavir/ritonavir had no significant benefits in reducing mortality and ARDS rates in patients with COVID-19 [85,86]. To date, available evidence regarding the efficacy of lopinavir/ritonavir in COVID-19 is weak. Since there is a lack of approved treatments for

https://doi.org/10.12701/yujm.2020.00633

COVID-19, clinicians should not abandon the use of lopinavir/ritonavir as the results or ongoing clinical trials are pending.

4) Convalescent plasma

Convalescent plasma has been used in patients with SARS whose conditions continued to deteriorate, and several studies reported a shorter hospital stay and lower mortality in patients treated with convalescent plasma than in those not treated with convalescent plasma [87-89]. There are several cases reported about critically ill patients who received convalescent plasma and recovered from SARS-CoV-2 infections [90,91]. These results indicate that convalescent plasma might serve as a potential therapeutic for critically ill patients infected with SARS-CoV-2.

5) Miscellaneous

In subgroups of patients with severe COVID-19 with a possible cytokine storm syndrome, some immunomodulating treatments including steroids, intravenous immunoglobulins, interleukin (IL)-1 blockers, and IL-6 receptor blockers are likely to be beneficial [92,93]. Anakinra (human IL-1 receptor antagonist) reduced the need for invasive mechanical ventilation and mortality among patients with severe forms of COVID-19 without serious side effects through randomized clinical trials [94].

5. Prevention

Vaccines are the most effective way to deal with infectious diseases. Three types of human coronaviruses (SARS-CoV, MERS-CoV, and SARS-CoV-2) have emerged over the past two decades, threatening the health of humankind; however, vaccinations against them are yet to be developed [2]. Several scientists and drug manufacturers worldwide are accelerating the development of COVID-19 vaccines [95,96]. Approximately 120 candidate molecules are under development for the vaccine, and several candidate SARS-CoV-2 vaccines are in phase 1 to 3 clinical trials. To date, for preventing the spread of SARS-CoV-2, the most effective methods are maintaining a physical distance of ≥ 1 m, use of face masks and respirators, eye protection, and regular handwashing [97]. Globally, health authorities should take immediate action to prevent the spread of the pandemic and develop an effective vaccine.

Conclusion

So far, numerous respiratory infectious diseases have threatened humankind. Although treatments for influenza are constantly being developed, many people continue to succumb to the illness every year. There is no clear cure for the respiratory disease caused by the novel coronavirus. Therefore, tremendous efforts, such as extensive research on viruses and clinical diseases and development of new drugs and vaccines, are of essence. Concerns regarding the threat posed to the global health security by SARS-CoV-2 are escalating with an increasing number of outbreaks globally. With an estimated number of over 12 million cases worldwide, the COVID-19 pandemic could continue until the end of the year. Given that an outbreak is potentially a threat to every member of the global community, extensive efforts to prevent, detect, and respond to SARS-CoV-2 at the earliest is crucial. The COVID-19 pandemic is potentially the largest global health issue since the influenza pandemic in 1918. There are huge efforts being made to discover potential treatments for COVID-19. Clinical trials emphasize the need and the ability to obtain high-quality evidence even during the pandemic. Global cooperation and efforts are required to develop effective drugs and vaccines.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

ORCID

Hyun Jung Kim, https://orcid.org/0000-0002-1878-1111

References

1. Johnson NP, Mueller J. Updating the accounts: global mortality of the 1918-1920 "Spanish" influenza pandemic. Bull Hist Med 2002;76:105–15.
2. Guarner J. Three emerging coronaviruses in two decades. Am J Clin Pathol 2020;153:420–1.
3. Dowell SF, Ho MS. Seasonality of infectious diseases and severe acute respiratory syndrome-what we don't know can hurt us. Lancet Infect Dis 2004;4:704–8.
4. Nicholson KG, Wood JM, Zambon M. Influenza. Lancet 2003;362:1733–45.
5. Ghendon Y. Introduction to pandemic influenza through history. Eur J Epidemiol 1994;10:451–3.
6. Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza; Bautista E, Chotpitayasunondh T, Gao Z, Harper SA, Shaw M, et al. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. N Engl J Med 2010;362:1708–19.
7. Lessler J, Reich NG, Cummings DA; New York City Department of Health and Mental Hygiene Swine Influenza Investiga-

tion Team. Outbreak of 2009 pandemic influenza A (H1N1) at a New York City school. N Engl J Med 2009;361:2628–36.
8. Hong K, Sohn S, Chun BC. Estimating influenza-associated mortality in Korea: the 2009-2016 seasons. J Prev Med Public Health 2019;52:308–15.
9. Paules C, Subbarao K. Influenza. Lancet 2017;390:697–708.
10. Zangrillo A, Biondi-Zoccai G, Landoni G, Frati G, Patroniti N, Pesenti A, et al. Extracorporeal membrane oxygenation (ECMO) in patients with H1N1 influenza infection: a systematic review and meta-analysis including 8 studies and 266 patients receiving ECMO. Crit Care 2013;17:R30.
11. Noah MA, Peek GJ, Finney SJ, Griffiths MJ, Harrison DA, Grieve R, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). JAMA 2011;306:1659–68.
12. Cho J, Lee HJ, Hong SB, Suh GY, Park MS, Kim SC, et al. Structure of intensive care unit and clinical outcomes in critically ill patients with influenza A/H1N1 2009. Korean J Crit Care Med 2012;27:65–9.
13. Dwyer DE, Smith DW, Catton MG, Barr IG. Laboratory diagnosis of human seasonal and pandemic influenza virus infection. Med J Aust 2006;185:S48–53.
14. Peaper DR, Landry ML. Rapid diagnosis of influenza: state of the art. Clin Lab Med 2014;34:365–85.
15. Uyeki TM, Bernstein HH, Bradley JS, Englund JA, File TM, Fry AM, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenzaa. Clin Infect Dis 2019;68:e1–47.
16. Hayden FG, Sugaya N, Hirotsu N, Lee N, de Jong MD, Hurt AC, et al. Baloxavir marboxil for uncomplicated influenza in adults and adolescents. N Engl J Med 2018;379:913–23.
17. Hirotsu N, Sakaguchi H, Sato C, Ishibashi T, Baba K, Omoto S, et al. Baloxavir marboxil in Japanese pediatric patients with influenza: safety and clinical and virologic outcomes. Clin Infect Dis 2020;71:971–81.
18. Ison MG, Portsmouth S, Yoshida Y, Shishido T, Mitchener M, Tsuchiya K, et al. Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza (CAPSTONE-2): a randomised, placebo-controlled, phase 3 trial. Lancet Infect Dis 2020;20:1204-14.
19. The Lancet. Preparing for seasonal influenza. Lancet 2018;391:180.
20. Hayden FG, Belshe R, Villanueva C, Lanno R, Hughes C, Small I, et al. Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. J Infect Dis 2004;189:440–9.
21. Hayden FG, Gubareva LV, Monto AS, Klein TC, Elliot MJ, Hammond JM, et al. Inhaled zanamivir for the prevention of influenza in families. Zanamivir Family Study Group. N Engl J Med 2000;343:1282–9.
22. Uyeki TM. Baloxavir for postexposure prophylaxis against influenza in households. N Engl J Med 2020;383:389–90.
23. Hak E, Hoes AW, Verheij TJ. Influenza vaccinations: who needs them and when? Drugs 2002;62:2413–20.
24. Peiris JS, Lai ST, Poon LL, Guan Y, Yam LY, Lim W, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 2003;361:1319–25.
25. Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery S, et al. A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 2003;348:1953–66.
26. Drosten C, Günther S, Preiser W, van der Werf S, Brodt HR, Becker S, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med 2003;348:1967–76.
27. Gu J, Korteweg C. Pathology and pathogenesis of severe acute respiratory syndrome. Am J Pathol 2007;170:1136–47.
28. Marra MA, Jones SJ, Astell CR, Holt RA, Brooks-Wilson A, Butterfield YS, et al. The genome sequence of the SARS-associated coronavirus. Science 2003;300:1399–404.
29. Lim S, Choi HS, Shin H, Ahn JH, Baik JJ, Choi YH, et al. Three cases of severe acute respiratory syndrome imported into South Korea. Korean J Med 2004;67:655–61.
30. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol 2016;14:523–34.
31. Liu CL, Lu YT, Peng MJ, Chen PJ, Lin RL, Wu CL, et al. Clinical and laboratory features of severe acute respiratory syndrome vis-a-vis onset of fever. Chest 2004;126:509–17.
32. Cheng VC, Lau SK, Woo PC, Yuen KY. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. Clin Microbiol Rev 2007;20:660–94.
33. Tsang KW, Ho PL, Ooi GC, Yee WK, Wang T, Chan-Yeung M, et al. A cluster of cases of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003;348:1977–85.
34. Rota PA, Oberste MS, Monroe SS, Nix WA, Campagnoli R, Icenogle JP, et al. Characterization of a novel coronavirus associated with severe acute respiratory syndrome. Science 2003;300:1394–9.
35. Wong KT, Antonio GE, Hui DS, Lee N, Yuen EH, Wu A, et al. Severe acute respiratory syndrome: radiographic appearances and pattern of progression in 138 patients. Radiology 2003;228:401–6.
36. Lee N, Hui D, Wu A, Chan P, Cameron P, Joynt GM, et al. A

https://doi.org/10.12701/yujm.2020.00633

major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003;348:1986–94.
37. Hui DS, Wong PC, Wang C. SARS: clinical features and diagnosis. Respirology 2003;8(Suppl 1):S20–4.
38. Chan PK, To WK, Ng KC, Lam RK, Ng TK, Chan RC, et al. Laboratory diagnosis of SARS. Emerg Infect Dis 2004;10:825–31.
39. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med 2006;3:e343.
40. Seto WH, Tsang D, Yung RW, Ching TY, Ng TK, Ho M, et al. Effectiveness of precautions against droplets and contact in prevention of nosocomial transmission of severe acute respiratory syndrome (SARS). Lancet 2003;361:1519–20.
41. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 2012;367:1814–20.
42. Hui DS, Azhar EI, Kim YJ, Memish ZA, Oh MD, Zumla A. Middle East respiratory syndrome coronavirus: risk factors and determinants of primary, household, and nosocomial transmission. Lancet Infect Dis 2018;18:e217–27.
43. Kim KH, Tandi TE, Choi JW, Moon JM, Kim MS. Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in South Korea, 2015: epidemiology, characteristics and public health implications. J Hosp Infect 2017;95:207–13.
44. Memish ZA, Perlman S, Van Kerkhove MD, Zumla A. Middle East respiratory syndrome. Lancet 2020;395:1063–77.
45. Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, Al-Rabiah FA, Al-Hajjar S, Al-Barrak A, et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect Dis 2013;13:752–61.
46. Arabi YM, Arifi AA, Balkhy HH, Najm H, Aldawood AS, Ghabashi A, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. Ann Intern Med 2014;160:389–97.
47. Choi WJ, Lee KN, Kang EJ, Lee H. Middle East respiratory syndrome-coronavirus infection: a case report of serial computed tomographic findings in a young male patient. Korean J Radiol 2016;17:166–70.
48. Ajlan AM, Ahyad RA, Jamjoom LG, Alharthy A, Madani TA. Middle East respiratory syndrome coronavirus (MERS-CoV) infection: chest CT findings. AJR Am J Roentgenol 2014;203:782–7.
49. Elkholy AA, Grant R, Assiri A, Elhakim M, Malik MR, Van Kerkhove MD. MERS-CoV infection among healthcare workers and risk factors for death: retrospective analysis of all laboratory-confirmed cases reported to WHO from 2012 to 2 June 2018. J Infect Public Health 2020;13:418–22.
50. World Health Organization. Laboratory biorisk management for laboratories handling human specimens suspected or confirmed to contain influenza A (H1N1) causing the current international epidemics. Geneva: World Health Organization; 2009.
51. Huang P, Wang H, Cao Z, Jin H, Chi H, Zhao J, et al. A rapid and specific assay for the detection of MERS-CoV. Front Microbiol 2018;9:1101.
52. World Health Organization. Infection prevention and control during health care for probable or confirmed cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infection: interim guidance [Internet]. Geneva: World Health Organization; 2019 [cited 2020 Jul 16]. https://www.who.int/csr/disease/coronavirus_infections/ipc-mers-cov/en/.
53. Chong YP, Song JY, Seo YB, Choi JP, Shin HS; Rapid Response Team. Antiviral treatment guidelines for Middle East respiratory syndrome. Infect Chemother 2015;47:212–22.
54. Mo Y, Fisher D. A review of treatment modalities for Middle East Respiratory Syndrome. J Antimicrob Chemother 2016;71:3340–50.
55. Baharoon S, Memish ZA. MERS-CoV as an emerging respiratory illness: a review of prevention methods. Travel Med Infect Dis 2019;32:101520.
56. Petrosillo N, Viceconte G, Ergonul O, Ippolito G, Petersen E. COVID-19, SARS and MERS: are they closely related? Clin Microbiol Infect 2020;26:729–34.
57. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, et al. Virology, epidemiology, pathogenesis, and control of COVID-19. Viruses 2020;12:372.
58. Rabaan AA, Al-Ahmed SH, Haque S, Sah R, Tiwari R, Malik YS, et al. SARS-CoV-2, SARS-CoV, and MERS-COV: a comparative overview. Infez Med 2020;28:174–84.
59. World Health Organization. Coronavirus disease (COVID-19): situation report, 176 [Internet]. Geneva: World Health Organization; 2020 [cited 2020 Jul 16]. https://apps.who.int/iris/handle/10665/333304.
60. Bourouiba L. Turbulent gas clouds and respiratory pathogen emissions: potential implications for reducing transmission of COVID-19. JAMA 2020;323:1837–8.
61. Lewis D. Is the coronavirus airborne? Experts can't agree. Nature 2020;580:175.
62. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. N Engl J Med 2020;382:970–1.
63. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et

al. Clinical characteristics of Covid-19 in New York City. N Engl J Med 2020;382:2372–4.
64. Baj J, Karakuła-Juchnowicz H, Teresiński G, Buszewicz G, Ciesielka M, Sitarz E, et al. COVID-19: specific and non-specific clinical manifestations and symptoms: the current state of knowledge. J Clin Med 2020;9:1753.
65. Lee Y, Min P, Lee S, Kim SW. Prevalence and duration of acute loss of smell or taste in COVID-19 patients. J Korean Med Sci 2020;35:e174.
66. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med 2020;382:e38.
67. Kim DW, Byeon KH, Kim J, Cho KD, Lee N. The correlation of comorbidities on the mortality in patients with COVID-19: an observational study based on the Korean National Health Insurance big data. J Korean Med Sci 2020;35:e243.
68. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA 2020;324:782–3.
69. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727–33.
70. Hong KH, Lee SW, Kim TS, Huh HJ, Lee J, Kim SY, et al. Guidelines for laboratory diagnosis of coronavirus disease 2019 (COVID-19) in Korea. Ann Lab Med 2020;40:351–60.
71. Kwon KT, Ko JH, Shin H, Sung M, Kim JY. Drive-through screening center for COVID-19: a safe and efficient screening system against massive community outbreak. J Korean Med Sci 2020;35:e123.
72. Mulangu S, Dodd LE, Davey RT Jr, Tshiani Mbaya O, Proschan M, Mukadi D, et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med 2019;381:2293–303.
73. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020;382:929–36.
74. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of Covid-19–preliminary report. N Engl J Med 2020 May 22 [Epub]. https://doi.org/10.1056/NEJMoa2007764.
75. Goldman JD, Lye DC, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med 2020 May 27 [Epub]. https://doi.org/10.1056/NEJMoa2015301.
76. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med 2020;382:2327–36.
77. Lee C, Ahn MY, Byeon K, Choi JP, Hahm C, Kim H, et al. Clinical experience with use of remdesivir in the treatment of severe acute respiratory syndrome coronavirus 2: a case series. Infect Chemother 2020;52:e46.
78. Norrie JD. Remdesivir for COVID-19: challenges of underpowered studies. Lancet 2020;395:1525–7.
79. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int J Antimicrob Agents 2020;55:105938.
80. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LC, Veiga VC, Avezum A, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. N Engl J Med 2020 Jul 23 [Epub]. https://doi.org/10.1056/NEJMoa2019014.
81. Hong KS, Jang JG, Hur J, Lee JH, Kim HN, Lee W, et al. Early hydroxychloroquine administration for rapid severe acute respiratory syndrome coronavirus 2 eradication. Infect Chemother 2020;52:e43.
82. Lim J, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ, et al. Case of the index patient who caused tertiary transmission of COVID-19 infection in Korea: the application of lopinavir/ritonavir for the treatment of COVID-19 infected pneumonia monitored by quantitative RT-PCR. J Korean Med Sci 2020;35:e79.
83. Kim JW, Kim EJ, Kwon HH, Jung CY, Kim KC, Choe JY, et al. Lopinavir-ritonavir versus hydroxychloroquine for viral clearance and clinical improvement in patients with mild to moderate coronavirus disease 2019. Korean J Intern Med 2020 Jun 16 [Epub]. https://doi.org/10.3904/kjim.2020.224.
84. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. N Engl J Med 2020;382:1787–99.
85. Zhang JJ, Lee KS, Ang LW, Leo YS, Young BE. Risk factors of severe dsease and efficacy of treatment in patients infected with COVID-19: a systematic review, meta-analysis and meta-regression analysis. Clin Infect Dis 2020 May 14 [Epub]. https://doi.org/10.1093/cid/ciaa576.
86. Cheng CY, Lee YL, Chen CP, Lin YC, Liu CE, Liao CH, et al. Lopinavir/ritonavir did not shorten the duration of SARS CoV-2 shedding in patients with mild pneumonia in Taiwan. J Microbiol Immunol Infect 2020;53:488–92.
87. Garraud O, Heshmati F, Pozzetto B, Lefrere F, Girot R, Saillol A, et al. Plasma therapy against infectious pathogens, as of yesterday, today and tomorrow. Transfus Clin Biol 2016;23:39–44.
88. Cheng Y, Wong R, Soo YO, Wong WS, Lee CK, Ng MH, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 2005;24:44–6.

https://doi.org/10.12701/yujm.2020.00633

89. Yeh KM, Chiueh TS, Siu LK, Lin JC, Chan PK, Peng MY, et al. Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. J Antimicrob Chemother 2005;56:919–22.
90. Bloch EM, Shoham S, Casadevall A, Sachais BS, Shaz B, Winters JL, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. J Clin Invest 2020;130:2757–65.
91. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA 2020;324:1–11.
92. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033–4.
93. RECOVERY Collaborative Group; Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with covid-19–preliminary report. N Engl J Med 2020 Jul 17 [Epub]. https://doi.org/10.1056/NEJMoa2021436.
94. Huet T, Beaussier H, Voisin O, Jouveshomme S, Dauriat G, Lazareth I, et al. Anakinra for severe forms of COVID-19: a cohort study. Lancet Rheumatol 2020;2:e393–400.
95. Thanh Le T, Andreadakis Z, Kumar A, Gómez Román R, Tollefsen S, Saville M, et al. The COVID-19 vaccine development landscape. Nat Rev Drug Discov 2020;19:305–6.
96. Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 vaccines at pandemic speed. N Engl J Med 2020;382:1969–73.
97. Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Schünemann HJ, et al. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. Lancet 2020;395:1973–87.

Yeungnam University Journal of Medicine
YUJM

Review article
eISSN 2384-0293
Yeungnam Univ J Med 2020;37(4):296-301
https://doi.org/10.12701/yujm.2020.00752

Frailty and elderly in urology: implications for postoperative complications

Phil Hyun Song

Department of Urology, Yeungnam University College of Medicine, Daegu, Korea

Received: September 3, 2020
Revised: September 16, 2020
Accepted: September 17, 2020

Corresponding author:
Phil Hyun Song
Department of Urology, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel : +82-53-620-3693
Fax : +82-53-627-5535
E-mail : sph04@hanmail.net

The geriatric population is at a greater risk of postoperative complications than young adults. This risk is associated with the physiologic decline seen in this population known as frailty. Unlike fitter patients, frail patients who undergo operative treatment have a greater likelihood of developing postoperative complications and endure prolonged hospital stays. This circumstance is comparable to the urological status. Therefore, tolerable measurement of frailty as a domain of preoperative health status has been suggested to ascertain vulnerability in elderly patients. In this review, we will elaborate on the concept of frailty and examine its importance with respect to surgical complications, focusing on the urological status.

Keywords: Complications; Frailty; Postoperative; Urology

Introduction

The demographic composition of the surgical population changes with the aging of the population. Older adults account for an increasing proportion of the surgical population, with >35% of all inpatient operations being performed in adults aged 65 years or older in the United States. This proportion is higher in medicine subspecialties, such as urology, where 65% of all surgeries are performed in adults aged 65 years and older [1] and is anticipated to increase in the future. This situation is similar in every country including South Korea. Therefore, it is essential to understand the unique physiology and characteristics of older adults to provide optimal urologic care for these patients.

The geriatric population is at a greater risk for postoperative complications than young adults. This risk is associated with the physiologic decline observed in this population known as frailty. Frailty is a state of decreased physiologic reserve that increases a patient's susceptibility to incapacity. Thus, by definition, frailty increases the risk of poor surgical outcomes. A few studies have reported outcomes, such as a higher risk of delirium, injury, intensive care unit (ICU) admissions, ICU stay, and death, in geriatric urologic patients than in young adults [2,3].

Previous concepts of postoperative risk estimation, such as the American Society of Anesthesiology (ASA) physical status classification and European Cooperative Oncology Group (ECOG) performance, have focused on single-organ systems to determine the risk of adverse postoperative cardiac, hepatic, pulmonary, or renal events [4,5]. Although these algorithms continue to play a role in the postoperative risk estimation of urologic patients, frailty has covered these strategies as an effective, efficient, and global estimation for surgical risk and represents a notable paradigm shift for the anticipation of postoperative complications [6]. In this review, we will elaborate on the concept of frailty and examine its importance with respect to surgical complications, with a focus on urological status.

Definition of frailty

Although no single operational definition is all-encompassing, a clear conceptual framework for frailty has been established. Frailty

is a state of extreme vulnerability to stressors that induces adverse health outcomes [7,8]. However, frailty is a complex, multidimensional, and cyclical state of decreased physiologic reserve that results in diminished resilience and adaptive capacity and increased vulnerability to stressors (Fig. 1) [9]. Frailty has also been related to the concept of health deficits, that, when accumulated over time, heightens an individual's vulnerability to adverse health outcomes [10].

The prevalence of frailty is high among the elderly and increases with age, as observed in 40% of patients aged 80 years or older compared with 10% of patients aged between 65 and 75 years [11]. Unlike fitter patients, frail patients who undergo surgery have a greater likelihood of developing postoperative complications, being discharged to care facilities, and having longer hospital stays. Postoperative complications can result in a series of events leading to loss of independence, decline in the quality of life, disability, increased healthcare costs, and even death [2,3]. Therefore, adequate measurement of frailty as a domain of preoperative health status has been proposed to ascertain vulnerability in elderly patients.

Measurement of frailty

Current recommendations state that all patients aged > 70 years and those with significant weight loss (> 5%) due to chronic illness should be screened for frailty [9]. However, it is not clear which frailty measure is optimal for screening and assessment. Over 70 different tools exist to measure frailty, few of which have been proven, and they range from a single item to more than 90 items. They also range in their intended purpose, with some frailty systems being designed as screening tools to risk-stratify patients, and others as more formal frailty estimations aimed at guiding treatment strategy. A brief summary of the most commonly used frailty assessment tools is provided below.

1. Individual assessment tools

Using a single-item estimation tool is a quick and easy means to quantify a patient's level of frailty. The most commonly used single-item tools that have been demonstrated to be reliable predictors of frailty are gait speed (the measured time it takes for a patient to walk a 5-m distance), grip strength (a marker of frailty via universal loss of muscle mass or myopathy associated with decreased physiologic reserve), and Timed Up-and-Go score (the measured time it takes for a patient to rise from a chair, walk 10 feet, turn around, and return to being seated) [12-14].

Although these single-item assessments can be convenient to use in a busy and time-constrained circumstance, they can also lack sensitivity and specificity and, when in isolation, should be used with caution [6].

2. FRAIL scale and Vulnerability Elders Survey-13

Developed by the Geriatric Advisory Panel of the International

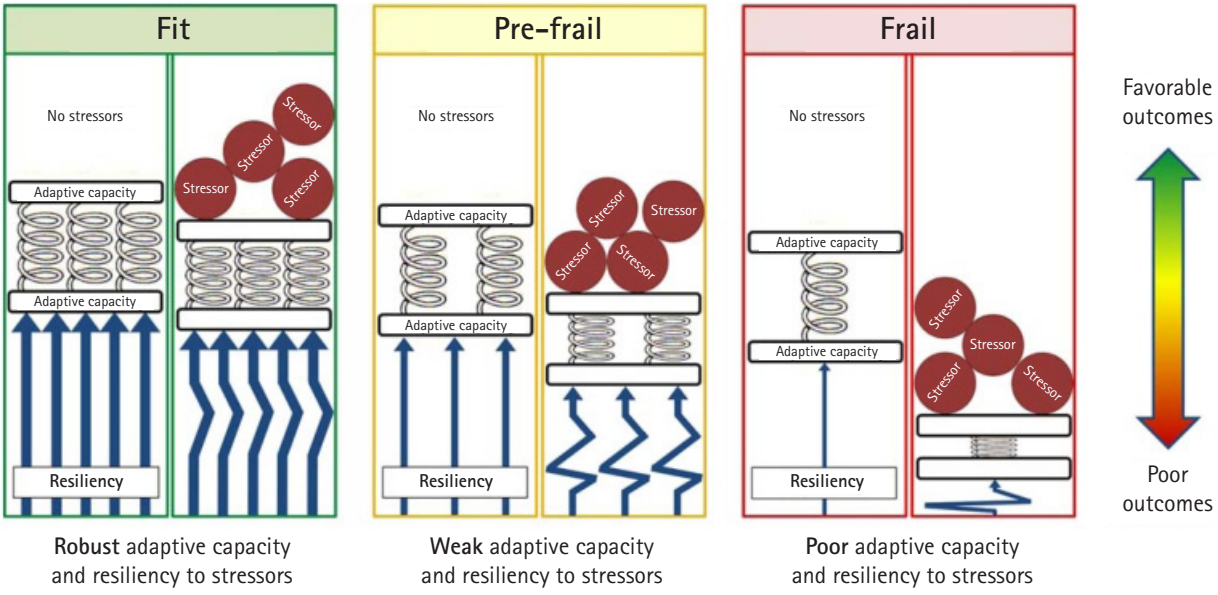


Fig. 1. Model for defining frailty. Fit patients have robust adaptive capacity and resilience to stressors, which lead to more favorable outcomes. Pre-frail patients have weakened adaptive capacity and resilience to stressors, and frail patients have poor adaptive capacity and resilience to stressors. Adapted from Ethun et al. [9] with permission of Wiley.

Academy of Nutrition and Aging, the fatigue, resistance, ambulation, illness, and loss of weight (FRAIL) scale is a validated screening method consisting of five straightforward questions (Table 1) [9,15]. Because it can be self-administered and does not crave a face-to-face examination, this tool can be an efficient and cost-effective tool to screen large groups of patients for frailty. However, this scale is applied most frequently in primary care or community environments and has not been investigated extensively as a screening method for patients with cancer [9,16].

The Vulnerability Elders Survey-13 (VES-13) is also a self-administered survey consisting of 13 items: one item for age and 12 for self-rated health, physical ability, and functional performance. However, unlike the FRAIL scale, this practical screening tool can be used as a reliable marker of frailty in patients with cancer. Despite these advantages, the VES-13 may be inaccurate because of patients' overestimation of their own competencies [17,18].

3. Phenotypic frailty

Phenotypic frailty is one of the most widely used frailty assessment tools in oncology and has been identified by the American Geriatric Society and the American College of Surgeons (ACS) as an adequate strategy for preoperatively measuring elderly patients. It is based on the notion that frailty results from age-associated biological changes across multiple domains, such as nutrition and energy metabolism. This method consists of five items (weight, strength, energy, speed, and activity) and needs a combination of questionnaires and in-office estimations (Table 2) [9,19].

Table 1. FRAIL scale

Letter	Item (questionnaire)
F	Fatigue (do you feel tired most or all the time?)
R	Resistance (can you climb one flight of stairs without difficulty?)
A	Ambulation (can you walk one block without assistance?)
I	Illness (do you have greater than five illnesses?)
L	Loss of weight (have you lost >5% of your usual weight in the last year?)

Scoring: 0 indicates robust, 1–2 indicates pre-frail, and 3 indicates frail. Adapted from Ethun et al. [9] with permission of Wiley.

Table 2. Phenotypic frailty

Item	Contents
Weight loss	≥10 lb weight loss in the past years
Weakness	Grip strength in lowest 20% based on sex and body mass index
Exhaustion	Self-reported exhaustion, fatigue, and/or loss of motivation
Slow gait speed	Time it takes to walk 15 ft at normal speed
Low activity	Kilocalories of expenditure based on self-reported physical activities

Adapted from Ethun et al. [9] with permission of Wiley.

4. Frailty index and modified frailty index

The frailty index (FI) was initiated from the Canadian Study of Health and Aging and is based on an accumulative deficit model [20]. This method proposes that the accumulation of medical, functional, and social shortfalls over an individual's lifetime induces a nonspecific, age-associated vulnerability, or, in other words, frailty [8]. The original FI includes 70 items, which vary from vague to specific symptoms, signs, diseases, and disabilities. Although many of the included items can be found in patient charts, several need more cumbersome and labor-intensive estimations, which makes FI less attractive in clinical practice. Therefore, Obeid et al. [21] proposed a modified FI (mFI), which maps the 70 variables from the original FI into 11 preexisting variables from the National Surgical Quality Improvement Program (NSQIP) database and has since been backed by the ACS (Table 3) [9].

5. Comprehensive geriatric assessment

Comprehensive geriatric assessment (CGA), a multidimensional measurement process for identifying and managing elderly patients, is one of the most extensively investigated and used methods in oncology. Using principles similar to those of the cumulative deficit model, the CGA focuses on some domains of a patient's psychosocial, medical, and functional abilities and can be a reliable assessment of frailty when used as a screening method in patients with cancer [22]. However, with 64 instruments of assessment, managing a full CGA can take hours to complete and is often impractical; hence, the CGA was altered to address these issues. For example, the Cancer-Specific Geriatric Assessment is a brief and

Table 3. Modified frailty index

No.	Component
1	Nonindependent functional status
2	History of diabetes mellitus
3	History of either chronic obstructive pulmonary disease or pneumonia
4	History of congestive heart failure
5	History of myocardial infarction
6	History of percutaneous coronary intervention, cardiac surgery, or angina
7	Hypertension requiring the use of medications
8	Peripheral vascular disease or rest pain
9	Impaired sensorium
10	Transient ischemic attack or cerebrovascular accident without residual deficit
11	Cerebrovascular accident with deficit

The proposed cutoff score (total number of variables present/total number of variables assessed) >0.36 indicates frail. Adapted from Ethun et al. [9] with permission of Wiley.

https://doi.org/10.12701/yujm.2020.00752

more focused method that combines both self-administered and in-office assisted estimations [23]. It contains six of the nine domains from the full CGA, and the methods for measuring those domains were specifically chosen for their reliability, brevity, validity, and prognostic ability in patients with cancer [24].

Frailty and postoperative complications, especially with respect to urological surgery

The decision regarding a patient's "fitness" for operative treatment has traditionally been based on fairly subjective and particularly simplistic assessments, which can be limited in their capacity to predict postoperative morbidity and mortality [13]. Because it transcends age or any single-organ system, frailty has been shown to be a stronger predictor of postoperative complications than some previous surgical risk-assessment methods [25,26]. Revenig et al. [27] reported that frailty was even predictive of postoperative complications among patients undergoing minimally invasive abdominal surgery.

Although less well investigated, the value of frailty, especially in urological oncologic surgery, is increasingly being investigated. It has been demonstrated that frailty is associated with worse long-term and short-term survival in patients undergoing surgery for various malignancies. For example, when frail patients were assessed using the NSQIP mFI, they demonstrated higher 30-day mortality rates than nonfrail patients undergoing surgery for bladder cancer (3.5% vs. 1.8%; $p=0.01$) [28]. Expanding the mFI to include 15 variables, Lascano et al. [29] found that, in patients undergoing operative treatments for urologic malignancies, such as cystectomy, prostatectomy, nephrectomy, and nephroureterectomy, there was a two to six times increased risk of death within 30 days for every 0.05 increase in the calculated mFI compared with that in nonfrail patients (mFI <0.05). They also reported that patients undergoing operative treatments for urologic malignancies with high frailty (mFI >0.20) had a significantly increased risk of major side effects (Clavien-Dindo grade IV) compared with nonfrail patients (odds ratio, 3.70; 95% confidence interval, 2.87–7.79; $p<0.0005$).

The mFI has also been used to evaluate patients treated with robotic-assisted radical prostatectomy (RARP) for prostate cancer. Levy et al. [30] also queried the NSQIP database to create a dataset of 23,000 patients who underwent RARP. An mFI score of ≥ 3 was related to a 12-fold increased risk of a Clavien-Dindo grade IV event compared with that in nonfrail patients.

Conclusion

Current knowledge on preoperative geriatric estimation in urologic patients is sparse. Frailty is emerging as one of the most significant predictors of postoperative complications, disease progression, and death. Therefore, preoperative recognition of frailty in such patients seems to be an important method in urological practice. Moreover, adequate stratification of preoperative frailty may induce a decrease in postoperative complications. It is also important that high-risk patients are routinely instructed to undergo training such as physical therapy, walking, and use of incentive spirometry in an effort to reduce postoperative complications. Thus, further research in urological environments, especially in multicenter randomized controlled trials, is required to develop a standardized cutoff value for frailty to provide better urologic patient care.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

ORCID

Phil Hyun Song, https://orcid.org/0000-0002-3801-258X

References

1. Hall MJ, DeFrances CJ, Williams SN, Golosinskiy A, Schwartzman A. National Hospital Discharge Survey: 2007 summary. Natl Health Stat Report 2010;(29):1–20.
2. Tognoni P, Simonato A, Robutti N, Pisani M, Cataldi A, Monacelli F, et al. Preoperative risk factors for postoperative delirium (POD) after urological surgery in the elderly. Arch Gerontol Geriatr 2011;52:e166–9.
3. Bjurlin MA, Goble SM, Fantus RJ, Hollowell CM. Outcomes in geriatric genitourinary trauma. J Am Coll Surg 2011;213:415–21.
4. Neuman MD, Bosk CL. What we talk about when we talk about risk: refining surgery's hazards in medical thought. Milbank Q 2012;90:135–59.
5. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 2014;64:e77–137.
6. Townsend NT, Robinson TN. Surgical risk and comorbidity in

older urologic patients. Clin Geriatr Med 2015;31:591–601.
7. Lu J, Cao LL, Zheng CH, Li P, Xie JW, Wang JB, et al. The preoperative frailty versus inflammation-based prognostic score: which is better as an objective predictor for gastric cancer patients 80 years and older? Ann Surg Oncol 2017;24:754–62.
8. Robinson TN, Walston JD, Brummel NE, Deiner S, Brown CH 4th, Kennedy M, et al. Frailty for surgeons: review of a National Institute on Aging conference on frailty for specialists. J Am Coll Surg 2015;221:1083–92.
9. Ethun CG, Bilen MA, Jani AB, Maithel SK, Ogan K, Master VA. Frailty and cancer: implications for oncology surgery, medical oncology, and radiation oncology. CA Cancer J Clin 2017;67:362–77.
10. Cohen RR, Lagoo-Deenadayalan SA, Heflin MT, Sloane R, Eisen I, Thacker JM, et al. Exploring predictors of complication in older surgical patients: a deficit accumulation index and the Braden Scale. J Am Geriatr Soc 2012;60:1609–15.
11. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. J Am Geriatr Soc 2012;60:1487–92.
12. Buettner S, Wagner D, Kim Y, Margonis GA, Makary MA, Wilson A, et al. Inclusion of sarcopenia outperforms the modified frailty index in predicting 1-year mortality among 1,326 patients undergoing gastrointestinal surgery for a malignant indication. J Am Coll Surg 2016;222:397–407.
13. Huisman MG, Audisio RA, Ugolini G, Montroni I, Vigano A, Spiliotis J, et al. Screening for predictors of adverse outcome in onco-geriatric surgical patients: a multicenter prospective cohort study. Eur J Surg Oncol 2015;41:844–51.
14. Chung CJ, Wu C, Jones M, Kato TS, Dam TT, Givens RC, et al. Reduced handgrip strength as a marker of frailty predicts clinical outcomes in patients with heart failure undergoing ventricular assist device placement. J Card Fail 2014;20:310–5.
15. Abellan van Kan G, Rolland YM, Morley JE, Vellas B. Frailty: toward a clinical definition. J Am Med Dir Assoc 2008;9:71–2.
16. Woo J, Yu R, Wong M, Yeung F, Wong M, Lum C. Frailty screening in the community using the FRAIL scale. J Am Med Dir Assoc 2015;16:412–9.
17. Saliba D, Elliott M, Rubenstein LZ, Solomon DH, Young RT, Kamberg CJ, et al. The Vulnerable Elders Survey: a tool for identifying vulnerable older people in the community. J Am Geriatr Soc 2001;49:1691–9.
18. Revenig LM, Canter DJ, Henderson MA, Ogan K, Kooby DA, Maithel SK, et al. Preoperative quantification of perceptions of surgical frailty. J Surg Res 2015;193:583–9.
19. Li JL, Henderson MA, Revenig LM, Sweeney JF, Kooby DA, Maithel SK, et al. Frailty and one-year mortality in major intra-abdominal operations. J Surg Res 2016;203:507–12.
20. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–95.
21. Obeid NM, Azuh O, Reddy S, Webb S, Reickert C, Velanovich V, et al. Predictors of critical care-related complications in colectomy patients using the National Surgical Quality Improvement Program: exploring frailty and aggressive laparoscopic approaches. J Trauma Acute Care Surg 2012;72:878–83.
22. Kellen E, Bulens P, Deckx L, Schouten H, Van Dijk M, Verdonck I, et al. Identifying an accurate pre-screening tool in geriatric oncology. Crit Rev Oncol Hematol 2010;75:243–8.
23. Hamaker ME, Jonker JM, de Rooij SE, Vos AG, Smorenburg CH, van Munster BC. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. Lancet Oncol 2012;13:e437–44.
24. White JV, Guenter P, Jensen G, Malone A, Schofield M; Academy of Nutrition and Dietetics Malnutrition Work Group, et al. Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). J Acad Nutr Diet 2012;112:730–8.
25. Arya S, Kim SI, Duwayri Y, Brewster LP, Veeraswamy R, Salam A, et al. Frailty increases the risk of 30-day mortality, morbidity, and failure to rescue after elective abdominal aortic aneurysm repair independent of age and comorbidities. J Vasc Surg 2015;61:324–31.
26. Jung HW, Jang IY, Lee YS, Lee CK, Cho EI, Kang WY, et al. Prevalence of frailty and aging-related health conditions in older Koreans in rural communities: a cross-sectional analysis of the aging study of Pyeongchang rural area. J Korean Med Sci 2016;31:345–52.
27. Revenig LM, Canter DJ, Master VA, Maithel SK, Kooby DA, Pattaras JG, et al. A prospective study examining the association between preoperative frailty and postoperative complications in patients undergoing minimally invasive surgery. J Endourol 2014;28:476–80.
28. Chappidi MR, Kates M, Patel HD, Tosoian JJ, Kaye DR, Sopko NA, et al. Frailty as a marker of adverse outcomes in patients with bladder cancer undergoing radical cystectomy. Urol Oncol 2016;34:256.
29. Lascano D, Pak JS, Kates M, Finkelstein JB, Silva M, Hagen E, et al. Validation of a frailty index in patients undergoing curative surgery for urologic malignancy and comparison with other risk stratification tools. Urol Oncol 2015;33:426.

https://doi.org/10.12701/yujm.2020.00752

30. Levy I, Finkelstein M, Bilal KH, Palese M. Modified frailty index associated with Clavien-Dindo IV complications in robot-assisted radical prostatectomies: a retrospective study. Urol Oncol 2017;35:425–31.

Yeungnam University Journal of Medicine
YUJM

Original article
eISSN 2384-0293
Yeungnam Univ J Med 2020;37(4):302-307
https://doi.org/10.12701/yujm.2020.00122

Usefulness of intraoperative determination of central lymph node metastasis by palpation in papillary thyroid cancer

Wan Wook Kim[1], Jeeyeon Lee[1], Jin Hyang Jung[1], Ho Yong Park[1], Won Hwa Kim[2], Hye Jung Kim[2], Ji-Young Park[3], Ralph P. Tufano[4]

[1]Department of Surgery, Kyungpook National University Chilgok Hospital, School of Medicine, Kyungpook National University, Daegu, Korea
[2]Department of Radiology, Kyungpook National University Chilgok Hospital, School of Medicine, Kyungpook National University, Daegu, Korea
[3]Department of Pathology, Kyungpook National University Chilgok Hospital, School of Medicine, Kyungpook National University, Daegu, Korea
[4]Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Received: March 4, 2020
Revised: April 3, 2020
Accepted: April 7, 2020

Corresponding author:
Wan Wook Kim
Department of Surgery, Kyungpook National University Chilgok Hospital, School of Medicine, Kyungpook National University, 807 Hoguk-ro, Buk-gu, Daegu 41404, Korea
Tel: +82-53-200-2705
Fax: +82-53-200-2027
E-mail: kww1324@naver.com

Background: This study evaluated the usefulness of judgment of central lymph node (LN) metastasis by surgeon's palpation in papillary thyroid cancer.
Methods: This study included 127 patients who underwent thyroidectomy and central compartment node dissection between October 2014 and February 2015. The criterion for suspicious LNs was hardness.
Results: Of the 20.5% (28/127) of suspicious for metastatic LNs according to surgeon determination, 92.8% (26/28) were confirmed to be metastatic in the final pathological examinations. Metastatic LNs were found in 38 (38.3%) of 99 patients without suspicious LNs, 29 of whom (76.3%) had micrometastases. The sensitivity, specificity, and positive and negative predictive values for the determination of LN metastasis by a surgeon were 40.6%, 96.8%, 92.9%, and 61.6%, respectively.
Conclusion: Determination of central LN metastasis by a surgeon's palpation may be useful to evaluate LNs owing to the high specificity and positive predictive values, especially in macrometastasis or high-risk LN disease.

Keywords: Determination; Lymph node; Metastasis; Palpation; Surgeon

Introduction

The incidence of papillary thyroid carcinoma (PTC) has increased globally [1]. Although PTC has a much better prognosis than those of many other cancers, cervical lymph node (LN) metastasis occurs in 30%–80% cases and reportedly increases local recurrence rates [2,3].

Central compartment node dissection (CCND) allows accurate LN staging, reduces local recurrence by clearing metastatic LN, and has a good effect on survival [4]. However, the indication and optimal extent of LN dissection for PTC remain controversial (prophylactic vs. therapeutic, ipsilateral vs. bilateral) because the sensitivity of ultrasonography (USG) and computed tomography (CT) for central cervical LN metastasis in thyroid cancer is low, with poor diagnostic performance [5,6]. In addition, prophylactic CCND may increase morbidity including hypocalcemia and re-

current laryngeal nerve (RLN) palsy; thus, the clinical benefit of survival gained from CCND is unclear [7]. However, CCND performed by experienced, high-volume surgeons (>25 total thyroidectomies/year) have relatively lower postoperative morbidity rates within the acceptable range [8].

LN metastasis is one of the important criteria for determining the extent of surgery (lobectomy vs. total thyroidectomy, ipsilateral vs. bilateral CCND) in thyroid cancer. Total thyroidectomy is preferred to lobectomy if unilateral cancer has multiple central LN metastases, and bilateral CCND may be required rather than ipsilateral CCND. A study of central LN metastasis of unilateral cancer with clinically node-negative status in our institution reported that ipsilateral LN metastasis was the most important high-risk factor for predicting contralateral LN metastasis [9].

Intraoperative frozen biopsy is a useful method to determine the extent of surgery to minimize unnecessary bilateral CCND by confirming LN metastasis. Although frozen biopsy is available in tertiary hospitals with sufficient pathologist support, it is not a feasible option in most other hospitals. In addition, frozen biopsy leads to longer operation times and increases costs for examination; moreover, pathologist skills and efforts are important; thus, there are rarely false-negative results in frozen biopsy.

Therefore, our research team questioned whether inspection and palpation by the surgeon could confirm central LN metastasis and replace the need for frozen biopsy during surgery. Hence, this study aimed to evaluate the accuracy and usefulness of single-surgeon inspection and palpation to evaluate central LN metastasis and determine the extent of surgery.

Materials and methods

This study was approved by the Institutional Review Board (IRB) of the Kyungpook National University Chilgok Hospital (IRB No: 2020-04-008).

Since 2010, the author (WWK) has performed approximately 300–400 thyroid surgeries per year. To evaluate whether the metastasis can be judged by inspection and palpation, for approximately 2 months before starting the study, all LNs were examined using the same methods after CCND and frozen biopsy was performed to confirm the presence of metastasis in suspicious LNs. This study retrospectively included 127 consecutive patients who underwent thyroidectomy and CCND between October 2014 to February 2015. All patients were diagnosed with PTC based on fine-needle aspiration biopsy before surgery and clinically negative LN (nonspecific or considered to be benign) by physical examination and high-resolution USG. All USGs were performed by a well-trained thyroid surgeon or a radiologist specializing in thyroids. The exclusion criteria were benign or follicular neoplasm or other malignancy, previous thyroid operation, clinically positive LN (suspicious metastatic LN), or presence of central/lateral LN metastasis. Regarding the extent of CCND, ipsilateral CCND was performed for unilateral PTC measuring less than 1 cm with negative LN, while bilateral CCND was performed in PTC with bilateral involvement or metastasis in ipsilateral central LN or grossly extrathyroidal extension. Ipsilateral CCND included pretracheal, paratracheal, and prelaryngeal LNs. Micrometastasis was defined as a maximum metastatic focus size <0.2 cm, while ≥0.2 cm was defined as macrometastasis. According to the American Thyroid Association Guidelines, all involved LNs sized <0.2 cm and <5 metastatic LNs were classified as low-risk LN disease; whereas >5 metastatic LNs, macroscopic LN metastasis (clinical N1), and ≥3 cm metastatic LNs were considered high-risk LN disease. One specialized thyroid surgeon (WWK) examined each LN and assessed the metastasis after CCND by inspection and palpation. The surgeons divided the LNs into benign and suspicious metastatic groups and only the suspicious metastatic LNs were numbered. The results were confirmed by frozen or permanent biopsy. In the surgeon's experience, the critical criterion for suspicious metastatic LN was hardness (≥6 points out of 10) rather than enlargement or discoloration. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of intraoperative determinations by the surgeon were examined on basis of the final pathology results. All statistics were analyzed using IMB SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

Results

The clinicopathologic results of the 127 patients are summarized in Table 1. A mean of 6.09±5.25 (range, 0–24) LNs was retrieved and a mean of 1.37±2.57 (range, 0–17) LNs were metastatic. LN metastases were present in 64 patients (50.4%), of whom 37 (57.8%) showed micrometastases, with a mean metastatic LN size of 0.28±0.24 cm (range, 0.1–1.2 cm). The intraoperative determinations and pathologic results of all patients are shown (Fig. 1). Twenty-eight patients (22.0%) had suspicious metastatic LNs based on the surgeon's determination, and a total of 128 suspicious metastatic LNs were harvested. A mean of 0.33±0.8 (range, 0–5) suspicious metastatic LNs were removed per patient. Of these 28 patients, 26 (92.9%) were diagnosed with metastasis based on permanent pathologic examination (Fig. 1). Eighteen (69.2%) and eight patients (30.8%) had macrometastasis and micrometastasis, respectively. High-risk nodal disease was found in 20 (71.4%) of these patients, while low-risk LN disease

Table 1. Clinicopathologic results of 127 patients

Characteristic	Value
Age (yr)	46.8 ± 9.7 (25–71)
Sex (female:male)	107:20 (84.3:15.7)
Lobectomy:total thyroidectomy	68:59 (53.5:46.5)
Tumor size (cm)	0.83 ± 0.6 (0.2–3.8)
PTMC	93 (73.2)
Extrathyroidal extension	64 (50.4)
Thyroiditis	50 (39.4)
Suspicious for metastatic LN determined by surgeon	28 (20.5)
Number removed from suspicious for metastatic LN	0.33 ± 0.8 (0–5)
Frozen biopsy for suspicious LN	17 (13.4)
Number of retrieved LN	6.09 ± 5.2 (0–24)
Number of metastatic LN	1.37 ± 2.5 (0–17)
Metastatic LN size (cm)	0.28 ± 0.24 (0.1–1.2)
Metastasis on LN	64 (50.4)
Micrometastasis on LN	37/64 (57.8)

Values are presented as mean ± standard deviation (range) or number (%).
PTMC, papillary thyroid microcarcinoma; LN, lymph node.

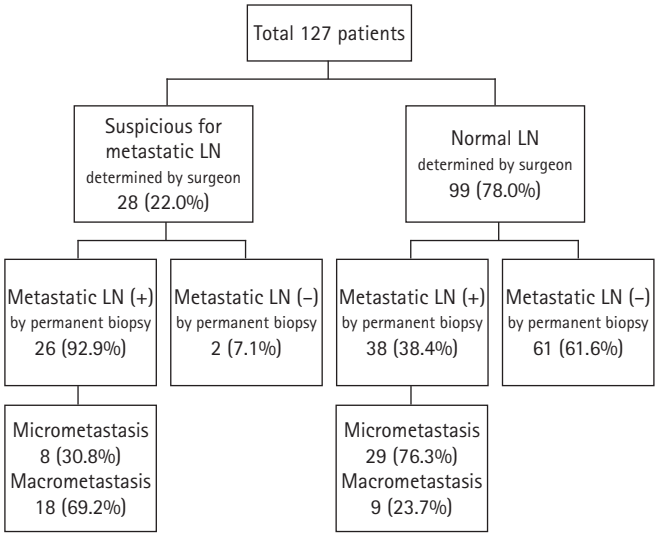


Fig. 1. Flowchart of lymph node (LN) assessment by palpation and pathology results of all 127 patients who underwent surgery.

was found in six patients (21.4%). Among 99 patients without suspicious metastatic LNs, 38 (38.4%) had metastasis, 29 (76.3%) had micrometastasis. All of these 29 patients had fewer than five micrometastases. Low-risk LN disease was found in 90 of the 99 patients (90.9%), including 61 patients without metastasis, while high-risk LN disease was observed in nine (9.1%) patients.

The diagnostic accuracy of the determination of central LN metastasis by surgeon inspection and palpation is shown in Table 2, including a 40.6% sensitivity (26/64), 96.8% specificity (61/63), 92.9% PPV (26/28), and 61.6% NPV (61/99). A patient with thyroiditis is likely to have multiple reactive LNs. It is difficult to distinguish metastasis by palpation as thyroiditis is a complicated factor. Therefore, 77 patients without thyroiditis were re-examined (Table 3). Of these, 12 patients had suspicious LNs and all were diagnosed with metastasis upon final pathological examination. Of the 65 patients considered to have normal LNs, 23 (35.3%) had metastasis, with micrometastasis present in 18 patients (18/23, 78.2%). Furthermore, the 23 patients with false-negative biopsy results mostly had low-risk LN disease. In patients without thyroiditis, the results of central LN metastasis determined by the surgeon included 34.2% sensitivity (12/35), 100% specificity (42/42), 100% PPV (12/12), and 64.6% NPV (42/65). The false-negative, false-positive, and accuracy rates were 65.7%, 0%, and 70.1%, respectively. No recurrence was observed during the mean 61.2-month follow-up period (range, 58.5–64.1 months).

Discussion

The extent of adequate CCND for differentiated thyroid carcinoma remains controversial. CCND reportedly improves patient survival rates and reduces the risk of recurrence when clinical LN metastasis is apparent [10,11]. However, concrete evidence is lacking to show that prophylactic CCND increases the survival rate in patients with differentiated thyroid cancer [12,13]. Although prophylactic CCND may be considered in patients aged >45 years and with T3/4 tumors, bilateral/multi-focal tumor, and extrathyroidal extension, and is not currently recommended for patients with clinical N0, CCND has been reported to reduce postoperative recurrence rates and allow accurate nodal staging to establish postoperative management and follow-up strategies [14]. In addition, CCND has also been reported to lower thyroglobulin levels after surgery [15,16].

LN metastasis in PTC, including micrometastasis, is commonly observed in approximately 30%–80% patients and is not uncommon in patients with clinical N0 on preoperative examination. LN metastasis is an important risk factor that should not be overlooked as it reportedly increases local recurrence rates and the risk of death in patients aged ≥45 years [11]. The optimal treatment strategy is to accurately determine the central LN metastasis through preoperative examination, perform comprehensive CCND if LN metastasis is suspicious, decrease the recurrence rate, and improve the survival rate. In addition, it is essential to minimize complications such as hypocalcemia and RLN palsy by avoiding unnecessary bilateral CCND through appropriate CCND extent.

https://doi.org/10.12701/yujm.2020.00122

Table 2. The diagnostic accuracy for determination of central lymph node (LN) metastasis by surgeon using inspection and palpation (n=127)

Variable	Permanent pathology after surgery	
	Metastatic LN (+) (n = 64)	Metastatic LN (–) (n = 63)
Suspicious for metastatic LN determined by surgeon (n = 28)	26 (92.9)	2 (7.1)
Normal LN determined by surgeon (n = 99)	38 (38.4)	61 (61.6)

Values are presented as number (%).

Table 3. The diagnostic accuracy for determination of central lymph node (LN) metastasis by surgeon in cases without thyroiditis (n=77)

Variable	Permanent pathology after surgery	
	Metastatic LN (+) (n = 35)	Metastatic LN (–) (n = 42)
Suspicious for metastatic LN determined by surgeon (n = 12)	12 (100)	0
Normal LN determined by surgeon (n = 65)	23 (35.4)	42 (64.6)

Values are presented as number (%).

However, surgeons find it challenging to decide whether to perform prophylactic CCND and determine the extent of CCND (ipsilateral/bilateral). LN evaluation using cervical USG is highly dependent on the examiner, as the diagnostic rate of USG for central cervical LN metastasis is as low as 20%–30% and those of other radiological examinations such as CT, MRI, and positron emission tomography-CT are reported to be as low as 30%–40% [17,18].

Frozen biopsy during thyroid surgery is useful to diagnose ambiguous thyroid cancer, confirm LN metastasis, and determine parathyroid gland histology. It also provides useful information to determine surgery extent. In our previous study, ipsilateral LN metastasis was the most potent high-risk factor for contralateral LN metastasis, suggesting that bilateral LN involvement is likely in these cases [7]. Therefore, total thyroidectomy and bilateral CCND may be good treatment options for multiple ipsilateral LN metastases on frozen section biopsy in patients with unilateral PTC to reduce the local recurrence rate by excising hidden metastatic LNs. However, frozen section biopsies require a clinically experienced pathologist and additional staff, along with increased cost and a minimum of 20–30 additional minutes for intraoperative examination. While waiting for frozen biopsy results, patients continue under extended anesthesia; prolonged operation time may have negative effects, especially in patients with comorbidities.

We have noted hardness or infiltration as a feature of metastatic LN from experience [19]. If the LN was not hard and enlarged, it was more likely to be reactive LN due to thyroiditis, as metastatic LNs are hard even if small. Black-colored LNs are not highly associated with metastasis. Because benign reactive LNs can also become large or discolored, enlargement or discoloration is not a direct feature of metastatic LNs. Although the hardness criterion was fairly subjective, we considered hardness greater than that of rubber (score > 6 of 10, where 10 is the hardest) to be suspicious. The more LNs surgeons palpate, the more clearly they could feel the difference. Benign LNs became softer when palpated while suspicious metastatic LNs remained firm even with continued palpation. As described in this study, surgeons can palpate and inspect all LNs after CCND and compare the results to the biopsy findings. The repetitive feedback will establish individual criteria based on the hardness for suspicious LNs.

In this study, it was difficult to distinguish between micrometastasis and benign LNs because the ratio of micrometastases was high and the metastatic LNs were small (mean size, 0.28 ± 0.24 cm). Therefore, the sensitivity and NPV were low and surgeon inspection and palpation had limitations. However, metastatic LNs with macrometastasis or extranodal extension were easier to distinguish from benign LNs. Of the 38 patients with false-negative results (38.4%), 29 (76.3%) had micrometastasis and low-risk nodal disease. Therefore, the clinical significance of LN metastasis in false-negative cases may not be significant as it is likely to be low-risk LN disease. In cases with a strong belief of metastasis in the suspicious LN (large, hard, multiple LNs, or extranodal extension) by palpation, we recommend total thyroidectomy and both CCND.

Recently, extranodal extension has been reported as a high-risk factor associated with disease-free survival, cause-specific survival, recurrence, and metastasis [20,21]. It is the most important nodal risk factor as patients with extranodal extension are associated with disease progression showing high thyroglobulin, nodal persistence, and systemic disease. Two patients (both excluded from this study) who underwent modified radical neck dissection due to lateral LN metastasis during this period had LN metastasis with extranodal extension. All were suspected to be metastasis by the

palpation method and all LNs biopsy results were confirmed to be metastases.

Approximately 40% of patients in this study had thyroiditis, with a large number of reactive LNs due to inflammatory reactions. Therefore, it is not easy to evaluate metastatic LNs by intraoperative palpation or preoperative USG in patients with thyroiditis. In this study, the sensitivity, specificity, PPV, and NPV of LN evaluation based on the surgeon's inspection and palpation were not reliable or accurate in patients with thyroiditis. However, in those without thyroiditis, the specificity and PPV of evaluation by LN palpation were 100%. Therefore, LN evaluation using inspection and palpation may be useful in identifying metastasis in patients suspected of LN metastasis, especially in patients without thyroiditis.

Surgeon inspection and confirmation of each LN is helpful not only to assess whether metastatic LN is present but also to determine any unintentional removal of the parathyroid gland (incidental parathyroidectomy). It is important to reduce the incidence of permanent hypoparathyroidism by autotransplantation if unintended parathyroid removal is found during the inspection.

Our study has some limitations. First, there may be errors in the accuracy of the test because not all LNs were examined individually. Second, there is a limit to using judgment by palpation as an absolute criterion because it is difficult to establish objective criteria for hardness; thus, it requires subjective judgment. Third, LN evaluation by this method is difficult before CCND, thereby lowering the sensitivity. In this study, a single surgeon performed nodal palpation, and we did not assess interobserver variation in a blinded fashion. The determination of LNs by surgeon palpation may be helpful to some extent; however, it should be confined to an auxiliary diagnostic method due to some limitations.

The determination of central LN metastasis by surgeon's inspection and palpation could be used to evaluate LNs owing to its high specificity and PPV, especially for macrometastasis or high-risk LN disease.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: HYP, WHK, HJK, JYP; Data curation: WWK, JHJ, JYP; Formal analysis: WWK, HYP; Methodology: JL; Investigation: WHK, HJK, JYP; Resources: HYP; Software: JYP; Supervision: HYP; Validation: WHK, HJK, JYP; Project administration: WHK; Visualization: RPT; Writing-original draft: WWK; Writing-review & editing: WWK, JHJ, RPT.

ORCID

Wan Wook Kim, https://orcid.org/0000-0002-7363-5889
Jeeyeon Lee, https://orcid.org/0000-0003-1826-1690
Jin Hyang Jung, https://orcid.org/0000-0003-2607-1686
Ho Yong Park, https://orcid.org/0000-0002-4380-0089
Won Hwa Kim, https://orcid.org/0000-0001-7137-9968
Hye Jung Kim, https://orcid.org/0000-0002-0263-0941
Ji-Young Park, https://orcid.org/0000-0002-7571-1064
Ralph P. Tufano, https://orcid.org/0000-0002-2219-3208

References

1. Ahn HS, Kim HJ, Welch HG. Korea's thyroid-cancer "epidemic": screening and overdiagnosis. N Engl J Med 2014;371:1765–7.
2. Lim YC, Choi EC, Yoon YH, Kim EH, Koo BS. Central lymph node metastases in unilateral papillary thyroid microcarcinoma. Br J Surg 2009;96:253–7.
3. Ito Y, Kudo T, Kobayashi K, Miya A, Ichihara K, Miyauchi A. Prognostic factors for recurrence of papillary thyroid carcinoma in the lymph nodes, lung, and bone: analysis of 5,768 patients with average 10-year follow-up. World J Surg 2012;36:1274–8.
4. Adam MA, Pura J, Goffredo P, Dinan MA, Reed SD, Scheri RP, et al. Presence and number of lymph node metastases are associated with compromised survival for patients younger than age 45 years with papillary thyroid cancer. J Clin Oncol 2015;33:2370–5.
5. Hwang HS, Orloff LA. Efficacy of preoperative neck ultrasound in the detection of cervical lymph node metastasis from thyroid cancer. Laryngoscope 2011;121:487–91.
6. Ahn JE, Lee JH, Yi JS, Shong YK, Hong SJ, Lee DH, et al. Diagnostic accuracy of CT and ultrasonography for evaluating metastatic cervical lymph nodes in patients with thyroid cancer. World J Surg 2008;32:1552–8.
7. Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, et al. Preoperative ultrasonographic examination for lymph node metastasis: usefulness when designing lymph node dissection for papillary microcarcinoma of the thyroid. World J Surg 2004;28:498–501.
8. Adam MA, Thomas S, Youngwirth L, Hyslop T, Reed SD, Scheri RP, et al. Is there a minimum number of thyroidectomies a surgeon should perform to optimize patient outcomes? Ann Surg 2017;265:402–7.
9. Kim WW, Park HY, Jung JH. Surgical extent of central lymph

https://doi.org/10.12701/yujm.2020.00122

node dissection in clinically node-negative papillary thyroid cancer. Head Neck 2013;35:1616–20.
10. Zaydfudim V, Feurer ID, Griffin MR, Phay JE. The impact of lymph node involvement on survival in patients with papillary and follicular thyroid carcinoma. Surgery 2008;144:1070–7.
11. Yang L, Shen W, Sakamoto N. Population-based study evaluating and predicting the probability of death resulting from thyroid cancer and other causes among patients with thyroid cancer. J Clin Oncol 2013;31:468–74.
12. Barczyński M, Konturek A, Stopa M, Nowak W. Prophylactic central neck dissection for papillary thyroid cancer. Br J Surg 2013;100:410–8.
13. Moreno MA, Edeiken-Monroe BS, Siegel ER, Sherman SI, Clayman GL. In papillary thyroid cancer, preoperative central neck ultrasound detects only macroscopic surgical disease, but negative findings predict excellent long-term regional control and survival. Thyroid 2012;22:347–55.
14. Sancho JJ, Lennard TW, Paunovic I, Triponez F, Sitges-Serra A. Prophylactic central neck disection in papillary thyroid cancer: a consensus report of the European Society of Endocrine Surgeons (ESES). Langenbecks Arch Surg 2014;399:155– 63.
15. Wang TS, Evans DB, Fareau GG, Carroll T, Yen TW. Effect of prophylactic central compartment neck dissection on serum thyroglobulin and recommendations for adjuvant radioactive iodine in patients with differentiated thyroid cancer. Ann Surg Oncol 2012;19:4217–22.
16. Hartl DM, Leboulleux S, Al Ghuzlan A, Baudin E, Chami L, Schlumberger M, et al. Optimization of staging of the neck with prophylactic central and lateral neck dissection for papillary thyroid carcinoma. Ann Surg 2012;255:777–83.
17. Jeong HS, Baek CH, Son YI, Choi JY, Kim HJ, Ko YH, et al. Integrated 18F-FDG PET/CT for the initial evaluation of cervical node level of patients with papillary thyroid carcinoma: comparison with ultrasound and contrast-enhanced CT. Clin Endocrinol (Oxf) 2006;65:402–7.
18. Weber AL, Randolph G, Aksoy FG. The thyroid and parathyroid glands. CT and MR imaging and correlation with pathology and clinical findings. Radiol Clin North Am 2000;38:1105–29.
19. Finn S, Toner M, Timon C. The node-negative neck: accuracy of clinical intraoperative lymph node assessment for metastatic disease in head and neck cancer. Laryngoscope 2002;112:630–3.
20. Lango M, Flieder D, Arrangoiz R, Veloski C, Yu JQ, Li T, et al. Extranodal extension of metastatic papillary thyroid carcinoma: correlation with biochemical endpoints, nodal persistence, and systemic disease progression. Thyroid 2013;23:1099–105.
21. Wu MH, Shen WT, Gosnell J, Duh QY. Prognostic significance of extranodal extension of regional lymph node metastasis in papillary thyroid cancer. Head Neck 2015;37:1336–43.

Yeungnam University Journal of Medicine
YUJM

Original article
eISSN 2384-0293
Yeungnam Univ J Med 2020;37(4):308-313
https://doi.org/10.12701/yujm.2020.00185

Clinical outcomes of hysterectomy for benign diseases in the female genital tract: 6 years' experience in a single institute

Hyo-Shin Kim[1], Yu-Jin Koo[2], Dae-Hyung Lee[2]

[1]Department of Obstetrics and Gynecology, Yeungnam University Hospital, Daegu, Korea
[2]Department of Obstetrics and Gynecology, Yeungnam University College of Medicine, Daegu, Korea

Received: March 17, 2020
Revised: April 7, 2020
Accepted: April 14, 2020

Corresponding author:
Yu-Jin Koo
Department of Obstetrics and Gynecology, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-620-3433
Fax: +82-53-654-0676
E-mail: yujinkoo@yu.ac.kr

Background: Hysterectomy is one of the major gynecologic surgeries. Historically, several surgical procedures have been used for hysterectomy. The present study aims to evaluate the surgical trends and clinical outcomes of hysterectomy performed for benign diseases at the Yeungnam University Hospital.
Methods: We retrospectively reviewed patients who underwent a hysterectomy for benign diseases from 2013 to 2018. Data included the patients' demographic characteristics, surgical indications, hysterectomy procedures, postoperative pathologies, and perioperative outcomes.
Results: A total of 809 patients were included. The three major indications for hysterectomy were uterine leiomyoma, pelvic organ prolapse, and adenomyosis. The most common procedure was total laparoscopic hysterectomy (TLH, 45.2%), followed by open hysterectomy (32.6%). During the study period, the rate of open hysterectomy was nearly constant (29.4%–38.1%). The mean operative time was the shortest in the single-port laparoscopic assisted vaginal hysterectomy (LAVH, 89.5 minutes), followed by vaginal hysterectomy (VH, 96.8 minutes) and TLH (105 minutes). The mean decrease in postoperative hemoglobin level was minimum in single-port LAVH (1.8 g/dL) and VH (1.8 g/dL). Conversion to open surgery or multi-port surgery occurred in five cases (0.6%). Surgical complications including wound dehiscence, organ injuries, and conditions requiring reoperation were observed in 52 cases (6.4%).
Conclusion: Minimally invasive approach was used for most hysterectomies for benign diseases, but the rate of open hysterectomy has mostly remained constant. Single-port LAVH and VH showed the most tolerable outcomes in terms of operative time and postoperative drop in hemoglobin level in selected cases.

Keywords: Female genital disease; Gynecological surgical procedures; Hysterectomy; Minimally invasive surgical procedures

Introduction

Hysterectomy is one of the major gynecologic surgeries. In Korea, more than 40,000 cases of hysterectomy are performed each year and it was ranked 6th among all main surgeries in Korea in 2017 according to the data by Korean National Health Insurance Service [1]. There are three major types of hysterectomy procedures: open abdominal surgery, vaginal surgery, and endoscopic surgery.

With the growing desire for minimally invasive surgery (MIS), endoscopic approaches, such as total laparoscopic hysterectomy (TLH), laparoscopy-assisted vaginal hysterectomy (LAVH), and robot-assisted laparoscopic hysterectomy (RALH), have become prevalent in the field of hysterectomy. In particular, RALH is a new minimally invasive technique that has some theoretical advantages including improved visualization through three-dimensional imaging, greater precision, and more accurate control of instrumentation in addition to improved ergonomics for the surgeons [2].

In June 2017, the American College of Obstetricians and Gynecologists (ACOG) published a committee opinion, presenting vaginal hysterectomy (VH) as an approach of choice and recommending laparoscopic hysterectomy (including LAVH) as an alternative when a VH is not indicated or feasible [3]. The choice of surgical approach for gynecologic malignancy might be limited; however, for benign diseases, various surgical approaches can be selected depending on the individual case. This study aimed to review the trends in surgical procedures of hysterectomy for benign diseases and to evaluate the surgical outcomes of each procedure performed in our center over a 6-year period.

Materials and methods

We retrospectively enrolled women who underwent hysterectomy for a benign genital tract disease during a 6-year period between January 1, 2013, and October 31, 2018, at the Department of Obstetrics and Gynecology of Yeungnam University Hospital, Daegu, Korea. The study was approved by the Institutional Review Board (IRB) at Yeungnam University Hospital (IRB No: 2019-12-050). Medical records of the participants, including outpatient records, imaging and laboratory reports, surgical records, postoperative progress notes, and pathologic reports were reviewed. Factors examined included patient's clinical characteristics, symptoms, preoperative diagnosis, surgical modes, concurrent procedures with hysterectomy, postoperative diagnosis, and surgical outcomes including complications.

Laparoscopic hysterectomy is typically classified into two categories, namely TLH and LAVH, depending on the extent of the procedure performed laparoscopically or vaginally. In TLH, the entire procedure, except the removal of the uterus, is performed laparoscopically. LAVH differs from TLH in that the procedures, including ligation of the uterine vessels, colpotomy, and suturing of the vaginal vault, are done using the vaginal approach. In our hospital, TLH has been performed only by multi-port approach, and meanwhile, LAVH has been performed through either a multi-port or a single-port approach, since a single-port hysterectomy was first introduced in 2018. In a laparoscopic multi-port surgery, four holes were made as follows: an umbilical hole for laparoscope and a suprapubic and two lateral holes for instruments. In a single-port surgery, a surgeon made an incision of 2 cm at the umbilicus and used a commercial multichannel port, Glove port (Nelis, Bucheon, Korea) to insert a rigid 5-mm 30° laparoscopic scope and two rigid 5-mm instruments. In our hospital, the DaVinci Si surgical system was introduced on September 6, 2013. RALH was also performed by either TLH or LAVH and by either a multi-port or a single-port approach. The hysterectomy of this present study was performed by a total of seven operators, and their surgical experience in hysterectomy varied from 3 years to over 20 years. RALH was performed by three operators and single-port LAVH was performed by a single operator.

The operative time was measured from the time of skin incision to the time of skin closure completion. In the case of RALH, the docking time from the port placement to the docking of the robot was included in the operative time. The postoperative hemoglobin (Hb) drop was calculated by subtracting the Hb level at the first postoperative day from the preoperative Hb level. For patients who received intra- or postoperative transfusion, the lowest Hb level measured before transfusion was used as postoperative Hb level. The patients who received transfusion without the Hb test were excluded from the calculation of the Hb drop. Only the cases with wound defect requiring resuturing were reported as complications of wound dehiscence.

Hospital stay was measured from the day after surgery to the day of discharge. Before 2016, patients who underwent laparoscopic hysterectomy were generally discharged on the 4–5th postoperative day, but after 2017, they were discharged on the 2nd postoperative day in line with on our hospital policy. For open surgery with pfannenstiel skin incision, patients are usually discharged on the 4–6th postoperative day and on the 5–7th postoperative day in the case of low-midline incision. Patients who have undergone VH are discharged on the 4–5th postoperative day.

Results

A total of eight hundred and nine patients were included in the analysis. The mean age of the patients was 53.4 years and the mean body mass index (BMI) was 24.6 kg/m^2 (Table 1). Patients with previous abdominal surgery accounted for 37.6%. The three most common symptoms were abnormal uterine bleeding (28.7%), protruding prolapse of pelvic organs (17.7%), and abdominal pain or discomfort (16.1%). The common indications for hysterectomy, namely preoperative diagnosis, were uterine leiomyoma (47.5%), pelvic organ prolapse (17.7%), and adeno-

Table 1. Clinical characteristics of the patients and surgical indications for hysterectomy (n=809)

Clinical characteristic	Value
Age (yr)	53.4 (30–88)
Gravidity (no. of times)	3.8 (0–15)
Parity (no. of times)	2.2 (0–8)
Body mass index (kg/m^2)	24.6 (16.4–40.4)
History of abdominopelvic surgery	304 (37.6)
Chief complaints	
No symptom	200 (24.7)
Abnormal uterine bleeding	232 (28.7)
Protruding prolapse of pelvic organs	143 (17.7)
Abdominal pain or discomfort	130 (16.1)
Dysmenorrhea	47 (5.8)
Palpable pelvic mass	21 (2.6)
Urinary symptoms	19 (2.3)
Vaginal discharge	9 (1.1)
Others	8 (1.0)
Surgical indications[a]	
Uterine leiomyoma	384 (47.5)
Pelvic organ prolapse	143 (17.7)
Adenomyosis or adenomyoma	108 (13.3)
Cervical intraepithelial neoplasia	71 (8.8)
Adnexal lesion	62 (7.7)
Endometrial hyperplasia or polyp	20 (2.5)
Postpartum uterine atony	7 (0.9)
Others	
Hematometra or hydrometra	3 (0.4)
Placenta accreta, increta	3 (0.4)
Abnormal uterine bleeding	2 (0.2)
Pelvic actinomycosis	2 (0.2)
Pelvic endometriosis	2 (0.2)
Hydatidiform mole	1 (0.1)
Tubo-ovarian abscess	1 (0.1)

Values are presented as mean (range) or number (%).
[a]A main diagnosis that was assumed clinically before hysterectomy was described.

Table 2. Surgical procedures for hysterectomy and postoperative diagnosis (n=809)

Surgical procedure	No. (%)
Hysterectomy procedure	
TAH	264 (32.6)
TLH	366 (45.2)
LAVH	40 (4.9)
Robot-assisted	
Robotic TLH	5 (0.6)
Robotic LAVH	3 (0.4)
Vaginal hysterectomy	131 (16.2)
Port number for laparoscopic or robotic surgery	
Single-port	15/414[a] (3.6)
Multi-port	399/414[a] (96.4)
Procedures combined with hysterectomy	
Bilateral salpingoophorectomy	259 (32)
Colporrhaphy	138 (17.1)
Unilateral salpingoophorectomy	71 (8.8)
Ovarian cystectomy	16 (2)
Others	20 (2.5)
Postoperative diagnosis	
Uterine leiomyoma	377 (46.6)
Prolapsed pelvic organs	143 (17.7)
Adenomyosis or adenomyoma	128 (15.8)
Cervical intraepithelial neoplasia	72 (8.9)
Endometrial or endocervical polyp	7 (0.9)
Uterine atony	7 (0.9)
Pelvic inflammatory disease	4 (0.5)
Endometrial hyperplasia	3 (0.4)
Placenta increta, accreta	3 (0.4)
Adnexal lesion	60 (7.4)
Unremarkable[b]	2 (0.2)
Others	
Adenomatoid tumor	1 (0.1)
STUMP	1 (0.1)
Hydatidiform mole	1 (0.1)

TAH, total abdominal hysterectomy; TLH, total laparoscopic hysterectomy; LAVH, laparoscopy-assisted vaginal hysterectomy; STUMP, smooth muscle tumor of uncertain malignant potential.
[a]Denominators are the number of the total case of laparoscopic and robotic surgery. [b]Endometrial hyperplasia was preoperatively expected, but the pathologic diagnosis was normal.

myosis or adenomyoma (13.3%).

The most frequently performed procedure was TLH (45.2%), followed by total abdominal hysterectomy (TAH, 32.6%), VH (16.2%), LAVH (4.9%), robotic TLH (0.6%), and robotic LAVH (0.4%) (Table 2). In three cases (0.4%), subtotal hysterectomy was done unexpectedly due to technical challenges of the total hysterectomy. Among 414 cases of laparoscopic or robotic surgery, 15 cases (3.6%) were done using the single-port approach (11 cases of LAVH, two cases of robotic TLH, and two cases of robotic LAVH). The pathologic result confirmed the postoperative diagnosis as uterine leiomyoma or adenomyosis in more than half of the patients (505 cases, 62.4%).

Mean operative time was shortest in single-port LAVH (89.5 minutes), followed by VH (96.8 minutes) and TLH (105 minutes) (Table 3). Mean decrease in postoperative Hb level was also minimal in single-port LAVH (1.8 g/dL) and VH (1.8 g/dL). The average number of hospital days was 2.2 days (range, 2–3 days) in single-port LAVH, 3.5 days (range, 2–13 days) in TLH, 5.4 days (range, 2–18 days) in multi-port LAVH, 6.3 days (range, 2–25 days) in RALH, 6.3 days (range, 2–38 days) in VH, and 7.4

https://doi.org/10.12701/yujm.2020.00185

Table 3. Operative time and postoperative hemoglobin drop according to the surgical procedures

Surgical outcome	Mean (range)
Operative time (min)	
TAH	137.1 (65–290)
LAVH	
Single-port	89.5 (70–125)
Multi-port	181.2 (80–495)
TLH	105.0 (60–250)
Robot	
Single-port	133.8 (75–240)
Multi-port	273.8 (215–325)
Vaginal hysterectomy	96.8 (60–170)
Hemoglobin drop after surgery (g/dL)	
TAH	1.9 (0–8.5)
LAVH	
Single-port	1.8 (0–3.6)
Multi-port	2.6 (0.9–5.5)
TLH	1.9 (0–5.9)
Robot	
Single-port	3.1 (1.9–4.9)
Multi-port	2.4 (1.6–4.1)
Vaginal hysterectomy	1.8 (0–6.1)

TAH, total abdominal hysterectomy; TLH, total laparoscopic hysterectomy; LAVH, laparoscopy-assisted vaginal hysterectomy.

Table 4. Perioperative outcomes including surgical complications (n=809)

Perioperative outcome	Value
Hospital stay (day)	5.3 (2–59)
Conversion to open surgery	4 (0.5)
Conversion from single-port to multi-port surgery	1 (0.1)
Transfusion due to surgical bleeding	61 (7.5)
Intra- and postoperative complications	52 (6.4)
Reoperation	
Hematoma removal and bleeding control	6 (0.7)
Wound dehiscence repair[a]	5 (0.6)
Ureter injury repair	4 (0.5)
Fistula repair	3 (0.4)
Incisional hernia repair	2 (0.2)
Bowel injury repair	1 (0.1)
Wound dehiscence[b]	
Low-midline skin incision site	6/109[c] (5.5)
Pfannenstiel skin incision site	5/153[c] (3.3)
Vaginal stump	4/809[c] (0.5)
Perineum after posterior colporrhaphy	1/138[c] (0.7)
Fistula	
Ureterovaginal	2 (0.2)
Sigmoid colovaginal	1 (0.1)
Organ injury	
Bladder	5 (0.6)
Ureter	5 (0.6)
Bowel	3 (0.4)
Bladder and ureter	1 (0.1)

Values are presented as mean (range) or number (%).
[a]The cases includes only the cases that required resuturing in the operating room under general anesthesia. [b]The cases includes only the cases that required resuturing. [c]Denominator refers to the number of the cases of low-midline skin incision, pfannenstiel skin incision, colpotomy, and posterior colporrhaphy, respectively.

days (range, 2–59 days) in TAH. In the entire group, the mean length of hospital stay was 5.3 days (Table 4).

Endoscopic surgery was converted to open surgery in four cases (0.5%), all from TLH to open surgery. Two of the converted cases were due to severe pelvic adhesion, and two other cases due to poor surgical exposure caused by huge uterine mass. Single-port surgery was converted to multi-port surgery in a case (0.1%), which was a conversion from single-port RALH to multi-port TLH due to severe pelvic adhesion. Among a total of five patients who experienced conversion, four were overweighted (BMI, 23–24.9 kg/m^2) or obese (BMI, ≥ 25 kg/m^2).

Transfusion due to surgical bleeding was done in 7.5% (Table 4). Intra- and postoperative complications were reported in 52 cases, including wound dehiscence, organ injury, fistula, wound hematoma or infection, bowel obstruction, incisional hernia, and thromboembolism. Twenty-one patients (2.6%) experienced reoperation due to complications: hematoma removal and bleeding control in six, wound dehiscence repair in five, ureter injury repair in four, fistula repair in three, incisional hernia repair in two, and bowel injury repair in one. The most common complication was wound dehiscence (2%), and a total of four cases with vaginal stump dehiscence were reported in TLH. Urinary injury and bowel injury occurred in 1.4% and 0.4%, respectively. Of the five cases of bladder injury, four were detected intraoperatively and treated through immediate primary repair. The other one was detected on 2nd postoperative day and received reoperation for surgical repair by the urology department. In the case of ureter injury, all five were detected on the days after surgery. One out of five underwent ureteral stent insertion, while the other four received ureteroneocystostomy. In the case of patients with both bladder and ureter injury, as was detected intraoperatively, immediate primary repair of bladder and ureteroneocystostomy were performed. Among three cases of bowel injury, two were detected intraoperatively, and an immediate primary repair was performed. Meanwhile, the other one was found on the 7th postoperative day and underwent a laparotomy for primary repair of rectal perforation and ileostomy. Two cases of ureterovaginal fistula occurred after multi-port LAVH and were treated through ureteral stent inser-

tion or ureteroneocystostomy. A case of sigmoid colovaginal fistula developed after TLH and was repaired by the colorectal surgery department.

The complication rate was highest in multi-port LAVH (7/29, 24.1%), followed by RALH (1/8, 12.5%), TAH (27/264, 10.2%), TLH (18/366, 4.9%), VH (4/131, 3.1%), and single-port LAVH (0/11). Likewise, the rate of reoperation was highest in multi-port LAVH (4/29, 13.8%), but no case of reoperation was found in both VH and single-port LAVH. None of the patients died as a result of hysterectomy.

Discussion

Uterine leiomyoma is the most common indication for hysterectomy and is also the most common disease that is revealed on the postoperative pathologic result [1]. According to data by the Korean National Health Insurance Service, hysterectomy due to uterine leiomyoma was the 20th most frequent operation among surgeries due to a single disease in 2017 [1]. That was the only gynecological surgery on the list of the top 20.

Fig. 1 shows a surgical mode for hysterectomy by year in a total of 809 patients. MIS such as TLH, LAVH, RALH, and VH has been performed approximately in two-thirds of the cases but the rate of open hysterectomy has remained almost constant (29.4%–38.1%) without noticeable decrease. This is probably because TAH is still preferable to MIS in some cases with huge uterine mass, severe pelvic adhesion, risk of malignancy, and patient's medical diseases. In addition, cases of cesarean hysterectomy, which cannot be replaced by MIS, were included in the cases of TAH.

A 2015 Cochrane meta-analysis reviewed randomized controlled trials and compared the clinical outcomes of different surgical approaches to hysterectomy for benign gynecological disease [4]. In the result, there were no significant differences in most of the surgical outcomes between TLH and LAVH, including hospital stay, intraoperative visceral injury, conversion to open surgery, vaginal cuff infection, transfusion, etc. The only significant difference was in operation time; LAVH (115.1 minutes) had a shorter operation time than TLH (140.4 minutes) (mean difference, −23.3 minutes; 95% confidence interval, −10.0 to −40.6). No evidence of a difference was found between single-port and multi-port laparoscopic hysterectomy for intraoperative complication, operation time, and hospital stay. However, the authors found that laparoscopic hysterectomy was associated with more urinary tract injuries than abdominal hysterectomy was. The incidence rate of urinary tract injury was 4.2% in TLH and 3.3% in LAVH, with no statistically significant difference. In our study, urinary tract injury was the most commonly encountered organ injury. It occurred in 1.9% of TLH (7 out of 366), but in 10% (4 out of 40) of LAVH, which is relatively high. This high incidence of urinary tract injury in LAVH group seems to be related with the surgeon's operative skill rather than the mode of hysterectomy because all events in LAVH group were occured in multi-port surgery by a single surgeon. No case of urinary tract injury was found in both VH and TAH.

In this study, single-port LAVH and VH showed the best surgical outcomes in terms of operation time, postoperative Hb drop, and surgical complication, although the number of cases was small and selection bias maybe exist. Compared to the results from the previously reported studies regarding LAVH [4-6], our

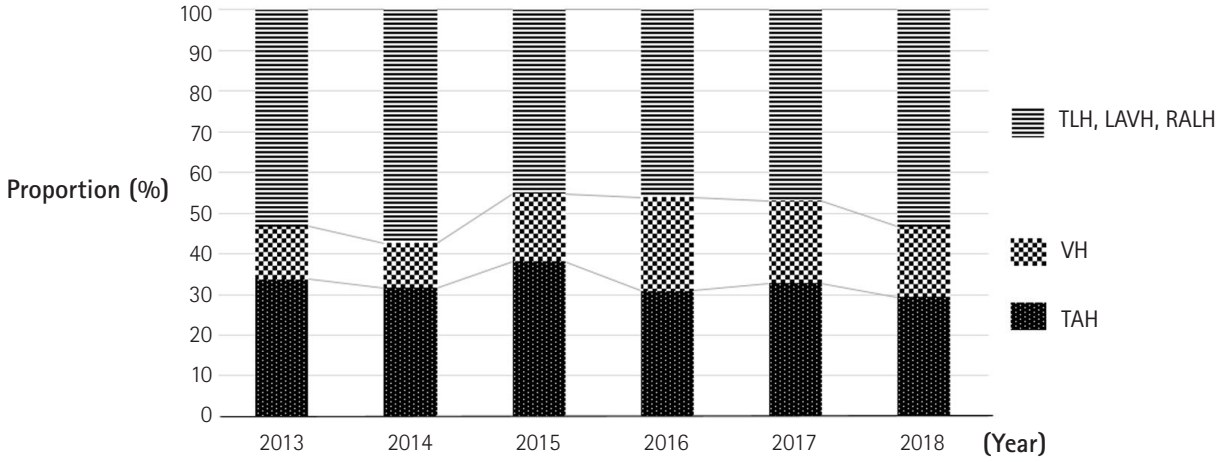


Fig. 1. Trend in procedures of hysterectomy for benign diseases during 6 years of experience. TLH, total laparoscopic hysterectomy; LAVH, laparoscopy-assisted vaginal hysterectomy; RALH, robot-assisted laparoscopic hysterectomy; VH, vaginal hysterectomy; TAH, total abdominal hysterectomy.

https://doi.org/10.12701/yujm.2020.00185

data shows tolerable surgical outcomes. In a German retrospective study [5], the mean operation time and postoperative Hb drop were 137 minutes and 1.8 g/dL, respectively, for LAVH (the port number was not described in the study). Another study reported 91.2 minutes of the mean operation time and 1.6 g/dL of Hb drop for single-port LAVH in a prospective setting [6]. The authors have suggested that both single-port TLH and single-port LAVH are feasible with similar surgical outcomes but single-port LAVH may be preferred in patients with a uterus with a large lower uterine segment.

Since single-port surgery has been introduced recently in our hospital and a surgeon had already become proficient in LAVH, it is no wonder that single-port LAVH showed the good clinical outcomes. Moreover, a surgeon may have performed single-port LAVH or VH in highly-selected cases, such as uterus with small masses and no adhesion. In other words, if the case is well-selected, single-port LAVH and VH are safe and profitable for benign uterine disease. In the case of VH, the surgical outcome might be undervalued in our study. We usually perform VH in patients with uterine prolapse; therefore, the good surgical outcomes might be offset by several factors such as patients' old age, medical disease, and concurrent procedures (e.g., colporrhaphy). Given the increasing global need for MIS and its possible cosmetic advantage, it is speculated that single-port LAVH has clear benefits and will be more popular. Therefore, it is necessary for clinicians to evaluate the trend in surgical approaches performed in their institute and to determine the clinical outcomes according to the different surgical procedures.

The present study has several limitations. First, it is a retrospective study. Second, the important confounding factors that can affect clinical outcomes, such as the surgeon's skill and the patient's clinical characteristics, were not analyzed according to the type of surgical approaches. Third, the number of patients in the subgroups of LAVH and RALH were too small, which precludes definite conclusions from being drawn. Future studies, with larger sample sizes and adjustments for potential confounders, are warranted to evaluate the significant differences between approaches.

In conclusion, the minimally invasive approach is used in most hysterectomies for benign diseases, but the rate of open hysterectomy has remained almost constant in our hospital. Single-port LAVH and VH seem to be the most feasible and safe, in terms of short operative time, minimal decrease in postoperative Hb level, and low incidence of complication in selected cases. Although the number of single-port surgeries was small, their remarkable superior outcomes suggest that single-port LAVH is potentially one of the best options for benign uterine disease.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: YJK; Data curation: HSK; Formal analysis: HSK, YJK; Project administration: YJK; Supervision: DHL; Writing-original draft: HSK; Writing-review & editing: YJK.

ORCID

Hyo-Shin Kim, https://orcid.org/0000-0002-8369-417X
Yu-Jin Koo, https://orcid.org/0000-0002-5114-8000
Dae-Hyung Lee, https://orcid.org/0000-0002-0219-0317

References

1. Korea National Health Insurance Service (NHIS). The main surgery statistical yearbook for 2017 [Internet]. Wonju: NHIS; 2018 [cited 2020 Mar 10]. https://www.nhis.or.kr/menu/boardRetriveMenuSet.xx?menuId=F3326.
2. Nevis IF, Vali B, Higgins C, Dhalla I, Urbach D, Bernardini MQ. Robot-assisted hysterectomy for endometrial and cervical cancers: a systematic review. J Robot Surg 2017;11:1–16.
3. Committee on Gynecologic Practice. Committee opinion no. 701: choosing the route of hysterectomy for benign disease. Obstet Gynecol 2017;129:e155–9.
4. Aarts JW, Nieboer TE, Johnson N, Tavender E, Garry R, Mol BW, et al. Surgical approach to hysterectomy for benign gynaecological disease. Cochrane Database Syst Rev 2015;(8):CD003677.
5. Elessawy M, Schollmeyer T, Mettler L, Jonat W, Schem C, von Hehn U, et al. The incidence of complications by hysterectomy for benign disease in correlation to an assumed preoperative score. Arch Gynecol Obstet 2015;292:127–33.
6. Song T, Kim MK, Kim ML, Jung YW, Yun BS, Seong SJ. A randomized comparison of laparoendoscopic single-site hysterectomies: total laparoscopic hysterectomy versus laparoscopically assisted vaginal hysterectomy. J Laparoendosc Adv Surg Tech A 2015;25:541–7.

Yeungnam University Journal of Medicine
YUJM

Original article
eISSN 2384-0293
Yeungnam Univ J Med 2020;37(4):314-320
https://doi.org/10.12701/yujm.2020.00129

Risk factors affecting amputation in diabetic foot

Jun Ho Lee[1], Ji Sung Yoon[2], Hyoung Woo Lee[2], Kyu Chang Won[2], Jun Sung Moon[2], Seung Min Chung[3], Yin Young Lee[3]

[1]Republic of Korea Army, Hwacheon, Korea
[2]Division of Endocrinology and Metabolism, Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea
[3]Division of Endocrinology and Metabolism, Department of Internal Medicine, Yeungnam University Hospital, Daegu, Korea

Received: March 4, 2020
Revised: April 9, 2020
Accepted: April 14, 2020

Corresponding author:
Ji Sung Yoon
Division of Endocrinology and Metabolism, Department of Internal Medicine, Yeungnam University College of Medicine, 170 Hyunchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-620-4049
Fax: +82-53-623-8006
E-mail: jsyoon9@ynu.ac.kr

Background: A diabetic foot is the most common cause of non-traumatic lower extremity amputations (LEA). The study seeks to assess the risk factors of amputation in patients with diabetic foot ulcers (DFU).
Methods: The study was conducted on 351 patients with DFUs from January 2010 to December 2018. Their demographic characteristics, disease history, laboratory data, ankle-brachial index, Wagner classification, osteomyelitis, sarcopenia index, and ulcer sizes were considered as variables to predict outcome. A chi-square test and multivariate logistic regression analysis were performed to test the relationship of the data gathered. Additionally, the subjects were divided into two groups based on their amputation surgery.
Results: Out of the 351 subjects, 170 required LEA. The mean age of the subjects was 61 years and the mean duration of diabetes was 15 years; there was no significant difference between the two groups in terms of these averages. Osteomyelitis (hazard ratio [HR], 6.164; 95% confidence interval [CI], 3.561–10.671), lesion on percutaneous transluminal angioplasty (HR, 2.494; 95% CI, 1.087–5.721), estimated glomerular filtration rate (eGFR; HR, 0.99; 95% CI, 0.981–0.999), ulcer size (HR, 1.247; 95% CI, 1.107–1.405), and forefoot ulcer location (HR, 2.475; 95% CI, 0.224–0.73) were associated with risk of amputation.
Conclusion: Osteomyelitis, peripheral artery disease, chronic kidney disease, ulcer size, and forefoot ulcer location were risk factors for amputation in diabetic foot patients. Further investigation would contribute to the establishment of a diabetic foot risk stratification system for Koreans, allowing for optimal individualized treatment.

Keywords: Amputation; Diabetic foot ulcer; Diabetes mellitus; Risk factors

Introduction

Diabetes is becoming increasingly prevalent worldwide due to aging, physical inactivity, westernized eating habits, population growth, and obesity; consequently, the incidences of diabetic feet are increasing. Diabetic patients are predicted to have a 25% probability of having at least one diabetic foot ulcer during their lifetime. Furthermore, a lower limb amputation due to a diabetic foot is carried out every 30 seconds worldwide, with rates being 30 to 40 times higher for diabetic patients than it is for individuals without the disease [1-3].

The cost of diabetic foot treatment accounts for approximately 25% of a diabetic patient's total hospital costs [4]. To reduce this burden, clinicians should focus on prevention as well as treatment of diabetic foot disease. Needless to say, amputation in patients with diabetic foot disease debilitates their ability to perform ev-

eryday tasks, which negatively affects their quality of life ; therefore, knowledge of the risk factors of diabetic foot amputation is an important issue [5]. Minute observation and prophylactic action for patients at high risk of having a diabetic foot and early detection of foot complications could reduce the occurrence of ulcerations and amputations [6].

The development of a diabetic foot ulcer has multifactorial causes, and its principal factors include: diabetic peripheral neuropathy, infection, peripheral arterial disease, and socioeconomic status [7]. Moreover, various features such as age, smoking, foot deformities, poor glycemic control, ulcer size, hypertension, white blood cell count, and lipid abnormalities have also been reported as risk factors for diabetic foot amputation [8-11]. However, previous studies on the risk factors of diabetic feet indicated inconsistent results. Therefore, the aim of this study was to determine the risk factors of amputation in Korean diabetic foot patients who received standard treatment from one institution.

Materials and methods

1. Subjects and data collection

This study was approved by the Institutional Review Board (IRB) of the Yeungnam University Hospital (IRB No: 2019-03-040). It followed the Declaration of Helsinki on medical protocol and ethics. The patients' personal information was withheld from the researchers.

This case control study involved 425 subjects who were admitted to the Yeungnam University Hospital due to a diabetic foot from January 1, 2010 to December 31, 2018. Due to lack of data, 74 of the 425 subjects were excluded, leaving 351 valid subjects. They were divided into two groups based on their amputation surgery.

2. Clinical information of patients

Medical records, including admission notes, were examined to obtain information on the patients and laboratory results collected during the first day of admission. The independent variables were selected based on previous studies to determine the risk factors of diabetic feet and amputation. Amputation was defined as surgery, which goes beyond the toe level. Minor debridement of soft tissue was not considered as amputation surgery.

Hypertension was defined as the use of anti-hypertensive medication or previously documented diagnoses. Ankle-brachial index (ABI) was calculated by dividing the systolic blood pressure of the ankle divided by the systolic blood pressure of the upper arm of the affected side. The mean value of the ABI of the two groups were compared and subjects with ABI of less than 0.9 were found to be abnormal.

Diabetic peripheral polyneuropathy was identified through the consultation records of the neurology department, electrophysiology studies, the Semmes Weinstein monofilament test, clinical scores (i.e., the Michigan Neuropathy Screening Instrument questionnaire), and medical record reviews. Diabetic retinopathy was identified through ophthalmologic records, including any history of photocoagulation and vitrectomy. Coronary artery disease was defined as any history of myocardial infarction, unstable angina, percutaneous transluminal coronary angioplasty, or coronary artery bypass surgery. Stroke was defined as any history of cerebral infarction or transient cerebral ischemia. Chronic kidney disease was defined as the estimated glomerular filtration rate < 60 mL/min/1.73 m^2, which was calculated using the Modification of Diet in Renal Disease formula: $186 \times (\text{creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742, \text{if female})$. The sarcopenia index (SI) was used to estimate skeletal muscle mass and was derived from the formula serum creatinine value/cystatin C value [12].

Information of previous amputation history was based on orthopedic surgery and plastic surgery department records. The ulcer size was defined as the longest diameter, in centimeters, from one end of an ulcer margin to the other; this was assessed by an endocrinologist at admission. The Wagner classification categorized the diabetic foot ulcers based on the depth and the presence of osteomyelitis or gangrene. A grade ranging from 0 to 5 was assigned to pre-ulcerative lesions; partial superficial ulcers; extensions into tendons, ligaments, fascia, or joint capsules without osteomyelitis; deep ulcers with osteomyelitis; partial forefoot necrosis; and extensive foot gangrene, respectively [13]. The location of the foot ulcers was classified as forefoot, midfoot, and hindfoot. Percutaneous transluminal angioplasty (PTA) was assessed through records of the vascular department while osteomyelitis was assessed through scans such as an magnetic resonance imaging or 3-phase bone scan.

3. Statistical analysis

IBM SPSS version 20.0 (IBM Corp, Armonk, NY, USA) was used for statistical analysis and a Student *t*-test was conducted to compare the quantitative variables of the two groups. A chi-square test was used to analyze the categorial variables, and the risk factors for amputation were determined through stepwise multiple logistic regression analysis. All *p*-values less than 0.05 were considered statistically significant.

Results

The baseline characteristics of both groups are summarized in

Table 1. Univariate analysis of subjects with or without amputation surgery

Variable	Non-amputation group (n = 181)	Amputation group (n = 170)	*p*-value[a]
Age (yr)	61.8 ± 12.6	62.4 ± 10.9	0.642
Body mass index (kg/m^2)	23.2 ± 4.3	23.0 ± 3.6	0.682
SBP (mmHg)	130.7 ± 17.5	130.8 ± 20.5	0.959
DBP (mmHg)	78.9 ± 10.7	77.1 ± 12.8	0.152
Length of hospitalization (day)	51.1 ± 54.9	53.7 ± 58.4	0.660
Duration of diabetes (yr)	15.4 ± 9.5	15.1 ± 10.0	0.821
Ankle-brachial index	1.1 ± 0.2	1.0 ± 0.3	0.027
Size of ulcer (cm)	2.6 ± 2.2	3.6 ± 2.6	0.0001
Sarcopenia index	101.7 ± 101.5	99.9 ± 95.5	0.861
WBC (x10^3/μL)	10.0 ± 5.3	11.2 ± 6.4	0.540
Hemoglobin (g/dL)	11.3 ± 2.0	11.1 ± 2.1	0.526
ESR (mm/hr)	60.2 ± 38.5	66.8 ± 36.3	0.100
hsCRP (mg/L)	6.7 ± 9.5	7.2 ± 9.2	0.603
Glycated hemoglobin (%)	8.9 ± 2.2	9.0 ± 2.3	0.565
Albumin (g/dL)	3.5 ± 0.8	3.4 ± 0.8	0.293
Total cholesterol (mg/dL)	158.0 ± 50.7	155.8 ± 61.6	0.730
Triglyceride (mg/dL)	139.9 ± 100.5	161.6 ± 172.0	0.173
HDL-C (mg/dL)	38.2 ± 15.4	33.8 ± 16.1	0.015
LDL-C (mg/dL)	93.1 ± 36.3	90.5 ± 41.1	0.533
Blood urea nitrogen (mg/dL)	23.2 ± 14.7	22.9 ± 16.7	0.843
Creatinine (mg/dL)	2.0 ± 4.3	1.8 ± 2.1	0.569
eGFR (mL/min/1.73 m^2)	68.7 ± 29.0	62.2 ± 28.6	0.035
ACR (mg/mmol)	761.5 ± 1,690.5	978.6 ± 2,394.2	0.531
Cystatin C (mg/dL)	1.8 ± 1.2	2.0 ± 1.49	0.212

Values are presented as mean ± standard deviation.
SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; ESR, erythrocyte sedimentation rate; hsCRP, high-sensitivity C-reactive protein; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; ACR, albumin creatinine ratio.
[a] *p*-value based on Student *t*-test.

Table 1. The mean age of the subjects and the mean duration of diabetes was 61 and 15 years, respectively; there was no significant difference between the two groups. Among the amputation group, 119 subjects underwent surgery below the ankle, while 51 subjects had above-the-knee or below-the-knee amputations.

The amputation group generally had significantly lower high density lipoprotein cholesterol (HDL-C) and eGFR, but a larger ulcer size. The chi-square test indicated that the amputation group had a higher incidence of previous amputation history (Table 2). The use of statins, antiplatelet drugs, anti-hypertensive drugs, and insulin did not show any significant difference between the two groups.

Among the 351 subjects, 193 showed positive wound culture results. The most common pathogens were *Staphylococcus aureus*, followed by *Pseudomonas aeruginosa*, and *Escherichia coli*. The two groups did not exhibit any differences in terms of pathogens.

According to the Wagner classification, the chi-square test indicated a significant difference between the two groups ($p = 0.0001$), whereas the multivariate regression analysis did not (Table 2).

The non-amputation group consisted of 110, 61, and 10 subjects with forefoot, midfoot, and hindfoot ulcers, respectively. On the other hand, the amputation group had 129, 37, and four subjects with forefoot, midfoot, and hindfoot ulcers, respectively.

The ABI of 126 subjects were each obtained from the non-amputation and the amputation group and 26 and 46 of them had decreased ABI value, respectively. The chi-square test ($p = 0.005$) showed a significance between the two groups and the decreased ABI indicates an increased risk of amputation. Due to insufficient data, the ABI was excluded from the regression analysis.

By means of multivariate regression analysis, the risk factors of amputation were identified as the presence of osteomyelitis of OR 6.164, a lesion on PTA of OR 2.494, a forefoot location of OR 2.475, an ulcer size of OR 1.247, and a kidney function of OR 0.99 (Table 3).

https://doi.org/10.12701/yujm.2020.00129

Table 2. Major risk factors of amputation

Variable	Non-amputation (n = 181)	Amputation (n = 170)	*p*-value[a]
Osteomyelitis	77 (42.5)	142 (83.5)	0.0001
Lesion on percutaneous transluminal angioplasty	10 (5.5)	30 (17.6)	0.0001
Diabetic peripheral polyneuropathy	120 (66.2)	97 (57.0)	0.095
Chronic kidney disease (eGFR < 60 mL/min/1.73 m^2)	49 (27.0)	66 (36.4)	0.019
ABI decreased (ABI < 0.9)	26 (n = 126, 20.6)	46 (n = 126, 36.5)	0.005
Previous amputation history	12 (6.6)	22 (12.9)	0.046
Hypertension	113 (62.4)	103 (60.6)	0.723
Smoking	79 (43.6)	82 (48.2)	0.358
Alcohol	60 (33.1)	70 (41.2)	0.108
Wagner classification			0.0001
Grade 0–1	72 (39.7)	30 (17.6)	
Garde 2	47 (26.0)	31 (18.2)	
Grade 3	36 (19.9)	52 (30.6)	
Grade 4–5	26 (14.4)	57 (33.5)	
Ulcer location			0.002
Forefoot	110 (60.8)	129 (75.9)	
Midfoot	61 (33.7)	37 (21.8)	
Hindfoot	10 (5.5)	4 (2.3)	

Values are presented as number (%).
eGFR, estimated glomerular filtration rate; ABI, ankle-brachial index.
[a] *p*-value based on chi-square test and Fisher exact test.

Table 3. Multivariate logistic regression analysis of diabetic foot amputation

Variable	*p*-value	Odds ratio	95% CI
Osteomyelitis	0.0001	6.164	3.561–10.671
Lesion on percutaneous transluminal angioplasty	0.031	2.494	1.087–5.721
Previous amputation history	0.089	2.092	0.894–4.894
Estimated glomerular filtration rate	0.027	0.99	0.981–0.999
Alcohol	0.065	1.637	0.97–2.763
Diabetic peripheral polyneuropathy	0.039	0.57	0.334–0.973
Size of ulcer	0.0001	1.247	1.107–1.405
Ulcer location			
Forefoot: midfoot	0.003	2.475	0.224–0.73
Forefoot: hindfoot	0.08	3.460	0.072–1.158

CI, confidence interval.

Discussion

While various risk factors of diabetic foot amputation may have been identified in previous research, this study found that osteomyelitis, ulcer size, chronic kidney disease, forefoot location, and peripheral arterial disease were associated with diabetic foot amputation. This diversity could be brought about by differences in the genetic profiles, treatment protocols, study designs, and cultural features of the study subjects.

Osteomyelitis is one of the most critical factors in diabetic foot treatment process. The removal of infected bones is crucial, as prior studies have suggested superior results from surgical therapy compared with medical therapy [14,15]. Moreover, surgical debridement was discovered to be necessary to control chronic bone infection because antimicrobial therapy alone showed low success rates in the event of osteomyelitis [16]. The presence of osteomyelitis was the most significant risk factor (OR, 6.164) for diabetic foot amputation in this study.

Arterial insufficiency causes an impairment of bloodstream (i.e., a shortage of nutrition, antibodies, and white blood cells), which leads to poor wound outcome. Claudication, diminished or absent lower extremity pulses, lower ankle blood pressure, ABI, and trans-

cutaneous oxygen pressure of the foot (foot TcPo2) were important risk factors of developing foot ulcer and amputation surgery, indicating peripheral artery disease in diabetic patients [17,18]. In this study, the presence of PTA lesions and lower ABIs were associated with an increased risk of amputation surgery. However, Sun et al. [19] demonstrated that a lower ABI was closely associated with risk of amputation only in Wagner grade 3 wounds, not in grades 2 or 4. They assumed that a Wagner grade 4 grade wound would have catastrophic necrosis, which limits the influence of circulation; and vice versa for grade 2 wounds. This is why further comprehensive studies (i.e., with a subdivision of subjects with a classification of diabetic foot severity) focusing on the relationship between peripheral artery disease and prognosis are needed.

Ulcers located on the forefoot area were found to be a greater risk factor for diabetic foot amputation compared with midfoot or hindfoot located ulcers. Due to its distal position, it would be reasonable to assume that the forefoot area has the least sufficient blood supply in the foot region, resulting in a shortage of oxygen, white blood cell, and nutrition.

Several studies have shown that a large foot ulcer size and a high Wagner classification grade considerably increased the risk of amputation [9,20]. This study found that a higher Wagner classification grade and ulcer size were significantly associated with the risk of amputation through a chi-square test and regression analysis, respectively. This was in accordance with the findings of previous observational studies that more extensive wounds require more extensive surgical procedures such as amputation [19,21].

Complications including diabetic microangiopathy often arise as a patient's diabetes progresses. Diabetic kidney disease is another complication, and it is known as a useful marker for the generalized vascular status of patients with diabetes. Additionally, patients with nephropathy are also prone to developing peripheral vascular disease [22]. Several studies have shown that the incidence of diabetic foot disease is more frequent among patients with albuminuria [23-25]. However, given the insufficient data on albuminuria, this study was unable to properly examine the relationship between albuminuria and amputation surgery.

Current dialysis for end-stage renal disease and chronic kidney disease were also identified as risk factors for diabetic feet and major amputation [21,26]. These results confirm that a lower eGFR and the presence of chronic kidney disease are associated with a higher risk of diabetic foot amputation.

Recently, sarcopenia has been demonstrated as an important risk factor of diabetic foot disease, which also influenced prognosis; however, the measurement of skeletal muscles entails expensive and complex imaging techniques [27]. Thus far, the gold standard of measuring skeletal muscle mass has been either body composition analysis or computed tomography. The SI is a novel biomarker for estimating muscle mass, which uses two molecules: cystatin C, which originates from all nucleated cells and creatinine from skeletal muscle cells. The SI is significantly correlated with abdominal computed tomography and showed superior outcomes compared with serum creatinine on its own [12,28,29]. The study sought to assess the value of the SI as a marker to predict the prognosis of diabetic feet and compare it with other already established prognostic factors. In this study, the SI did not show statistically significant results. Since several studies have demonstrated the relationship between the SI and the prognosis of diabetic foot ulcers, this could be regarded as a limitation of the calculation formula.

The strength of this study is in its ethnic-specific design, wherein the chosen subjects share a common cultural, dietary lifestyle. Moreover, all of the subjects also underwent standard treatment protocols due to the single center-based recruitment process. These features greatly reduced biases present in previous studies that were brought about by the subjects' heterogeneous characteristics as well as the diverse treatment protocols among multicenters.

Conducting a larger scale study similar to this could lead to the establishment of a diabetic foot risk stratification system for Koreans.

The study has several limitations. Because this was a hospitalization-based single center design, a selection bias could not be excluded and the subjects may not have reflected the loco-regional population. So further multicenter studies are needed. This study was retrospective design, therefore independent variables were could not be fully assessed, and causality between each factors and outcome cannot be definitely established.

Osteomyelitis, a large ulcer size, nephropathy, forefoot location, and peripheral artery disease were identified as risk factors for amputation in hospitalized diabetic foot ulcer patients. Understanding their influence on amputation outcomes is necessary to develop risk stratification system, management, and treatment protocols for patients with diabetic feet. Through risk categorization, a multidisciplinary team for diabetic feet could receive timely assistance on decision-making (e.g., admission timing and invasive procedures), providing the best possible treatment for individualized patients.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

https://doi.org/10.12701/yujm.2020.00129

Author contributions

Conceptualization: JHL, JSY, HWL, KCW, JSM, YYL; Data curation: JHL, SMC; Formal analysis: JSY, KCW, JSM, YYL; Methodology: JHL, JSY, JSM, YYL; Investigation: JHL, JSY, HWL, KCW, YYL; Project administration: JHL; Supervision: JSY, KCW, JSM; Resources: JSY; Visualization: JHL, SMC; Writing-original draft: JHL; Writing-review & editing: JHL, JSM.

ORCID

Jun Ho Lee, https://orcid.org/0000-0002-5551-862X
Ji Sung Yoon, https://orcid.org/0000-0003-3091-3700
Hyoung Woo Lee, https://orcid.org/0000-0002-0773-1581
Kyu Chang Won, https://orcid.org/0000-0001-5945-3395
Jun Sung Moon, https://orcid.org/0000-0003-1569-3068
Seung Min Chung, https://orcid.org/0000-0003-3336-7557
Yin Young Lee, https://orcid.org/0000-0003-3684-8735

References

1. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet 2005;366:1719–24.
2. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA 2005;293:217–28.
3. Bakker K, Foster AV, van Houtum WH, Riley P; International Working Group on the Diabetic Foot. Diabetes and foot care: time to act. Brussels (BE): International Diabetes Federation and the International Working Group on the Diabetic Foot; 2005.
4. Songer TJ. The role of cost-effectiveness analysis and health insurance in diabetes care. Diabetes Res Clin Pract 2001;54(Suppl 1):S7–11.
5. Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Risk stratification systems for diabetic foot ulcers: a systematic review. Diabetologia 2011;54:1190–9.
6. Boulton AJ, Kirsner RS, Vileikyte L. Clinical practice: neuropathic diabetic foot ulcers. N Engl J Med 2004;351:48–55.
7. Markakis K, Bowling FL, Boulton AJ. The diabetic foot in 2015: an overview. Diabetes Metab Res Rev 2016;32(Suppl 1):169–78.
8. Fleischer AE, Wrobel JS, Leonards A, Berg S, Evans DP, Baron RL, et al. Post-treatment leukocytosis predicts an unfavorable clinical response in patients with moderate to severe diabetic foot infections. J Foot Ankle Surg 2011;50:541–6.
9. Oyibo SO, Jude EB, Tarawneh I, Nguyen HC, Armstrong DG, Harkless LB, et al. The effects of ulcer size and site, patient's age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers. Diabet Med 2001;18:133–8.
10. Chaturvedi N, Stevens LK, Fuller JH, Lee ET, Lu M. Risk factors, ethnic differences and mortality associated with lower- extremity gangrene and amputation in diabetes. The WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia 2001;44(Suppl 2):S65–71.
11. Resnick HE, Carter EA, Sosenko JM, Henly SJ, Fabsitz RR, Ness FK, et al. Incidence of lower-extremity amputation in American Indians: the Strong Heart Study. Diabetes Care 2004;27:1885–91.
12. Kashani KB, Frazee EN, Kukralova L, Sarvottam K, Herasevich V, Young PM, et al. Evaluating muscle mass by using markers of kidney function: development of the sarcopenia index. Crit Care Med 2017;45:e23–9.
13. Monteiro-Soares M, Martins-Mendes D, Vaz-Carneiro A, Sampaio S, Dinis-Ribeiro M. Classification systems for lower extremity amputation prediction in subjects with active diabetic foot ulcer: a systematic review and meta-analysis. Diabetes Metab Res Rev 2014;30:610–22.
14. Aragon-Sanchez FJ, Cabrera-Galvan JJ, Quintana-Marrero Y, Hernandez-Herrero MJ, Lazaro-Martinez JL, Garcia-Morales E, et al. Outcomes of surgical treatment of diabetic foot osteomyelitis: a series of 185 patients with histopathological confirmation of bone involvement. Diabetologia 2008;51:1962–70.
15. Ha Van G, Siney H, Danan JP, Sachon C, Grimaldi A. Treatment of osteomyelitis in the diabetic foot. Contribution of conservative surgery. Diabetes Care 1996;19:1257–60.
16. Jeffcoate WJ, Lipsky BA. Controversies in diagnosing and managing osteomyelitis of the foot in diabetes. Clin Infect Dis 2004;39(Suppl 2):S115–22.
17. Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Davignon DR, Smith DG. A prospective study of risk factors for diabetic foot ulcer. The Seattle Diabetic Foot Study. Diabetes Care 1999;22:1036–42.
18. Adler AI, Boyko EJ, Ahroni JH, Smith DG. Lower-extremity amputation in diabetes: the independent effects of peripheral vascular disease, sensory neuropathy, and foot ulcers. Diabetes Care 1999;22:1029–35.
19. Sun JH, Tsai JS, Huang CH, Lin CH, Yang HM, Chan YS, et al. Risk factors for lower extremity amputation in diabetic foot disease categorized by Wagner classification. Diabetes Res Clin Pract 2012;95:358–63.
20. Chuan F, Tang K, Jiang P, Zhou B, He X. Reliability and validity of the perfusion, extent, depth, infection and sensation (PEDIS) classification system and score in patients with diabetic foot ulcer. PLoS One 2015;10:e0124739.
21. Won SH, Chung CY, Park MS, Lee T, Sung KH, Lee SY, et al.

Risk factors associated with amputation-free survival in patient with diabetic foot ulcers. Yonsei Med J 2014;55:1373–8.
22. Chuengsamarn S, Rattanamongkolgul S, Jirawatnotai S. Association between serum uric acid level and microalbuminuria to chronic vascular complications in Thai patients with type 2 diabetes. J Diabetes Complications 2014;28:124–9.
23. Al-Maskari F, El-Sadig M. Prevalence of risk factors for diabetic foot complications. BMC Fam Pract 2007;8:59.
24. Pradeepa R, Anjana RM, Unnikrishnan R, Ganesan A, Mohan V, Rema M. Risk factors for microvascular complications of diabetes among South Indian subjects with type 2 diabetes: the Chennai Urban Rural Epidemiology Study (CURES) Eye Study-5. Diabetes Technol Ther 2010;12:755–61.
25. Aragon-Sanchez J, Lazaro-Martinez JL, Garcia-Alvarez Y, Morales EG, Hernandez-Herrero MJ. Albuminuria is a predictive factor of in-hospital mortality in patients with diabetes admitted for foot disease. Diabetes Res Clin Pract 2014;104:e23–5.
26. Winkley K, Stahl D, Chalder T, Edmonds ME, Ismail K. Risk factors associated with adverse outcomes in a population-based prospective cohort study of people with their first diabetic foot ulcer. J Diabetes Complications 2007;21:341–9.
27. Cheng Q, Hu J, Yang P, Cao X, Deng X, Yang Q, et al. Sarcopenia is independently associated with diabetic foot disease. Sci Rep 2017;7:8372.
28. Shlipak MG, Mattes MD, Peralta CA. Update on cystatin C: incorporation into clinical practice. Am J Kidney Dis 2013;62:595–603.
29. Kyhse-Andersen J, Schmidt C, Nordin G, Andersson B, Nilsson-Ehle P, Lindstrom V, et al. Serum cystatin C, determined by a rapid, automated particle-enhanced turbidimetric method, is a better marker than serum creatinine for glomerular filtration rate. Clin Chem 1994;40:1921–6.

https://doi.org/10.12701/yujm.2020.00129

Yeungnam University Journal of Medicine
YUJM

Original article
eISSN 2384-0293
Yeungnam Univ J Med 2020;37(4):321-328
https://doi.org/10.12701/yujm.2020.00353

Perioperative outcomes of interrupted anticoagulation in patients with non-valvular atrial fibrillation undergoing non-cardiac surgery

Bo Eun Park, Myung Hwan Bae, Hyeon Jeong Kim, Yoon Jung Park, Hong Nyun Kim, Se Yong Jang, Jang Hoon Lee, Dong Heon Yang, Hun Sik Park, Yongkeun Cho, Shung Chull Chae

Department of Internal Medicine, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, Korea

Received: May 15, 2020
Revised: June 9, 2020
Accepted: June 17, 2020

Corresponding author:
Myung Hwan Bae
Division of Cardiology, Department of Internal Medicine, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, 130 Dongdeok-ro, Jung-gu, Daegu 41944, Korea
Tel: +82-53-200-5525
Fax: +82-53-426-2959
E-mail: bmh0325@knu.ac.kr

Background: This study aimed to investigate the incidences of and risk factors for perioperative events following anticoagulant discontinuation in patients with non-valvular atrial fibrillation (NVAF) undergoing non-cardiac surgery.
Methods: A total of 216 consecutive patients who underwent cardiac consultation for suspending perioperative anticoagulants were enrolled. A perioperative event was defined as a composite of thromboembolism and major bleeding.
Results: The mean anticoagulant discontinuation duration was 5.7 (±4.2) days and was significantly longer in the warfarin group ($p<0.001$). Four perioperative thromboembolic (1.9%; three strokes and one systemic embolization) and three major bleeding events (1.4%) were observed. The high CHA_2DS_2-VASc and HAS-BLED scores and a prolonged preoperative anticoagulant discontinuation duration (4.4±2.1 vs. 2.9±1.8 days; $p=0.028$) were associated with perioperative events, whereas the anticoagulant type (non-vitamin K antagonist oral anticoagulants or warfarin) was not. The best cut-off levels of the HAS-BLED and CHA_2DS_2-VASc scores were 3.5 and 2.5, respectively, and the preoperative anticoagulant discontinuation duration for predicting perioperative events was 2.5 days. Significant differences in the perioperative event rates were observed among the four risk groups categorized according to the sum of these values: risk 0, 0%; risk 1, 0%; risk 2, 5.9%; and risk 3, 50.0% ($p<0.001$). Multivariate logistic regression analysis showed that the HAS-BLED score was an independent predictor for perioperative events.
Conclusion: Thromboembolic events and major bleeding are not uncommon during perioperative anticoagulant discontinuation in patients with NVAF, and interrupted anticoagulation strategies are needed to minimize these.

Keywords: Anticoagulants; Atrial fibrillation; Perioperative period; Surgery; Thromboembolism

Introduction

Atrial fibrillation (AF) increases the morbidity and mortality risks in affected patients and is closely related to stroke incidence [1-5]. Anticoagulation is important to reduce these risks. Warfarin has been used for preventing stroke for many decades; recently, non-vitamin K antagonist oral anticoagulants (NOACs) have been developed and used for this purpose [6-11]. If patients with AF who are undergoing anticoagulant therapy need surgery, anticoagulant discontinuation is required for certain duration owing to concerns regarding the increased risk of intraoperative bleeding [6-9]. However, anticoagulant discontinuation can increase the risk of periopera-

tive stroke; thus, it is necessary to determine the appropriate anticoagulant discontinuation duration to minimize the risk of perioperative stroke and bleeding. Current guidelines on anticoagulant use in patients with AF have suggested the perioperative anticoagulant discontinuation duration according to the bleeding risk associated with the surgery; conversely, they take into account the pharmacokinetic characteristics of anticoagulants and do not reflect the results of clinical studies [7,10-12]. Consequently, in this study, we investigated the incidences of and risk factors for thromboembolism and major bleeding following perioperative anticoagulant discontinuation in patients with non-valvular AF (NVAF) undergoing non-cardiac surgery.

Materials and methods

The study was approved by the by the Institutional Review Board (IRB) of the Kyungpook National University Hospital (IRB No: 2019-11-040). Informed consent was waived by the board.

This observational study included 216 consecutive patients with NVAF who consulted the Department of Cardiology for suspending their perioperative anticoagulant use at the Kyungpook National University Hospital between March 2015 and September 2019. Patients with a mechanical prosthetic heart valve or moderate to severe mitral valve stenosis, as well as those with newly diagnosed AF or those who did not take anticoagulants (NOACs or warfarin), were excluded. All surgeries/interventions were categorized into three groups depending on the surgical bleeding risks according to the 2018 European Heart Rhythm Association Practical Guidelines on the NOACs use in patients with AF [11]: those not necessarily requiring discontinuation (dental intervention, ophthalmology, endoscopy/cystoscopy without biopsy, and superficial surgery), those with a low bleeding risk (endoscopy/cystoscopy with biopsy, prostate or bladder biopsy, and angiography), and those with a high bleeding risk (thoracic, abdominal, orthopedic, spinal, and vascular surgeries, complex endoscopic procedures, and extracorporeal shock wave lithotripsy).

The demographic and clinical characteristics of the patients were examined, including age, sex, body weight, pre-medication, laboratory findings, and cardiovascular risk factors (hypertension, diabetes mellitus, previous history of myocardial infarction, stroke/transient ischemic attack [TIA], congestive heart failure, vascular disease, and chronic kidney disease). The CHA_2DS_2-VASc and HAS-BLED scores were used to assess the stroke and bleeding risks. The left atrial anteroposterior diameter (mm) and left ventricular ejection fraction (LVEF, %) were measured using two-dimensional echocardiography. Regarding laboratory data, the creatinine levels and international normalized ratio values were obtained on the date closest to the actual surgery date. Furthermore, information on pre-hospital medication including warfarin, NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban), and concomitant antiplatelet agents was collected. The anticoagulant discontinuation duration was measured by taking into consideration the actual time the drug was last taken. Heparin bridging therapy used a twice-daily low molecular weight heparin and was discontinued 24 hours before the planned surgery or procedure.

A perioperative event was defined as a composite of stroke, systemic embolism, and major bleeding owing to anticoagulant discontinuation of up to 30 days postoperatively. Stroke was defined as a sudden focal neurological deficit consistent with the territory of a cerebral artery occlusion documented by a brain imaging study. Moreover, systemic embolism was defined as a sudden vascular occlusion in an organ or extremity. Major bleeding was defined as clinically overt bleeding with a decrease of at least 2 g/dL in hemoglobin levels or transfusion of at least two units of packed red blood cells or that resulting in death.

Data are expressed as mean ± standard deviation and percentages for continuous and categorical variables, respectively. All comparisons between the baseline variables were performed using the Student t-test and chi-square test for continuous and categorical variables, respectively. All p-values were two-sided, and $p < 0.05$ was considered significant. Multivariate logistic regression analysis was used for identifying independent predictors of a perioperative event. The receiver operating characteristics (ROC) curve analysis was performed to determine the cut-off values for predicting a perioperative event. All statistical analyses were performed using the IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

Results

All surgery types (n = 216) were classified into the following three groups according to the risk of bleeding; those not necessarily requiring discontinuation (n = 44), those with a low bleeding risk (n = 3), and those with a high bleeding risk (n = 169) (Table 1). Major orthopedic surgery was the most common type (n = 57), followed by abdominal (n = 45), spinal (n = 21), ophthalmological (n = 18), and vascular (n = 12) surgeries.

The baseline characteristics of the 216 patients (mean age, 73 ± 8 years; 127 males [58.8%]) are shown in Table 2. Hypertension (58.8%) and diabetes mellitus (30.6%) were common comorbidities, and 46 patients (21.3%) had previously experienced a stroke/TIA. The mean LVEF was 55% ± 9%, and the mean left atrial anteroposterior diameter was 48 ± 8 mm. Regarding the laboratory findings, the mean estimated glomerular filtration rate was 78 ± 33 mL/min; furthermore, 52 patients (24.1%) had a history

https://doi.org/10.12701/yujm.2020.00353

Table 1. Surgery type according to the bleeding risk (n=216)

Variable	Number
Not necessarily requiring discontinuation	44
Dental interventions	4
Cartaract operation	18
Endoscopy/cystoscopy	11
Superficial surgery	11
Low bleeding risk	3
Endoscopy/cystoscopy with biopsy	1
Prostate or bladder biopsy	1
Digital subtraction angiography	1
High bleeding risk	169
Thoracic surgery	4
Abdominal surgery	45
Major orthopedic surgery	57
Spinal surgery	21
Transurethral prostate/bladder resection	6
Extracorporeal shock wave lithotripsy	5
Complex endoscopic procedure (EMR, ERCP)	6
Vascular surgery	12
Others[a)]	13

EMR, endoscopic mucosal resection; ERCP, endoscopic retrograde cholangiopancreatography.
[a)]Neck lymph node core needle biopsy, subclavicular lymph node excisional biopsy, etc.

of chronic kidney disease. The mean CHA_2DS_2-VASc and HAS-BLED scores were 3.3 ± 1.5 and 1.9 ± 1.0, respectively.

NOACs and warfarin were prescribed for 138 and 78 patients, respectively. Rivaroxaban (41.3%) was the most commonly prescribed NOAC, followed by apixaban (23.9%), edoxaban (19.6%), and dabigatran (15.2%). The serum creatinine levels as well as male patient and heparin bridging therapy frequencies were higher in the warfarin group than in the NOACs group. However, there were no between-group differences regarding age; body weight; LVEF; left atrial size; renal function; platelet count and hemoglobin level, concomitant antiplatelet agent prescription; comorbidities such as diabetes mellitus, ischemic heart disease, stroke/TIA, heart failure, vascular disease, and chronic kidney disease; and surgery types according to the bleeding risk. Moreover, the mean CHA_2DS_2-VASc (NOACs, 3.3 ± 1.4 vs. warfarin, 3.1 ± 1.8; p = 0.410) and HAS-BLED (1.9 ± 0.9 vs. 2.0 ± 1.1; p = 0.519) scores were not different between the groups. The mean anticoagulant discontinuation duration was 5.7 ± 4.2 days, with the duration being significantly longer in the warfarin group (8.6 ± 4.9 vs. 4.0 ± 2.5 days; p < 0.001) (Fig. 1).

Four thromboembolic events (1.9%; three strokes and one systemic embolization) and three major bleeding events (1.4%) occurred during the perioperative period (Table 3). The clinical characteristics of patients with perioperative stroke or major bleeding are shown in Table 4. Of them, NOACs and warfarin were prescribed in four and three patients, respectively. The CHA_2DS_2-VASc (4.9 ± 2.0 vs. 3.2 ± 1.5; p = 0.005) and HAS-BLED (3.6 ± 1.1 vs. 1.8 ± 0.9; p < 0.001) scores were higher and the preoperative anticoagulant discontinuation duration (4.4 ± 2.1 vs. 2.9 ± 1.8 days; p = 0.028) was longer in patients with perioperative events than in those without them (Table 3). When all patients with low or high surgical bleeding risk were analyzed except those who did not need to stop taking anticoagulants before surgery/intervention, the CHA_2DS_2-VASc and HAS-BLED scores were higher and the duration of preoperative anticoagulant discontinuation was longer in patients with perioperative events (Table 3). Major bleeding events were significantly increased in patients treated with perioperative heparin bridging therapy (5.6% vs. 0%, p = 0.015). However, there was no significant difference in perioperative events according to the heparin bridging therapy status. Moreover, the anticoagulant type (NOACs or warfarin) and surgery type according to bleeding risk did not affect the perioperative event occurrence.

The area under the ROC curve for predicting the perioperative events was 0.868 (95% confidence interval [CI], 0.722–1.000) for the HAS-BLED score, 0.747 (95% CI, 0.587–0.908) for the CHA_2DS_2-VASc score, and 0.733 (95% CI, 0.508–0.958) for the preoperative anticoagulant discontinuation duration (Fig. 2). The best cut-off levels of the HAS-BLED and CHA_2DS_2-VASc scores were 3.5 and 2.5, respectively, and the preoperative anticoagulant discontinuation duration as per the ROC curve analysis was 2.5 days. When the patients were categorized into four risk score groups according to the sum of the values defined by the cut-off levels, significant differences in the perioperative event rate were observed among the groups: risk 0 (0%), 1 (0%), 2 (5.9%), and 3 (50.0%) (p < 0.001; Fig. 3). Multivariate logistic regression analysis showed that the HAS-BLED score (hazard ratio, 5.812; 95% CI, 1.930–17.502) was an independent predictor for perioperative events after adjusting for the CHA_2DS_2-VASc score and preoperative anticoagulant discontinuation duration (Table 5).

Discussion

Among our study patients, thromboembolic events and major bleeding occurred in 1.9% and 1.4% of patients, respectively, who stopped anticoagulation therapy before surgery. Perioperative events are common in patients with high CHA_2DS_2-VASc and HAS-BLED scores or in those with prolonged anticoagulant discontinuation duration. However, no differences were observed in the perioperative events according to the anticoagulant (NOACs or warfarin) and surgery types.

Table 2. Baseline clinical characteristics of the patients according to anticoagulant type

Characteristic	All patients (n = 216)	NOACs (n = 138)	Warfarin (n = 78)	*p*-value
Age (yr)	72.9 ± 7.7	73.2 ± 7.6	72.3 ± 8.1	0.418
Male sex	127 (58.8)	74 (53.6)	53 (67.9)	0.04
Body weight (kg)	63.0 ± 11.5	62.2 ± 12.2	64.2 ± 10.2	0.232
Comorbidities				
Hypertension	127 (58.8)	89 (64.5)	38 (48.7)	0.024
Diabetes mellitus	66 (30.6)	43 (31.2)	23 (29.5)	0.798
Ischemic heart disease	24 (11.1)	15 (10.9)	9 (11.5)	0.881
Stroke/TIA	46 (21.3)	25 (18.1)	21 (26.9)	0.129
Congestive heart failure	16 (7.4)	11 (8.0)	5 (6.4)	0.674
Vascular disease	18 (8.3)	10 (7.2)	8 (10.3)	0.442
CHA_2DS_2-VASc score	3.3 ± 1.5	3.3 ± 1.4	3.1 ± 1.8	0.41
HAS-BLED score	1.9 ± 1.0	1.9 ± 0.9	2.0 ± 1.1	0.519
Chronic kidney disease	52 (24.1)	28 (20.3)	24 (30.8)	0.084
Echocardiography				
Left ventricular ejection fraction (%)	55.1 ± 9.2	56.0 ± 9.2	53.6 ± 9.1	0.078
Left atrium size, AP diameter (mm)	47.7 ± 7.7	47.0 ± 7.9	48.9 ± 7.8	0.081
Laboratory findings				
Serum creatinine (mg/dL)	1.1 ± 0.8	0.9 ± 0.3	1.3 ± 1.3	0.008
eGFR (mL/min)	77.8 ± 32.7	80.0 ± 29.1	74.0 ± 38.1	0.23
Hemoglobin (g/dL)	12.7 ± 1.8	12.7 ± 1.7	12.9 ± 1.9	0.412
Platelet ($\times 10^3/\mu L$)	205.9 ± 77.0	206.5 ± 66.1	204.8 ± 93.7	0.874
Medication				
Concomitant antiplatelet agents	26 (12.0)	15 (10.9)	11 (14.1)	0.495
Heparin bridging therapy	54 (25.0)	15 (10.9)	39 (50.0)	< 0.001
Type of NOACs				
Apixaban	-	33 (23.9)	-	
Dabigatran	-	21 (15.2)	-	
Edoxaban	-	27 (19.6)	-	
Rivaroxaban	-	57 (41.3)	-	
Surgical bleeding risk				0.395
Not necessarily requiring discontinuation	44 (20.4)	30 (21.7)	14 (17.9)	
Low bleeding risk	3 (1.4)	3 (2.2)	0	
High bleeding risk	169 (78.2)	105 (76.1)	64 (82.1)	

Values are presented as mean ± standard deviation or number (%).
NOACs, non-vitamin K antagonist oral anticoagulants; TIA, transient ischemic attack; AP, anteroposterior; eGFR, estimated glomerular filtration rate.

Patients with AF are at a high risk of developing thromboembolic events and require adequate anticoagulant therapy [6-11]. However, a significant number of patients undergoing anticoagulant therapy may require surgery or other procedures, and the doctors in charge of these interventions may recommend discontinuing the anticoagulant for as long as possible due to the risk of bleeding. NOACs have shorter half-lives and achieve effective drug concentrations faster than warfarin [11-20]. Therefore, anticoagulant use guidelines for patients with AF recommend the cessation of NOACs for 48 hours in case of a high bleeding risk surgery and for 24 hours in case of a low bleeding risk surgery [11]. However, the anticoagulant discontinuation duration recommended by these guidelines is based on the pharmacokinetic characteristics of drugs; moreover, there have been few studies investigating the proper perioperative anticoagulant discontinuation duration [8,9,21-25].

In the warfarin era, several studies showed that perioperative warfarin discontinuation for a brief period (≤ 5 days) is associated with a low risk of thromboembolism [4,24]. However, there are few studies examining the relationship between the anticoagulant discontinuation duration and a perioperative event in the NOACs era, except for the recent perioperative anticoagulation use for surgery evaluation (PAUSE) study [26].

https://doi.org/10.12701/yujm.2020.00353

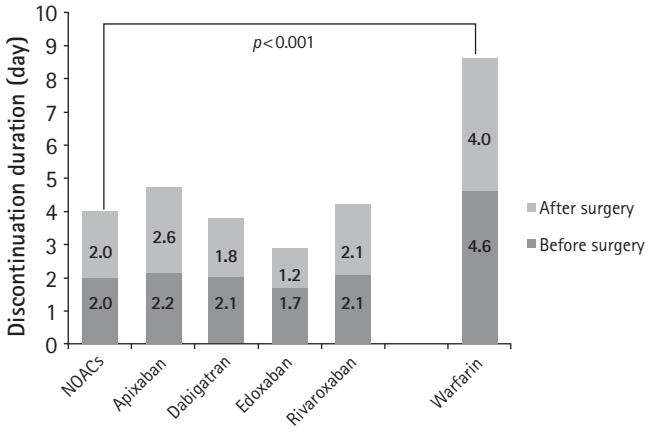


Fig. 1. Duration of perioperative anticoagulant discontinuation according to anticoagulant type (non-vitamin K antagonist oral anticoagulants [NOACs] vs. warfarin).

In our study, the mean preoperative anticoagulant discontinuation duration was 2 days for NOACs and 4.6 days for warfarin, which is not significantly different from the duration recommended in the guidelines [11]. Nevertheless, a perioperative event occurred in 3.2% of patients. In particular, long preoperative anticoagulant discontinuation duration was associated with perioperative events, and the thromboembolism frequency in our study (1.9%) was relatively higher than that of the PAUSE study (0.33%) [26]. Unlike the study environment in which the anticoagulant discontinuation duration is strictly controlled, it is believed that this difference may occur because the actual anticoagulant discontinuation duration is often different from the recommended period, at the discretion of the attending physician in real practice. It is sometimes impossible to use anticoagulants after surgery due to exces-

Table 3. Clinical characteristics of the patients according to the presence or absence of thromboembolism and/or bleeding

Characteristic	All patients (n = 216)			Low/high bleeding risk patients (n = 172)		
	Events (+) (n = 7)	Events (–) (n = 209)	*p*-value	Events (+) (n = 6)	Events (–) (n = 166)	*p*-value
Age (yr)	74.4 ± 5.4	72.8 ± 7.8	0.585	74.3 ± 6.0	72.6 ± 7.8	0.582
Male sex	4 (57.1)	123 (58.9)	1.000	3 (50.0)	96 (57.8)	0.700
Body weight (kg)	65.0 ± 10.3	62.9 ± 11.6	0.633	65.3 ± 11.2	63.2 ± 11.2	0.642
Comorbidities						
Hypertension	7 (100)	120 (57.4)	0.043	6 (100)	99 (59.6)	0.083
Diabetes mellitus	3 (42.9)	63 (30.1)	0.439	3 (50.0)	53 (31.9)	0.392
Ischemic heart disease	1 (14.3)	23 (11.0)	0.567	1 (16.7)	16 (9.6)	0.470
Stroke/TIA	3 (42.9)	43 (20.6)	0.168	3 (50.0)	36 (21.7)	0.131
Congestive heart failure	2 (28.6)	14 (6.7)	0.087	2 (33.3)	8 (4.8)	0.040
Vascular disease	2 (28.6)	16 (7.7)	0.107	1 (16.7)	12 (7.2)	0.380
CHA_2DS_2-VASc score	4.9 ± 2.0	3.2 ± 1.5	0.005	5.0 ± 2.1	3.3 ± 1.5	0.007
HAS-BLED score	3.6 ± 1.1	1.8 ± 0.9	< 0.001	3.8 ± 1.0	1.9 ± 0.9	< 0.001
Chronic kidney disease	3 (42.9)	49 (23.4)	0.363	2 (33.3)	39 (23.5)	0.629
Echocardiography						
Left ventricular ejection fraction (%)	52.9 ± 12.8	55.2 ± 9.1	0.509	52.2 ± 13.9	55.9 ± 8.5	0.303
Left atrium size, AP diameter (mm)	46.6 ± 7.7	47.7 ± 7.7	0.708	4.8 ± 0.8	4.8 ± 0.8	0.988
Laboratory findings						
Serum creatinine (mg/dL)	0.9 ± 0.3	1.1 ± 0.8	0.660	0.9 ± 0.2	1.1 ± 0.9	0.571
eGFR (mL/min)	76.4 ± 25.2	77.8 ± 33.0	0.912	80.0 ± 25.6	79.1 ± 34.3	0.951
Hemoglobin (g/dL)	11.6 ± 1.8	12.8 ± 1.8	0.079	11.5 ± 1.9	12.7 ± 1.8	0.094
Platelet ($\times 10^3/\mu L$)	225.7 ± 33.8	205.2 ± 78.0	0.490	231.3 ± 33.2	205.5 ± 82.7	0.448
Medication						
Concomitant antiplatelet agents	2 (28.6)	24 (11.5)	0.202	2 (33.3)	21 (12.7)	0.185
Heparin bridging therapy	4 (57.1)	50 (23.9)	0.067	4 (66.7)	45 (27.1)	0.056
Anticoagulants						
NOACs	4 (57.1)	134 (64.1)	0.705	3 (50.0)	105 (63.3)	0.672
Warfarin	3 (42.9)	75 (35.9)	0.705	3 (50.0)	61 (36.7)	0.672
High bleeding risk surgery	6 (85.7)	163 (78.0)	1.000	6 (100)	163 (98.2)	1.000
Discontinuation duration (day)						
Before surgery	4.4 ± 2.1	2.9 ± 1.8	0.028	4.7 ± 2.3	3.0 ± 1.8	0.029
After surgery	1.8 ± 4.4	2.8 ± 3.4	0.539	1.8 ± 0.4	3.1 ± 3.8	0.444
Total	5.7 ± 2.6	5.7 ± 4.2	0.978	6.2 ± 2.5	6.1 ± 4.5	0.985

Values are presented as mean ± standard deviation or number (%).
TIA, transient ischemic attack; AP, anteroposterior; eGFR, estimated glomerular filtration rate; NOACs, non-vitamin K antagonist oral anticoagulants.

Table 4. Clinical characteristics of patients with perioperative thromboembolism or major bleeding

Patient	Sex	Age (yr)	Name of surgery	CHA_2DS_2-VASc score	HAS-BLED score	Anticoagulant	INR at event	Discontinuation duration (day) (before/after)	Heparin bridging therapy	Perioperative event
1	Female	74	Craniotomy/aneurysm clipping	5	4	Rivaroxaban 20 mg	–	9 (7/2)	–	Stroke
2	Female	78	Femur fracture[a]	8	4	Warfarin	2.1	8 (6/2)	+	Stroke
3	Female	75	Total hysterectomy	7	5	Warfarin	2.49	7 (5/2)	+	Major bleeding
4	Male	75	Planned tooth extraction	4	2	Apixaban 5 mg	–	3 (3/0)	–	Systemic embolism
5	Male	76	Femur fracture[b]	3	4	Warfarin	2.68	5 (3/2)	+	Major bleeding
6	Male	63	Planned gastric EMR	3	2	Edoxaban 60 mg	–	6 (6/0)	–	Stroke
7	Male	80	Acetabular fracture[c]	4	4	Rivaroxaban 10 mg	–	2 (1/1)	+	Major bleeding

INR, international normalized ratio; EMR, endoscopic mucosal resection.
[a]Closed reduction-internal fixation with proximal femur nail antirotation. [b]Total hip replacement arthroplasty. [c]Open reduction-internal fixation with reconstruction plate.

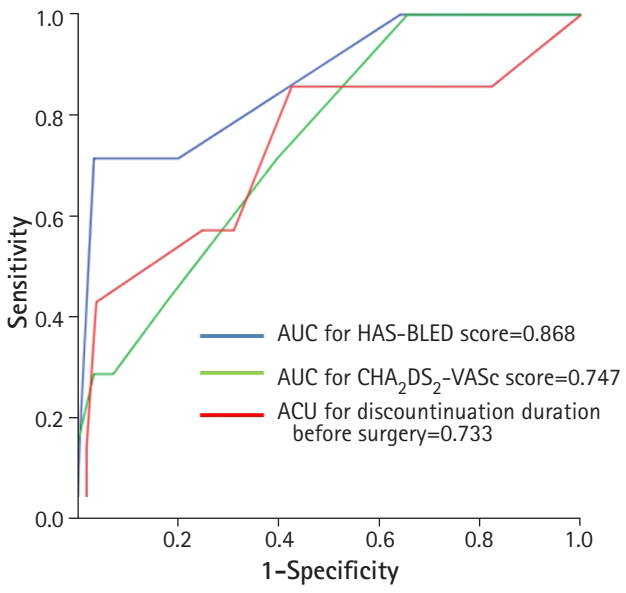


Fig. 2. Receiver operating characteristics curve analyses of the HAS-BLED and CHA_2DS_2-VASc scores and duration of preoperative anticoagulant discontinuation for predicting perioperative events. AUC, area under the curve.

sive bleeding or high bleeding risk, and therefore, it is challenging to clearly suggest the anticoagulant discontinuation duration after surgery. However, the recommended preoperative anticoagulant discontinuation duration on the basis of pharmacokinetic characteristics is relatively clear [11,21-23,25]; therefore, the minimum preoperative anticoagulant discontinuation duration that can prevent postoperative bleeding can reduce perioperative events. The results of our study are meaningful in supporting this point.

Heparin bridging therapy during the perioperative period is known to increase bleeding in patients taking NOACs or warfarin [26,27], which is consistent with our study results. However, the use of heparin bridging therapy did not significantly change the occurrence of any perioperative events including thromboembolism and major bleeding.

The CHA_2DS_2-VASc score is used to assess the thromboembolic risk in patients with NVAF. The higher the score, the higher the risk of thromboembolism; thus, anticoagulation is recommended. The HAS-BLED is a scoring system that was developed to assess the risk of major bleeding in patients taking anticoagulants; patients with a score >3 are considered to be a high-risk group for major bleeding and must exercise caution when taking anticoagulants. However, there has been no study on whether these scoring systems are useful for predicting stroke and major bleeding risks in patients with NVAF undergoing non-cardiac surgery. In the present study, we showed that a CHA_2DS_2-VASc score >2.5 and a HAS-BLED score >3.5 are associated with high perioperative events when anticoagulation therapy is discontinued for a certain hospitalization period. In addition, on analyzing these scoring systems along with the preoperative anticoagulant discontinuation duration, a significantly different perioperative event rate was observed between the high-risk (score, 3; 50.0%) and the low-risk (score, 0–1; 0%) groups. Therefore, perioperative management including an appropriate anticoagulant discontinuation strategy is more important in these high-risk groups.

This study has some limitations. First, this was a single-center, retrospective study. In addition, because we included patients treated since 2015, when NOACs began to be used to prevent stroke in patients with atrial fibrillation, a small number of patients were included. Second, our study included only those patients who had received consultation at the Department of Cardiology before undergoing surgery; therefore, patients who had discontinued antico-

https://doi.org/10.12701/yujm.2020.00353

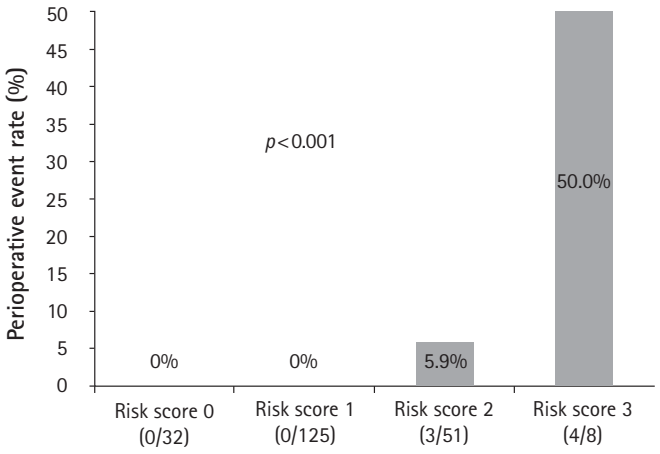


Fig. 3. Perioperative event rate categorized according to the cut-off levels of the HAS-BLED and CHA_2DS_2-VASc scores and duration of preoperative anticoagulant discontinuation. Significant differences in perioperative event rates are observed among the risk 0 (0%), 1 (0%), 2 (5.9%), and 3 (50.0%) groups ($p<0.001$). HAS-BLED score > 3.5: 1, CHA_2DS_2-VASc > 2.5: 1, discontinuation duration before surgery > 2.5 days: 1.

Table 5. Multivariate logistic regression analysis for perioperative stroke/major bleeding

Variable	Odds ratio	95% confidence interval	*p*-value
CHA_2DS_2-VASc score	0.934	0.494–1.768	0.835
HAS-BLED score	5.812	1.930–17.502	0.002
Discontinuation duration before surgery	1.504	0.986–2.295	0.058

agulant use without consultation could have been missed. Third, it is challenging to determine whether the cause of major bleeding was the surgery itself or an early resumption of anticoagulant use. However, considering that all patients who experienced major bleeding resumed anticoagulant use within 2 days of surgery and that major bleeding occurred at least 4 days postoperatively, anticoagulant use most likely affected the major bleeding.

In conclusion, thromboembolic events and major bleeding are not uncommon during perioperative anticoagulant discontinuation in patients with NVAF. The high CHA_2DS_2-VASc and HAS-BLED scores and prolonged anticoagulant discontinuation duration are associated with perioperative events. Therefore, optimal strategies for interrupted anticoagulation are needed in patients with NVAF who are at a high risk of perioperative events.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: MHB, BEP, SCC; Data curation: MHB, SYJ; Formal analysis: HJK, HNK, SYJ, YC; Methodology: MHB, BEP, YJP, HSP; Project administration: JHL; Visualization: BEP, DHY; Investigation: BEP; Resources: HJK, HNK; Software: SYJ; Supervision: YC; Writing-original draft: MHB, BEP; Writing-review & editing: MHB, BEP, HJK, YJP, HSP, HNK, SYJ, YC, SCC, DHY, JHL.

ORCID

Bo Eun Park, https://orcid.org/0000-0002-5245-9863
Myung Hwan Bae, https://orcid.org/0000-0001-7677-4895
Hyeon Jeong Kim, https://orcid.org/0000-0002-3496-3142
Yoon Jung Park, https://orcid.org/0000-0001-5132-226X
Hong Nyun Kim, https://orcid.org/0000-0002-9903-1848
Se Yong Jang, https://orcid.org/0000-0002-4981-879X
Jang Hoon Lee, https://orcid.org/0000-0002-7101-0236
Dong Heon Yang, https://orcid.org/0000-0002-1646-6126
Hun Sik Park, https://orcid.org/0000-0001-7138-1494
Yongkeun Cho, https://orcid.org/0000-0001-9455-0190
Shung Chull Chae, https://orcid.org/0000-0002-9871-6976

References

1. Lip GY, Lim HS. Atrial fibrillation and stroke prevention. Lancet Neurol 2007;6:981–93.
2. Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB. Impact of atrial fibrillation on mortality, stroke, and medical costs. Arch Intern Med 1998;158:229–34.
3. Hughes M, Lip GY; Guideline Development Group; National Clinical Guideline for Management of Atrial Fibrillation in Primary and Secondary Care; National Institute for Health and Clinical Excellence. Stroke and thromboembolism in atrial fibrillation: a systematic review of stroke risk factors, risk stratification schema and cost effectiveness data. Thromb Haemost 2008;99:295–304.
4. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001;285:2370–5.
5. Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med 2003;349:1019–26.
6. Rivera-Caravaca JM, Roldán V, Esteve-Pastor MA, Valdés M, Vicente V, Lip GY, et al. Cessation of oral anticoagulation is an

important risk factor for stroke and mortality in atrial fibrillation patients. Thromb Haemost 2017;117:1448–54.
7. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, et al. Updated European Heart Rhythm Association practical guide on the use of non-vitamin-K antagonist anticoagulants in patients with non-valvular atrial fibrillation: executive summary. Eur Heart J 2017;38:2137–49.
8. Wysokinski WE, McBane RD, Daniels PR, Litin SC, Hodge DO, Dowling NF, et al. Periprocedural anticoagulation management of patients with nonvalvular atrial fibrillation. Mayo Clin Proc 2008;83:639–45.
9. Doherty JU, Gluckman TJ, Hucker WJ, Januzzi JL Jr, Ortel TL, Saxonhouse SJ, et al. 2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation: a report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol 2017;69:871–98.
10. Larsen TB, Skjøth F, Nielsen PB, Kjældgaard JN, Lip GY. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. BMJ 2016;353:i3189.
11. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018;39:1330–93.
12. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955–62.
13. Birman-Deych E, Radford MJ, Nilasena DS, Gage BF. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. Stroke 2006;37:1070–4.
14. Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet 2010;376:975–83.
15. Lopes RD, Alexander JH, Al-Khatib SM, Ansell J, Diaz R, Easton JD, et al. Apixaban for reduction in stroke and other ThromboembоLic events in atrial fibrillation (ARISTOTLE) trial: design and rationale. Am Heart J 2010;159:331–9.
16. Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L; Randomized Evaluation of Long-Term Anticoagulation Therapy Investigators. Newly identified events in the RE-LY trial. N Engl J Med 2010;363:1875–6.
17. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093–104.
18. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–92.
19. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–91.
20. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.
21. Levy JH. Discontinuation and management of direct-acting anticoagulants for emergency procedures. Am J Med 2016;129(11 Suppl):S47–53.
22. Kornej J, Potpara T, Lip GY. Anticoagulation management in nonvalvular atrial fibrillation: current and future directions. Pol Arch Med Wewn 2013;123:623–34.
23. Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. N Engl J Med 1997;336:1506–11.
24. Garcia DA, Regan S, Henault LE, Upadhyay A, Baker J, Othman M, et al. Risk of thromboembolism with short-term interruption of warfarin therapy. Arch Intern Med 2008;168:63–9.
25. Raval AN, Cigarroa JE, Chung MK, Diaz-Sandoval LJ, Diercks D, Piccini JP, et al. Management of patients on non-vitamin K antagonist oral anticoagulants in the acute care and periprocedural setting: a scientific statement from the American Heart Association. Circulation 2017;135:e604–33.
26. Douketis JD, Spyropoulos AC, Duncan J, Carrier M, Le Gal G, Tafur AJ, et al. Perioperative management of patients with atrial fibrillation receiving a direct oral anticoagulant. JAMA Intern Med 2019;179:1469–78.
27. Siegal D, Yudin J, Kaatz S, Douketis JD, Lim W, Spyropoulos AC. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. Circulation 2012;126:1630–9.

https://doi.org/10.12701/yujm.2020.00353

Yeungnam University Journal of Medicine
YUJM

Case report
eISSN 2384-0293
Yeungnam Univ J Med 2020;37(4):329-331
https://doi.org/10.12701/yujm.2020.00108

Negative myoclonus associated with tramadol use

Seong Yoon Bae[1], Se-Jin Lee[2]

[1]Department of Neurology, Daegu Fatima Hospital, Daegu, Korea
[2]Department of Neurology, Yeungnam University College of Medicine, Daegu, Korea

Received: March 2, 2020
Revised: March 29, 2020
Accepted: April 1, 2020

Corresponding author:
Se-Jin Lee
Department of Neurology,
Yeungnam University College of Medicine, 170 Hyeonchung-ro
Nam-gu, Daegu 42415, Korea
Tel: +82-53-620-3683
Fax: +82-53-627-1688
E-mail: sejinmayo@ynu.ac.kr

Negative myoclonus (NM) is a shock-like jerky involuntary movement caused by a sudden, brief interruption of tonic muscle contraction. NM is observed in patients diagnosed with epilepsy, metabolic encephalopathy, and drug toxicity and in patients with brain lesions. A 55-year-old man presented with NM in both his arms and neck. He has taken medications containing tramadol at a dose of 80–140 mg/day for 5 days due to common cold. He had no history of seizures. Acute lesions were not observed during magnetic resonance imaging, and abnormal findings in his laboratory tests were not noted. His NM resolved completely after the discontinuation of tramadol and the oral administration of clonazepam. Our case report suggests that tramadol can cause NM in patients without seizure history or metabolic disorders, even within its therapeutic dose.

Keywords: Negative myoclonus; Myoclonus; Seizure; Tramadol

Introduction

Negative myoclonus (NM) is a brief involuntary jerky movement caused by a sudden lapse of tonic muscle contraction in the affected body segments. NM may appear not only in normal individuals physiologically during fear or sleep transition but also in patients with metabolic encephalopathy as flapping tremor (asterixis) [1-3]. Anticonvulsants, such as gabapentin and pregabalin, may also induce NM [4]. Tramadol, a synthetic codeine, is an analgesic used to treat various types of pain and is known to provoke generalized tonic-clonic seizure or myoclonus [5-8]. However, based on the Korean literature, studies assessing the presence of NM due to tramadol use have not been conducted yet. We hereby report a case of NM caused by the therapeutic dose of tramadol.

Case

This study was approved by the Institutional Review Board (IRB) of the Yeungnam University Hospital (IRB No: 2020-04-010).

A 55-year-old man visited the emergency room following the complaint of sudden involuntary movements of both his arms and neck at night. When he was raising his arms to wash his face or to hold a light object, his arms abruptly lapsed and jerked downward. His symptoms progressed overnight. When he tried to take a posture of holding a brush to practice calligraphy, his right arm twitched and jerked downward; thus, he pointed the paper repetitively with brush. When he tried to raise his head upright, his head jerked backward.

He has taken medications containing tramadol, acetaminophen, acetylcysteine, and prednisolone for 5 days as a remedy to common cold. The daily dose of tramadol administered was approximately 80–140 mg. He has been taking aspirin and atorvastatin for 3 years due to asymptomatic cerebral infarction and dyslipidemia. He had no history of seizures, and his chronic hepatitis B was treated 4 years ago. He was a light drinker and had not consumed alcohol for 2 weeks prior to taking the medications due to

common cold.

When he arrived at the hospital, his vital signs were unremarkable. The patient was alert and appeared normal during his cranial nerve examination and motor and sensory function tests without pathologic reflexes. When he stretched both arms forward with dorsiflexion of the wrists in the sitting position, NM was provoked irregularly every 3 seconds, and it was not observed at rest. While he was extending his head upright, NM was also provoked on the head at a lower frequency compared with that of his arms.

There were no abnormal findings in complete blood cell count, urinalysis, and liver function, electrolyte, kidney function, blood ammonia concentration, or thyroid function test. Acute lesion was not observed on brain magnetic resonance imaging (MRI).

We presumed this case as NM associated with tramadol based on patient's medical history, laboratory tests, and brain MRI. We discontinued the patient's medications including tramadol and prescribed oral clonazepam 0.5 mg once. The following morning, his symptoms completely improved, and electroencephalography (EEG) revealed no abnormal findings. He was discharged on the third day of admission and had no recurrence of NM for 3 years.

Discussion

Tramadol is a widely used analgesic for acute and chronic pain because it is less likely to be abused and has fewer side effects including respiratory depression than other opioid analgesics [9]. The maximum recommended daily dose of tramadol is 400 mg. It is well known that tramadol can provoke seizure and myoclonus within its therapeutic doses [5,7,8].

A French epidemiologic study on the incidence of drug-induced myoclonus reported that 12% of drug-induced myoclonus was caused by opioid agents, 25% of them were due to tramadol [5]. The incidence of tramadol-induced NM is possibly underestimated considering the presence of mild and transient symptoms observed in substantial patients after taking tramadol.

Tramadol acts as a weak mu-opioid receptor agonist and inhibits γ-aminobutyric acid receptor; it can eventually provoke seizure and myoclonus [10]. Furthermore, tramadol inhibits the reuptake of serotonin at the synaptic cleft and increases the concentration of serotonin in the synaptic cleft. It has been reported that the serotonin neurotransmitter system plays a role in the development of gabapentin-induced myoclonus [11-13]. These are the well-known pathogenic mechanisms of myoclonus.

Patient with NM cannot sustain a posture because the affected limbs or neck are suddenly lapse and jerk downward by brief interruption of tonic muscle contraction. NM does not occur at rest, while positive myoclonus may appear at rest or during voluntary movement. Our patient developed sudden, brief, involuntary, and shock-like jerky movements while keeping of certain postures, such as elevating his arms forward and extending his neck. However, these symptoms completely disappeared at rest. On neurological examination, these movements were easily reproduced during sustained postures, which were irregular, repetitive, and symmetric. These clinical features were consistent with NM.

In our case, the patient suddenly showed NM after taking tramadol and dramatically recovered by the administration of clonazepam and discontinuation of tramadol. He had no history of seizure or myoclonus. Furthermore, there were no significant abnormal findings in the laboratory tests or brain MRI. Therefore, we concluded this case as NM associated with tramadol use.

There have been several case reports and case series of drug-induced NM, including gabapentin and pregabalin [4,14]. Drug-induced NM is usually believed to be of subcortical origin because of the absence of cortical correlates of NM in the electrophysiological tests [2,15]. In our case, the characteristics of NM were similar to those of asterixis in that it was multifocal, bilateral, and symmetric and occurred without any external stimuli. Asterixis, the most characteristic subtype of NM, is known to be of subcortical origin and can occur in drug-induced disorders and toxic metabolic encephalopathies [2].

In general, subcortical NM shows good response to clonazepam as in our case. Although we did not perform simultaneous EEG-electromyography or somatosensory evoked potential test because the patient's symptoms improved completely after the administration of clonazepam, we suggest that this case is likely to be NM of subcortical origin.

Clinicians must be significantly cautious of the possible occurrence of myoclonus or seizure in patients taking tramadol. We suggest that tramadol can potentially induce an NM, even in patients taking tramadol within its therapeutic dose and without history of seizure or myoclonus.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: SYB, SL; Data curation: SYB; Formal analysis: SL; Investigation: SYB; Supervision, Validation: SL; Writing-original draft: SYB; Writing-review & editing: SL.

https://doi.org/10.12701/yujm.2020.00108

ORCID
Seong Yoon Bae, https://orcid.org/0000-0003-1592-3601
Se-Jin Lee, https://orcid.org/0000-0001-7438-691X

References

1. Rubboli G, Tassinari CA. Negative myoclonus. An overview of its clinical features, pathophysiological mechanisms, and management. Neurophysiol Clin 2006;36:337–43.
2. Kojovic M, Cordivari C, Bhatia K. Myoclonic disorders: a practical approach for diagnosis and treatment. Ther Adv Neurol Disord 2011;4:47–62.
3. Eberhardt O, Topka H. Myoclonic disorders. Brain Sci 2017;7:103.
4. Kim JB, Jung JM, Park MH, Lee EJ, Kwon DY. Negative myoclonus induced by gabapentin and pregabalin: a case series and systematic literature review. J Neurol Sci 2017;382:36–9.
5. Brefel-Courbon C, Gardette V, Ory F, Montastruc JL. Drug-induced myoclonus: a French pharmacovigilance database study. Neurophysiol Clin 2006;36:333–6.
6. Jovanovic-Cupic V, Martinovic Z, Nesic N. Seizures associated with intoxication and abuse of tramadol. Clin Toxicol (Phila) 2006;44:143–6.
7. Talaie H, Panahandeh R, Fayaznouri M, Asadi Z, Abdollahi M. Dose-independent occurrence of seizure with tramadol. J Med Toxicol 2009;5:63–7.
8. Boostani R, Derakhshan S. Tramadol induced seizure: a 3-year study. Caspian J Intern Med 2012;3:484–7.
9. Grond S, Sablotzki A. Clinical pharmacology of tramadol. Clin Pharmacokinet 2004;43:879–923.
10. Rehni AK, Singh I, Kumar M. Tramadol-induced seizurogenic effect: a possible role of opioid-dependent gamma-aminobutyric acid inhibitory pathway. Basic Clin Pharmacol Toxicol 2008;103:262–6.
11. Pappert EJ, Goetz CG, Stebbins GT, Belden M, Carvey PM. 5-Hydroxytryptophan-induced myoclonus in guinea pigs: mediation through 5-HT1/2 receptor subtypes. Eur J Pharmacol 1998;347:51–6.
12. Pranzatelli MR. Serotonin and human myoclonus. Rationale for the use of serotonin receptor agonists and antagonists. Arch Neurol 1994;51:605–17.
13. Asconape J, Diedrich A, DellaBadia J. Myoclonus associated with the use of gabapentin. Epilepsia 2000;41:479–81.
14. Park KD, Kim MK, Lee SJ. Negative myoclonus associated with pregabalin. Yeungnam Univ J Med 2018;35:240–3.
15. Li JY, Cunic DI, Paradiso G, Gunraj C, Pal PK, Lang AE, et al. Electrophysiological features of myoclonus-dystonia. Mov Disord 2008;23:2055–61.

Yeungnam University Journal of Medicine
YUJM

Case report
eISSN 2384-0293
Yeungnam Univ J Med 2020;37(4):332-336
https://doi.org/10.12701/yujm.2020.00178

Prevention of thiopurine-induced early leukopenia in a Korean pediatric patient with Crohn's disease who turned out to possess homozygous mutations in *NUDT15* R139C

Jaewoan Bae[1], Byung-Ho Choe[1,2], Ben Kang[1,2]

[1]Department of Pediatrics, School of Medicine, Kyungpook National University, Daegu, Korea
[2]Crohn's and Colitis Association in Daegu-Gyeongbuk (CCAiD), Daegu, Korea

Received: March 16, 2020
Revised: April 30, 2020
Accepted: May 7, 2020

Corresponding author:
Ben Kang
Department of Pediatrics, School of Medicine, Kyungpook National University, 680 Gukchaebosang-ro, Jung-gu, Daegu 41944, Korea
Tel: +82-53-200-2749
Fax: +82-53-200-2029
E-mail: benkang@knu.ac.kr

Homozygous mutations in *NUDT15* R139C are known as the major factor associated with thiopurine-induced early leukopenia, particularly in Asian patients. Therefore, *NUDT15* genotyping is currently recommended before thiopurine treatment to identify patients who are NUDT15 poor metabolizers and consider the use of an alternative immunomodulatory therapy. We report a case of a 12-year-old Korean girl with Crohn's disease (CD), in whom thiopurine-induced leukopenia was prevented by initiation of azathioprine (AZA) therapy at a low dose (0.5 mg/kg/day) and early detection of significant hair loss and white blood cell (WBC) count decrease at 17 days from the start of AZA treatment. The WBC count dropped from 8,970/μL to 3,370/μL in 2 weeks, and AZA treatment was stopped because of concerns of potential leukopenia in the near future. Her WBC count recovered to 5,120/μL after 3 weeks. Gene analysis later revealed that she had a homozygous mutation in *NUDT15* R139C, resulting in a poor metabolizing activity of NUDT15. In situations when *NUDT15* genotyping is unavailable, initiation of AZA therapy at 0.5 mg/kg/day with close observation of hair loss and WBC counts within 2 weeks may be an alternative way to prevent thiopurine-induced early leukopenia in Asian children with CD.

Keywords: Alopecia; Azathioprine; Inflammatory bowel disease; Leukopenia; NUDT15

Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease, which can affect the entire gastrointestinal (GI) tract [1]. Approximately 25% of patients with CD are diagnosed <20 years; moreover, the incidence of CD has notably increased in children [1-4]. Pediatric-onset CD is known to have a more aggressive disease course than that of adult-onset CD, requiring an early introduction of immunomodulators and/or anti-tumor necrosis factor (anti-TNF) agents [5,6].

Thiopurines, namely azathioprine (AZA) and 6-mercaptopurine (MP), are among the most widely used immunomodulators for the treatment of pediatric CD [7]. They are usually used as a monotherapy or combination therapy with an anti-TNF agent [7]. However, thiopurine-related adverse events, such as leukopenia, have been frequently reported in patients with CD, particularly in Asian patients [8,9]. Moreover, some patients develop severe life-threatening leukopenia during early thiopurine therapy [9-11].

Although mutations in the *TPMT* gene has been considered the major factor associated with leukopenia in Western countries, the life-threatening thiopurine-induced early leukopenia could not be explained by *TPMT* gene polymorphisms alone in Korean patients because the incidence of *TPMT* variants in the Korean population is lower than that in the Caucasian populations [12]. How-

ever, a recent genome-wide association study has shown that thiopurine-induced early leukopenia is strongly associated with a common missense variant of the *NUDT15* gene encoding R139C in Koreans [10]. Therefore, *NUDT15* genotyping is recommended before thiopurine treatment to identify patients susceptible to thiopurine-induced early leukopenia, particularly in Asians [13]. However, its application in real life is still limited owing to its high costs.

We report a case of a 12-year-old girl with CD, in whom thiopurine-induced early leukopenia was prevented by starting AZA at a low dose followed by discontinuation of AZA owing to significant hair loss and an extensive decrease in WBC count at 2 weeks after treatment. Genotyping later revealed that she had a homozygous mutation in *NUDT15* R139C.

Case

This study was approved by the Institutional Review Board (IRB) of Kyungpook National University Chilgok Hospital (IRB No: 2020-05-001).

A 12-year-old Korean girl was admitted due to abdominal pain and diarrhea for 3 months. She also had weight loss of 8 kg during this period without any decrease in her growth velocity. Past medical history of the patient and family was unremarkable.

On admission, her vital signs were stable and within normal limits. Abdominal tenderness without rebound tenderness was evident in the right lower quadrant. An anal fissure and perianal skin tag were also observed on physical examination. Her sexual maturity was Tanner stage 4. Initial laboratory tests showed a WBC count 10,680/μL, hemoglobin 11.1 g/dL, platelet count 694,000/μL, erythrocyte sedimentation rate (ESR) 77 mm/hr, C-reactive protein (CRP) 8.3 mg/dL, and albumin 3 g/dL. Stool occult blood test was positive, and fecal calprotectin level was > 2,000 μg/g. No pathogens were detected on stool culture and stool polymerase chain reaction (PCR). Ileocolonoscopy revealed skipped lesions of small to very large ulcers from the terminal ileum to the rectum (Fig. 1). Small aphthous ulcers were also observed in the esophagus and stomach on upper GI endoscopy. Cryptitis and crypt abscesses were observed throughout the terminal ileum and colon on histology; however, the acid-fast bacillus smear and culture, as well as PCR for tuberculosis were negative. Magnetic resonance enterography (MRE) revealed multiple skipped lesions throughout the ileum and colon without evidence of stenosing or fistulizing complications in the abdomen. Supplementary pelvic magnetic resonance imaging conducted with the MRE showed T2 hyperintensity at the 1 o'clock and 12 o'clock intersphincteric area without evident tract-like structures. Chest radiography showed no abnormal findings in the lungs, and the interferon-gamma release assay was negative. The patient was diagnosed with CD with a phenotype of A1b, L3+L4ab, B1, G0 according to the Paris classification. Her pediatric Crohn's disease activity index (PCDAI) score was 60, and simple endoscopic score for CD (SES-CD) was 31.

Treatment was started with exclusive enteral nutrition (EEN), mesalazine, and AZA. AZA was initiated at a dose of 17 mg/day (0.5 mg/kg/day). The patient was discharged 10 days after admission. Her laboratory examinations conducted on the day of discharge showed a WBC count 8,970/μL, hemoglobin 9.7 g/dL, platelet count 584,000/μL, ESR 65 mm/hr, CRP 0.1 mg/dL, and albumin 3.2 g/dL. Her PCDAI score was 40.

A follow-up was conducted at the outpatient clinic 2 weeks after discharge. Her laboratory exams revealed a WBC count 3,370/μL,

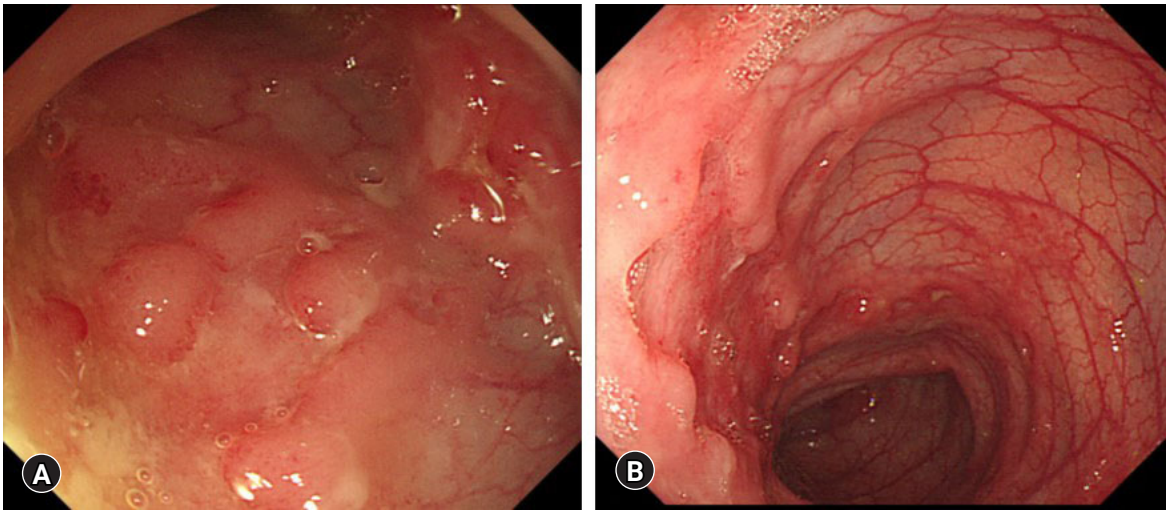


Fig. 1. Endoscopic images at diagnosis. Multiple ulcers of various sizes are noted in the terminal ileum (A) and colon (B).

hemoglobin 10.2 g/dL, platelet count 402,000/μL, ESR 11 mm/hr, CRP 0.04 mg/dL, and albumin 4.1 g/dL. Her GI symptoms improved, and PCDAI score was 15. However, she complained of significant hair loss. Owing to the hair loss and extensive decrease in WBC counts, AZA was discontinued because of concerns of potential thiopurine-induced leukopenia in the near future. The results of *TPMT* and *NUDT15* gene analysis conducted during her first admission were pending.

After 3 weeks, her laboratory examinations showed a WBC count 5,120/μL, hemoglobin 12.7 g/dL, platelet count 285,000/μL, ESR 5 mm/hr, CRP 0.01 mg/dL, and albumin 4.4 g/dL (Fig. 2). Her PCDAI score was 0, and her hair loss improved. *TPMT* and *NUDT15* gene analysis revealed *TPMT *1/*1* genotype (normal metabolizer) and a homozygous mutation in *NUDT15* R139C comprising a diplotype of *NUDT15 *3/*3* (poor metabolizer), respectively.

EEN was continued for 2 additional weeks (a total of 8 weeks). Oral methotrexate was started at a dose of 12.5 mg/week as an alternative immunomodulatory therapy to AZA. She maintained clinical remission (PCDAI < 10) with methotrexate and mesalazine treatment. However, after 4 months, her symptoms relapsed, and infliximab was started. Currently, she is maintaining clinical remission with infliximab, methotrexate, and mesalazine for more than 1 year, and ileocolonoscopy performed 1 year after infliximab initiation revealed mucosal healing (SES-CD, 0).

Discussion

In this case, we were able to observe that thiopurine-induced early leukopenia could be prevented in patients with homozygous mutations in *NUDT15* R139C (NUDT15 poor metabolizers) without knowledge of the results for *NUDT15* gene analysis by starting AZA therapy at low doses with short-term monitoring of WBC counts and close observation of the associated symptoms, such as hair loss.

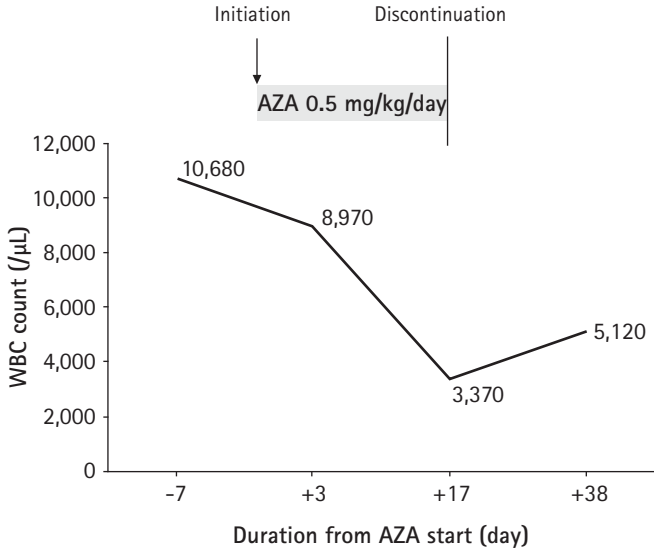


Fig. 2. Changes in white blood cell counts after the initiation and discontinuation of azathioprine in the patient. AZA, azathioprine; WBC, white blood cell.

Thiopurines are among the most commonly used immunomodulators for the treatment of pediatric CD [7]. The recommended doses of AZA and 6-MP for the treatment of pediatric CD are 2–2.5 mg/kg/day and 1–1.5 mg/kg/day, respectively, in patients with normal TPMT metabolism [7]. Although treatment is usually started at these doses in Western countries, adult gastroenterologists in Asian countries tend to use a dose-escalating strategy by starting AZA therapy at low doses of 0.5–1 mg/kg/day and then increasing the dose gradually to the target dose along with close monitoring of the laboratory results and potential adverse events in 1–2-week intervals during the first 2 months of treatment [13-15]. This difference in AZA dosing regimens in real-life practice in Asian countries is mainly attributed to the high incidence of thiopurine-induced leukopenia in Asian patients even at lower doses than those used in Western countries [8,10]. Although this thiopurine dose-escalating strategy is popular among adult gastroenterologists in Asia, many pediatric gastroenterologists in Asia still prescribe AZA therapy at initial doses of 2–2.5 mg/kg/day, which are associated with a high incidence of thiopurine-induced leukopenia.

The high incidence of this life-threatening adverse event in Asian populations cannot be explained by variants in the *TPMT* gene, the major genetic factor associated with thiopurine-induced leukopenia in Caucasian populations, because the frequency of *TPMT* mutations in Asians (1%–3%) is lower than that in Caucasians (10%) [16]. Moreover, Yang et al. [10] showed a variant in the *NUDT15* gene, R139C, was the major factor associated with thiopurine-induced early leukopenia in Korean patients. This *NUDT15* variant showed a strong association with thiopurine-induced early leukopenia (< 8 weeks after treatment) in Koreans with an odds ratio of 35.6 [10]. Further studies have shown that the frequency of *NUDT15* mutations is extremely rare in European populations, where 0.5% and 0% are NUDT15 intermediate and poor metabolizers, respectively, whereas in Asian populations, 22%–28% and 2%–3% are NUDT15 intermediate and poor metabolizers, respectively [17,18]. Moreover, early leukopenia of grade 3 (WBC count, 1,000–1,999/μL) or grade 4 (WBC count < 1,000/μL) was observed in patients with homozygous *NUDT15* R139C mutations even at low initial AZA doses (0.5–1 mg/kg/day) within 8 weeks after initiation of AZA treatment [14,15]. Therefore, *NUDT15* genotyping is currently recommended before thiopurine treatment to identify patients who are

https://doi.org/10.12701/yujm.2020.00178

NUDT15 poor metabolizers and consider the use of an alternative immunomodulatory therapy in those susceptible to thiopurine-induced early leukopenia [19]. For NUDT15 intermediate metabolizers, it is recommended to start with AZA doses of 0.6–2.4 mg/kg/day, and adjust the doses based on the degree of myelosuppression [19].

However, the application of *NUDT15* genotyping in real-life practice is limited mainly owing to its high cost. Additionally, the results of *NUDT15* genotyping might be still unavailable at the time of thiopurine therapy initiation, as in the current case. We have been conducting both *NUDT15* and *TPMT* genotyping in patients who are scheduled for AZA treatment at our center since 2017. However, it usually takes approximately 1 month for the test results to come out. The case reported here presented with severe disease activity with a PCDAI score, 60 and SES-CD, 31; therefore, AZA therapy was initiated at a dose of 0.5 mg/kg/day on the day after diagnosis along with EEN without waiting for the *NUDT15* genotyping results. A surprisingly massive decrease in WBC count (by 6,600/μL) within a 2-week treatment period with AZA at 0.5 mg/kg/day was observed. Similarly, Asada et al. [14] reported a median decrease in WBC count by 4,550/μL within 2 weeks of AZA treatment at doses of 0.75 mg/kg/day in NUDT15 poor metabolizers. Hair loss was another clue that the extensive decrease in WBC count was associated with AZA treatment. Alopecia is commonly observed prior to thiopurine-induced leukopenia in Asian patients [11,14,15,20]. Therefore, the presence of both an extensive decrease in WBC count within 2 weeks after thiopurine therapy initiation and significant hair loss could be an indicator for thiopurine-induced early leukopenia in patients with CD.

In conclusion, we report a case of a 12-year-old Korean girl with CD, in whom thiopurine-induced leukopenia was prevented by initiation of AZA therapy at a low dose (0.5 mg/kg/day) followed by discontinuation of AZA owing to significant hair loss and an extensive decrease in WBC count at 2 weeks after treatment. Genotyping later revealed that she had a homozygous mutation in NUDT15 R139C (NUDT15 poor metabolizer). Pediatric gastroenterologists should keep in mind that in situations when *NUDT15* genotyping is unavailable, initiation of AZA therapy at 0.5 mg/kg/day with close monitoring of hair loss and WBC counts within 2 weeks may be an alternative way to prevent thiopurine-induced early leukopenia in Asian children with CD.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Funding

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (No. 2017R1C1B5076980).

Author contributions

Conceptualization, Data curation: all authors; Formal analysis: BHC, BK; Investigation: JB, BK; Supervision: BHC, BK; Writing-original draft: JB; Writing-review & editing: BHC, BK.

ORCID

Jaewoan Bae, https://orcid.org/0000-0003-3607-2148
Byung-Ho Choe, https://orcid.org/0000-0001-9899-9120
Ben Kang, https://orcid.org/0000-0002-8516-9803

References

1. Rosen MJ, Dhawan A, Saeed SA. Inflammatory bowel disease in children and adolescents. JAMA Pediatr 2015;169:1053–60.
2. Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. Inflamm Bowel Dis 2011;17:423–39.
3. Hong SJ, Cho SM, Choe BH, Jang HJ, Choi KH, Kang B, et al. Characteristics and incidence trends for pediatric inflammatory bowel disease in Daegu-Kyungpook Province in Korea: a multi-center study. J Korean Med Sci 2018;33:e132.
4. Kang B, Kim JE, Jung JH, Choe JY, Kim MJ, Choe YH, et al. Korean children and adolescents with Crohn's disease are more likely to present with perianal fistulizing disease at diagnosis compared to their European counterparts. Pediatr Gastroenterol Hepatol Nutr 2020;23:49–62.
5. Kang B, Choi SY, Kim HS, Kim K, Lee YM, Choe YH. Mucosal healing in paediatric patients with moderate-to-severe luminal Crohn's disease under combined immunosuppression: escalation versus early treatment. J Crohns Colitis 2016;10:1279–86.
6. Kang B, Choe YH. Early biologic treatment in pediatric Crohn's disease: catching the therapeutic window of opportunity in early disease by treat-to-target. Pediatr Gastroenterol Hepatol Nutr 2018;21:1–11.
7. Ruemmele FM, Veres G, Kolho KL, Griffiths A, Levine A, Escher JC, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J Crohns Colitis 2014;8:1179–207.
8. Kim JH, Cheon JH, Kim WH. The frequency and the course of the adverse effects of azathioprine/6-mercaptopurine treatment in patients with inflammatory bowel disease. Korean J Gastro-

enterol 2008;51:291–7.
9. Chun JY, Kang B, Lee YM, Lee SY, Kim MJ, Choe YH. Adverse events associated with azathioprine treatment in korean pediatric inflammatory bowel disease patients. Pediatr Gastroenterol Hepatol Nutr 2013;16:171–7.
10. Yang SK, Hong M, Baek J, Choi H, Zhao W, Jung Y, et al. A common missense variant in NUDT15 confers susceptibility to thiopurine-induced leukopenia. Nat Genet 2014;46:1017–20.
11. Lee YJ, Hwang EH, Park JH, Shin JH, Kang B, Kim SY. NUDT15 variant is the most common variant associated with thiopurine-induced early leukopenia and alopecia in Korean pediatric patients with Crohn's disease. Eur J Gastroenterol Hepatol 2016;28:475–8.
12. Kim HY, Lee SH, Lee MN, Kim JW, Kim YH, Kim MJ, et al. Complete sequence-based screening of TPMT variants in the Korean population. Pharmacogenet Genomics 2015;25:143–6.
13. Lee KM, Kim YS, Seo GS, Kim TO, Yang SK; IBD Study Group of the Korean Association for the Study of Intestinal Diseases. Use of thiopurines in inflammatory bowel disease: a consensus statement by the Korean Association for the Study of Intestinal Diseases (KASID). Intest Res 2015;13:193–207.
14. Asada A, Nishida A, Shioya M, Imaeda H, Inatomi O, Bamba S, et al. NUDT15 R139C-related thiopurine leukocytopenia is mediated by 6-thioguanine nucleotide-independent mechanism in Japanese patients with inflammatory bowel disease. J Gastroenterol 2016;51:22–9.
15. Zhu X, Wang XD, Chao K, Zhi M, Zheng H, Ruan HL, et al. NUDT15 polymorphisms are better than thiopurine S-methyltransferase as predictor of risk for thiopurine-induced leukopenia in Chinese patients with Crohn's disease. Aliment Pharmacol Ther 2016;44:967–75.
16. Collie-Duguid ES, Pritchard SC, Powrie RH, Sludden J, Collier DA, Li T, et al. The frequency and distribution of thiopurine methyltransferase alleles in Caucasian and Asian populations. Pharmacogenetics 1999;9:37–42.
17. Yang JJ, Landier W, Yang W, Liu C, Hageman L, Cheng C, et al. Inherited NUDT15 variant is a genetic determinant of mercaptopurine intolerance in children with acute lymphoblastic leukemia. J Clin Oncol 2015;33:1235–42.
18. Kim HT, Choi R, Won HH, Choe YH, Kang B, Lee K, et al. NUDT15 genotype distributions in the Korean population. Pharmacogenet Genomics 2017;27:197–200.
19. Relling MV, Schwab M, Whirl-Carrillo M, Suarez-Kurtz G, Pui CH, Stein CM, et al. Clinical pharmacogenetics implementation consortium guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update. Clin Pharmacol Ther 2019;105:1095–105.
20. Kakuta Y, Naito T, Onodera M, Kuroha M, Kimura T, Shiga H, et al. NUDT15 R139C causes thiopurine-induced early severe hair loss and leukopenia in Japanese patients with IBD. Pharmacogenomics J 2016;16:280–5.

https://doi.org/10.12701/yujm.2020.00178

Yeungnam University Journal of Medicine
YUJM

Case report
eISSN 2384-0293
Yeungnam Univ J Med 2020;37(4):337-340
https://doi.org/10.12701/yujm.2020.00402

Ureterosciatic hernia causing obstructive uropathy successfully managed with minimally invasive procedures

Yeong Uk Kim[1], Jae Ho Cho[2], Phil Hyun Song[3]

[1]Department of Urology, Yeungnam University Hospital, Daegu, Korea
[2]Department of Radiology, Yeungnam University College of Medicine, Daegu, Korea
[3]Department of Urology, Yeungnam University College of Medicine, Daegu, Korea

Received: May 26, 2020
Revised: June 27, 2020
Accepted: July 8, 2020

Corresponding author:
Phil Hyun Song
Department of Urology, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-620-3693
Fax: +82-53-627-5535
E-mail: sph04@hanmail.net

Ureterosciatic hernia is extremely rare. In ureteral herniation, ureter prolapses occur through either the greater or lesser sciatic foramen. Atrophy of the piriformis muscle, hip joint diseases, and defects in the parietal pelvic fascia are predisposing factors for the development of ureterosciatic hernia. Most symptomatic patients have been treated surgically, with conservative treatment reserved only for asymptomatic patients. To the best of our knowledge, long-term follow-up outcomes after ureterosciatic hernia management are sparse. In this paper, we report the case of a 68-year-old woman who presented with colicky left abdominal pain. After computed tomography (CT) scan and anterograde pyelography, she was diagnosed ureterosciatic hernia with obstructive uropathy. We performed ureteral balloon dilatation and double-J ureteral stent placement. After this minimally invasive procedure, CT scan demonstrated that the left ureter had returned to its normal anatomical position without looping into the sciatic foramen. The patient remained asymptomatic with no adverse events 7 years after the minimally invasive procedures. This brief report describes ureterosciatic hernia successfully managed with minimally invasive procedures with long-term follow-up outcomes.

Keywords: Hernia; Minimally invasive surgical procedures; Treatment outcome; Ureter

Introduction

Obstructive uropathy can be caused by fibrotic ureteral stricture, ureteral calculi, ureteral malignancy, and several types of external compression. Ureteral hernia is rare, hence its very limited literature worldwide, but potentially serious because it may lead to ureteral obstruction. Of the many types of ureteral hernias, ureterosciatic hernia is extremely rare, with only 30 reported cases of ureterosciatic hernia as of 2018 [1,2]. Most symptomatic patients undergo surgical procedures, while those who are asymptomatic receive conservative treatment. To the best of our knowledge, long-term follow-up outcomes after ureterosciatic hernia management are sparse. This brief report describes ureterosciatic hernia successfully managed with minimal invasive procedures with long-term follow-up outcomes.

Case

This report was approved by the Institutional Review Board (IRB) of the Yeungnam University Hospital (IRB No: 2020-06-047). Written informed consent was obtained from the patient for publication of this case report and accompanying images.

In 2013, a 68-year-old Korean woman sought consult at our hospital because of colicky left abdominal pain for several days. The patient was generally in good health, with stable vital signs and a normal body mass index. Laboratory examinations revealed mild leukocytosis. On physical examination, she complained of left costovertebral angle tenderness. Her past medical history in-

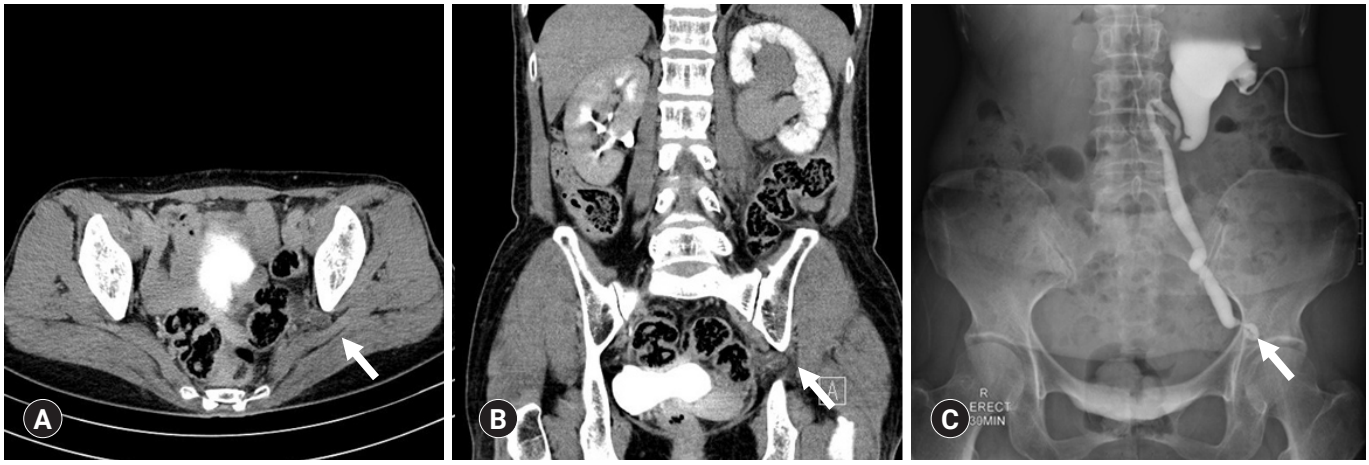


Fig. 1. Postcontrast axial (A), coronal (B) computed tomography (CT), and a left anterograde pyelography (AGP, C) show left hydronephroureter with herniation into sciatic foramen (arrows). These CT and AGP reveal a 'curlicue ureter' sign as the knuckle of the herniated ureter passed laterally to the medial wall of the pelvis (arrows).

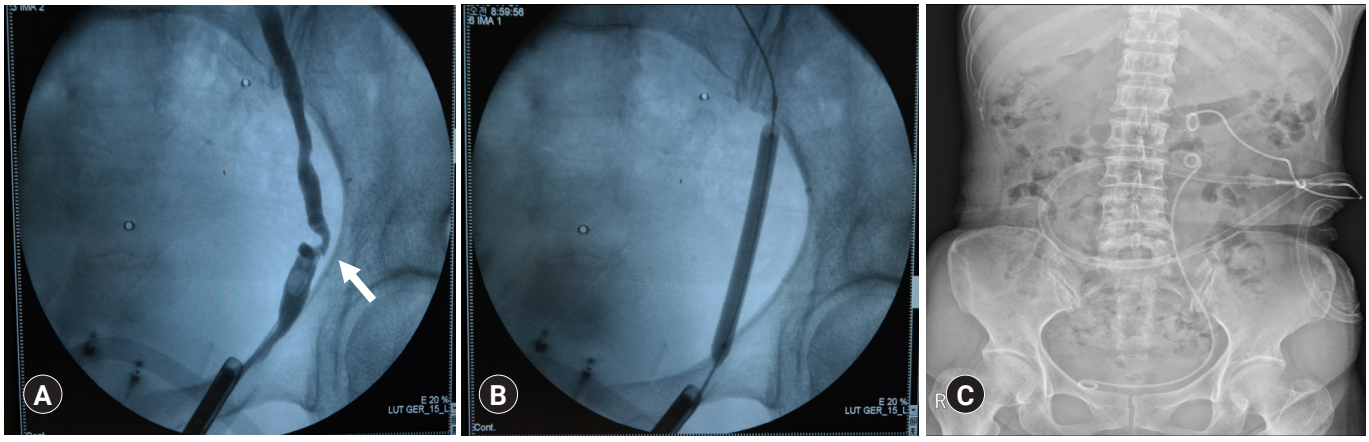


Fig. 2. A left retrograde pyelography reveals a 'curlicue ureter' sign as the knuckle of the herniated ureter (A, arrow). Ureteral balloon dilation is performed in this herniated ureter (B) and left double-J ureteral stent is placed after ureteral balloon dilation (C).

cluded a gynecological operation for a left ovarian abscess in 2009. After physical examination we carried out radiological evaluation; simple X-ray images did not reveal any abnormal lesion. We then decided to use more detailed radiological imaging modalities. Computed tomography (CT) scan, normally used for evaluating of urinary tract stone or obstructive uropathy, identified that the left ureter was grossly dilated, and that the loop of the ureter was displaced through the sciatic notch (Fig. 1A, 1B). No evidence of calculi or masses was seen in kidney and ureter. To resolve left hydronephrosis, left percutaneous nephrostomy (PCN) was done. The patient was then hospitalized for 8 days for conservative treatment. After 72 hours from nephrostomy insertion, a left anterograde pyelography was done, and this demonstrated a grossly dilated left ureter with herniation through the sciatic foramen (Fig. 1C). Six days post admission, we performed the ureteral balloon dilation and double-J ureteral stent placement under image guidance successfully (Fig. 2). On the next day, the left PCN was removed. A month after the balloon procedure, the double-J stent was removed at outpatient department. After ureteral balloon dilation and double-J ureteral stent insertion, CT scan was repeated and this demonstrated that the left ureter was no longer looped into the sciatic foramen and had returned to its normal anatomical position (Fig. 3). Seven years after the minimally invasive procedures, the patient remained asymptomatic with no adverse events, based on follow-ups every 2 years.

Discussion

Ureteral herniation into the sciatic foramen is extremely rare [2]. The most-reported ureteral herniation site is the inguinal canal, and the ureter may even herniate into the scrotum [3].

Concerning anatomy and pathogenesis, the sacrospinous liga-

https://doi.org/10.12701/yujm.2020.00402

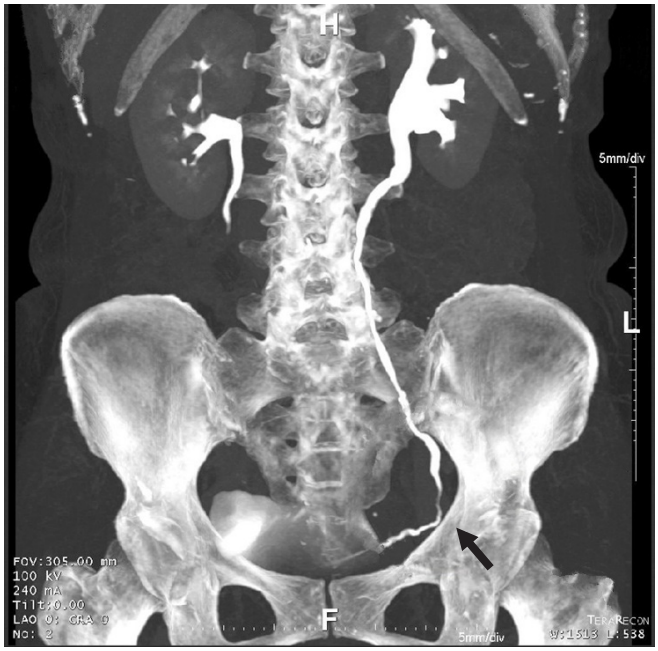


Fig. 3. Follow-up postcontrast coronal computed tomography shows the left ureter was no longer looped into the sciatic foramen and had returned to its normal anatomical position (arrow).

ment divides the sciatic notch into the greater and lesser sciatic foramen. In ureteral herniation, ureter prolapses occur through this sciatic notch. The greater sciatic foramen is further subdivided by the piriformis muscle into the superior and inferior compartments of the piriformis and it is considered to be a potential space because the piriformis completely occupies the greater sciatic foramen [4]. Sciatic hernias seem to be more predominant in elderly females because of their larger sciatic foramen and wider pelvis [5]. The predisposing factors for the development of ureterosciatic hernia include atrophy of the piriformis muscle, hip joint diseases, and defects in the parietal pelvic fascia [6]. In our case, the patient did not suffer from any hip diseases, but she had undergone a gynecological operation for an ovarian abscess.

The clinical presentation of ureterosciatic hernia can either be asymptomatic or symptomatic, such as renal colic. Moreover, the symptoms related to the herniation of other organs such as the ovary, small and large intestines, and sciatic nerve may be present, unlike in ureteral stricture [7]. In our case, the patient had a renal colic due to ureteral obstruction. Witney-Smith et al. [1] have reported that ureterosciatic hernia can cause pyelonephritis and occasionally severe urinary sepsis.

Radiological investigations including intravenous pyelography, antegrade pyelography, and CT are extremely important. This disease may be identified with intraoperative retrograde pyelography. A curling ureter, also referred to as the 'curlicue ureter,' has a pathognomonic radiologic appearance in which a loop of ureter is displaced laterally, inferiorly, and posteriorly through the sciatic notch on urography [4].

Asymptomatic ureterosciatic hernia was treated with closed observation in previous cases [8]. However, in most symptomatic patients, surgical corrections using open or laparoscopic options are performed, including excision of the hernia with reduction of ureter length and reimplantation of the remaining ureter. In this aspect, there are some differences in the management between ureterosciatic hernia and ureteral stricture because the treatment of a ureteral stricture is essential to preserve the renal functions. Although surgical treatment was relatively straightforward in our patient, surgical exposure may be somewhat challenging in other patients. From a clinical point of view, minimally invasive procedures such as ureteroscopy or retrogradely double-J stent placement are optimal strategies. Balloon dilation can also be considered for treatment of ureteral stricture caused by previously performed other operations as in our case [2,4].

Because ureterosciatic hernia is extremely rare, long-term follow-up outcomes are sparse, unlike in ureteral stricture cases. In our case, minimally invasive procedures including balloon dilation and retrograde double-J stent placement were successfully performed, and there was no evidence of recurrent hernia or subjective symptoms even 7 years postoperatively. More case reports for ureterosciatic hernias are needed to decide on an optimal treatment.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: all authors; Data curation and Investigation: YUK; Formal analysis and Supervision: JHC, PHS; Methodology: PHS; Visualization: JHC; Writing-original draft: YUK; Writing-review & editing: JHC, PHS.

ORCID

Yeong Uk Kim, https://orcid.org/0000-0002-8783-9567
Phil Hyun Song, https://orcid.org/0000-0002-3801-258X

References

1. Witney-Smith C, Undre S, Salter V, Al-Akraa M. An unusual case of a ureteric hernia into the sciatic foramen causing urinary

sepsis: successfully treated laparoscopically. Ann R Coll Surg Engl 2007;89:W10–2.
2. Nakazawa Y, Morita N, Chikazawa I, Miyazawa K. Ureterosciatic hernia treated with ureteral stent placement. BMJ Case Rep 2018;2018:bcr2017222908.
3. Rommel FM, Boline GB, Huffnagle HW. Ureterosciatic hernia: an anatomical radiographic correlation. J Urol 1993;150:1232–4.
4. Weintraub JL, Pappas GM, Romano WJ, Kirsch MJ, Spencer W. Percutaneous reduction of ureterosciatic hernia. AJR Am J Roentgenol 2000;175:181–2.
5. Hayashi N, Suwa T, Kimura F, Okuno A, Ishizuka M, Kakizaki S, et al. Radiographic diagnosis and surgical repair of a sciatic hernia: report of a case. Surg Today 1995;25:1066–8.
6. Tsuzaka Y, Saisu K, Tsuru N, Homma Y, Ihara H. Laparoscopic repair of a ureteric sciatic hernia: report of a case. Case Rep Urol 2014;2014:787528.
7. Losanoff JE, Basson MD, Gruber SA, Weaver DW. Sciatic hernia: a comprehensive review of the world literature (1900-2008). Am J Surg 2010;199:52–9.
8. Tsai PJ, Lin JT, Wu TT, Tsai CC. Ureterosciatic hernia causes obstructive uropathy. J Chin Med Assoc 2008;71:491–3.

https://doi.org/10.12701/yujm.2020.00402

Yeungnam University Journal of Medicine
YUJM

Case report
eISSN 2384-0293
Yeungnam Univ J Med 2020;37(4):341-344
https://doi.org/10.12701/yujm.2020.00472

Clinical characteristics of hereditary neuropathy with liability to pressure palsy presenting with monoparesis in the emergency department

Changho Kim[1], **Jin-Sung Park**[2]

[1]Department of Emergency Medicine, Kyungpook National University Chilgok Hospital, School of Medicine, Kyungpook National University, Daegu, Korea
[2]Department of Neurology, Kyungpook National University Chilgok Hospital, School of Medicine, Kyungpook National University, Daegu, Korea

Received: June 9, 2020
Revised: July 17, 2020
Accepted: July 17, 2020

Corresponding author:
Jin-Sung Park
Department of Neurology, Kyungpook National University Chilgok Hospital, School of Medicine, Kyungpook National University, 807 Hoguk-ro, Buk-gu, Daegu 41404, Korea
Tel: +82-53-200-2753
Fax: +82-53-200-2029
E-mail: neurojspark@gmail.com

Hereditary neuropathy with liability to pressure palsy (HNPP) is a rare neurological genetic disease caused by deletion of the peripheral myelin protein 22 gene and presents in childhood or young adulthood. We report four cases of HNPP with typical and rare presentations, reflecting the broad clinical spectrum of this disease. Two patients presented with mononeuropathies that are frequently observed in HNPP; the remaining two presented with bilateral neuropathy or mononeuropathy anatomically present in the deep layer. This reflects the broad clinical presentation of HNPP, and clinicians should differentiate these conditions in young patients with monoparesis or bilateral paresis. Although HNPP is currently untreatable, early diagnosis in the emergency department can lead to early detection, eventually resulting in less provocation and recurrence which may cause early motor nerve degeneration.

Keywords: Hereditary sensory and motor neuropathy; Paresis; Peripheral myelin protein 22; Rare disease; Young adult

Introduction

Hereditary neuropathy with liability to pressure palsy (HNPP) is an autosomal dominant genetic disease that is clinically characterized by recurrent monoparesis and sensory loss, frequently caused by focal compression or trauma [1]. The diagnosis is confirmed by genetic testing and approximately 80% of patients show deletion of chromosome 17p11.2 of the peripheral myelin protein 22 (*PMP22*) gene and the remaining 20% have a pathogenic variant in *PMP22* [2].

The prevalence of HNPP is known to range from 0.84 to 16 per 100,000 people, with ethnic differences [3]. Interestingly, a recent Korean study showed a significantly higher prevalence of 58.9 per 100,000 people, compared to other studies. While this higher prevalence in the Korean population needs further research, it was explained to an extent by the methodology used; the Korean study was a neonatal screening study, while other studies were performed on symptomatic patients. However, we cannot dismiss the possibility of higher frequency of HNPP in the Korean population and its under-recognition. Here, we summarize the clinical features of young male patients with HNPP who came to our emergency department, with this study aiming to improve the identification of HNPP for early and efficient diagnosis.

Cases

This study was approved by the Institutional Review Board (IRB) of the Kyungpook National University Chilgok Hospital (IRB

No: KNUCH 2019-06-018). Informed and written consent was obtained from the patients for the case series.

1. Case 1

A 34-year-old male presented to our emergency department with left-hand weakness since the morning of the consult. The patient also complained of paresthesia in his left hand. The initial neurological examination showed profound weakness of Medical Research Council (MRC) grade 3 in his left 4th and 5th fingers, along with paresthesia. The results of brain computed tomography (CT) and magnetic resonance imaging (MRI) were normal; and after consultation with the Department of Neurology, nerve conduction and electromyography studies were performed. The electrophysiological study showed multifocal peripheral neuropathy with demyelinating features in all tested nerves, along with conduction block in the left ulnar nerve. The patient's uncle also had a history of symptoms of paralysis. The patient also had a history of recurrent monoparesis and recovery. Genetic testing of the *PMP22* gene confirmed gene deletion. At the last follow-up 3 months after the initial presentation, there was nearly full improvement of the symptomatic ulnar neuropathy at the elbow.

2. Case 2

A 27-year-old male presented to our emergency department with wrist drop in his right hand after his girlfriend slept on his arm the night before. The initial neurological examination showed weakness in wrist dorsiflexion with an MRC grade 2 and paresthesia in the wrist. The results of brain CT and MRI were normal. An electrophysiological study conducted in the Department of Neurology showed multifocal peripheral neuropathy with demyelination in all tested nerves. The conduction block was observed in the symptomatic right radial nerve. A further probe into the patient's family history revealed that his uncle had experienced similar symptoms a few years ago but recovered without significant sequelae. Subsequent genetic analysis revealed deletion of *PMP22*. At the last follow-up 3 months after the initial presentation, the patient recovered without any weakness, and a genetic diagnosis of HNPP was made.

3. Case 3

A 22-year-old man visited our emergency department with bilateral foot drop. The symptom occurred after crouching for 6 hours while wearing long boots. He also complained of paresthesia in both soles. Brain CT result was normal, and he was immediately referred to the Department of Neurology for consultation. The initial neurological examination showed bilateral weakness in ankle dorsiflexion (MRC grade 3) and bilateral paresthesia in the superficial peroneal nerve territories. This patient denied any family history of similar symptoms. The nerve conduction study showed multifocal demyelinating features in all tested nerves with significant conduction block in both peroneal nerves. Upon confirmation of *PMP22* gene deletion, the patient was eventually diagnosed with HNPP. After 4 months, complete recovery was observed.

4. Case 4

A 23-year-old male presented with weakness in the left arm after deep sleep. The initial neurological examination showed proximal left arm weakness with an MRC grade 3. Interestingly, the patient had history of wrist drop on the right side after a strenuous drill during his military service. He also recalled that his wrist drop improved after 6 months. He denied any family history of similar symptoms. Result of brain CT and MRI were normal, and after consultation with the Department of Neurology, a nerve conduction study and electromyography were performed. These studies revealed multifocal peripheral neuropathy with demyelination, superimposed by suprascapular neuropathy in the left side. The nerve conduction study showed significantly reduced compound muscle action potential in left suprascapular nerve with active denervations observed in the left supraspinatus and infraspinatus muscles only. Upon confirmation of *PMP22* gene deletion, the patient was eventually diagnosed with HNPP. At the end of 3 months, the weakness showed significant improvement.

Discussion

HNPP is an autosomal dominant hereditary neuropathy caused by deletion of the *PMP22* gene. The PMP22 protein is commonly found in the peripheral nerves and plays an important role in myelin compaction; its underexpression is known to cause HNPP [4]. Mild nerve injuries in a common entrapment site are known to cause demyelination and remyelination, leading to altered axonal properties and axonal degeneration in the distal segments. This phenomenon can partly explain the cause of focal entrapment neuropathies in the distal regions as the presenting symptom of HNPP. Notably, *PMP22* deletion causes HNPP, while *PMP22* duplication causes Charcot-Marie-Tooth disease type 1A. Simultaneous genetic testing via multiplex ligation-dependent probe amplification is possible and is covered by the national insurance system in Korea.

Clinically, a typical case of HNPP presents with a mononeuropathy and is known to involve superficial nerves instead of deep innervated nerves. A previous study showed recurrent involvement of the peroneal nerve around the fibular head, ulnar nerve at

https://doi.org/10.12701/yujm.2020.00472

the elbow, and radial nerves with a frequency of 35%, 20%, and 8%, respectively [5]. Along with other nerves (peroneal neuropathy at the fibular head and ulnar neuropathy at wrist level), the median nerve at the wrist is one of the most common compression sites among the patients with HNPP. But an isolated idiopathic carpal tunnel syndrome is rare [2]. Typically, the first symptom occurs as a mononeuropathy in the second or third decade of life, which is consistent with our patients' ages.

The diagnosis of HNPP can be made via electrophysiological study, along with confirmation of *PMP22* deletion via genetic analysis. Studies have shown characteristic findings in the nerve conduction study suggestive of HNPP. The general electrophysiological findings of HNPP show features of polyneuropathy with demyelinating features superimposed by focal entrapment neuropathies with slow sensory conduction velocities [6-8]. A recent study that involved HNPP patients under the age of 30 years showed demyelinating features in symptomatic and asymptomatic nerves, with the highest involvement in the ulnar, peroneal, and median nerves. Moreover, there was a significant prolongation of distal motor latency in the tested nerves with slow motor velocities [9]. Another study found a significantly accentuated distal slowing in the median and peroneal nerves with less involvement of ulnar and tibial nerves [10]. These findings are consistent with our case reports, especially in those with a typical HNPP presentation.

Our case series demonstrates both typical and rare types of HNPP showing heterogeneity of clinical presentation to the emergency department (Table 1). The mean age at presentation was 26.5 years, and all patients were male. The typical cases (cases 1 and 2) presented with mononeuropathy in the common entrapment sites in the distal nerves. Therefore, the HNPP diagnosis was quick. However, cases 3 and 4 were rare HNPP cases. There have been reports on extremely rare cases, where the patient has presented with recurrent Bell's palsy [11] and more commonly with proximal limb weakness [10]. A recent study retrospectively reviewed 51 HNPP patients under the age of 30 years and found peroneal and ulnar neuropathy in 30% of the patients and described one case of long thoracic and femoral neuropathy that is usually unaffected by compression [8]. Interestingly, in South Korea, where young males are obligated to serve the military, a different pattern of frequency was observed. A 4-year retrospective study of the medical records in the Korean army hospital showed that the most common initial presentation of HNPP was a brachial plexus lesion that showed proximal arm weakness and paresthesia [12]. The authors found brachial plexus lesions in more than 50% of HNPP patients, which is not in accordance with previous studies in other countries. Moreover, the Korean study stated that the cause of the brachial plexopathy was strenuous push-ups and exercise. This is very similar to case 3 in our study, wherein the patient first experienced symptoms during military service. In case 4, the patient had a very uncommon suprascapular neuropathy which is not usually observed in HNPP. Recent studies have reported a few cases of suprascapular neuropathy in its notch at the supraspinatus fossa caused by strenuous physical activities; this correlates with our patient who also experienced arm weakness after strenuous exercise during his military service [13].

Another report showed an interesting case of bilateral foot drop in an 83-year-old Japanese patient, who experienced symptoms after sitting with their lower legs crossed under their thighs; this presentation was indicative of bilateral common peroneal neuropathy [14]. The patient in case 3, also showed a similar history of prolonged crouching while wearing long boots that caused bilateral common peroneal neuropathy. This is an important finding because HNPP is known to present with mononeuropathy, but the Japanese case and case 3 of our study presented with symmetric bilateral compressive neuropathy.

These rare findings reflect the broad clinical spectrum of HNPP and the different environmental factors among countries that result in a variety of initial presentations in HNPP. More studies are needed to understand the Korean phenotypes in HNPP, as well as HNPP in patients over 30 years old; our case series demonstrates the need for more documented cases from different countries.

The limitation of this retrospective case series is the number of patients enrolled. This was inevitable because we only enrolled

Table 1. Clinical features of HNPP patients

Patient	Sex/age (yr)	Position	Clinical presentation	Trigger	Family history
1	Male/34	Ulnar nerve	Left-hand weakness and paresthesia Weakness in the left 4th and 5th fingers (MRC grade 3) along with paresthesia	Sleep-related compression	Yes
2	Male/27	Radial nerve	Wrist drop in the right hand after it was slept on	Sleep-related compression	Yes
3	Male/22	Bilateral peroneal nerve	Bilateral foot drop and paresthesia in both soles	After prolonged crouching	No
4	Male/23	Suprascapular nerve	Proximal left arm weakness with MRC grade 3	After carrying a heavy backpack	No

HNPP, hereditary neuropathy with liability to pressure palsy; MRC, Medical Research Council.

HNPP patients who primarily visited our emergency department and not our out-patient clinic. Although HNPP is still an untreatable genetic disease, environmental factors that can aggravate monoparesis and eventually lead to further deterioration should be avoided. As there is no specific clue that can lead to the diagnosis of HNPP, it is important for neurologists and emergency department doctors to be aware of these conditions to make a differential diagnosis leading to an early diagnosis and prevent further deterioration of the vulnerable peripheral nerves in patients with HNPP.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization, Formal analysis, Investigation, and Supervision: JSP; Data curation: CK; Writing-original draft: CK; Writing-review & editing: JSP.

ORCID

Changho Kim, https://orcid.org/0000-0002-7552-8200
Jin-Sung Park, https://orcid.org/0000-0001-5506-9206

References

1. Dubourg O, Mouton P, Brice A, LeGuern E, Bouche P. Guidelines for diagnosis of hereditary neuropathy with liability to pressure palsies. Neuromuscul Disord 2000;10:206–8.
2. Bird TD. Hereditary neuropathy with liability to pressure palsies. 1998 Sep 28 [updated 2014 Sep 25]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJ, Stephens K, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020 [cited 2020 Jun 5]. https://www.ncbi.nlm.nih.gov/books/NBK1392/.
3. Park JE, Noh SJ, Oh M, Cho DY, Kim SY, Ki CS. Frequency of hereditary neuropathy with liability to pressure palsies (HNPP) due to 17p11.2 deletion in a Korean newborn population. Orphanet J Rare Dis 2018;13:40.
4. Schenone A, Nobbio L, Caponnetto C, Abbruzzese M, Mandich P, Bellone E, et al. Correlation between PMP-22 messenger RNA expression and phenotype in hereditary neuropathy with liability to pressure palsies. Ann Neurol 1997;42:866–72.
5. Celik Y, Kilincer C, Hamamcioglu MK, Balci K, Birgili B, Cobanoglu S, et al. Hereditary neuropathy with liability to pressure palsies in a Turkish patient (HNPP): a rare cause of entrapment neuropathies in young adults. Turk Neurosurg 2008;18:82–4.
6. Ichikawa K, Nezu A. Hereditary neuropathy with liability to pressure palsies in childhood: report of a case and a brief review. Brain Dev 2005;27:152–4.
7. Andersson PB, Yuen E, Parko K, So YT. Electrodiagnostic features of hereditary neuropathy with liability to pressure palsies. Neurology 2000;54:40–4.
8. Hong YH, Kim M, Kim HJ, Sung JJ, Kim SH, Lee KW. Clinical and electrophysiologic features of HNPP patients with 17p11.2 deletion. Acta Neurol Scand 2003;108:352–8.
9. Robert-Varvat F, Jousserand G, Bouhour F, Vial C, Cintas P, Echaniz-Laguna A, et al. Hereditary neuropathy with liability to pressure palsy in patients under 30 years old: neurophysiological data and proposed electrodiagnostic criteria. Muscle Nerve 2018;57:217–21.
10. Li J, Krajewski K, Shy ME, Lewis RA. Hereditary neuropathy with liability to pressure palsy: the electrophysiology fits the name. Neurology 2002;58:1769–73.
11. Drouet A, Guilloton L, Latour P, Ribot C. Recurrent facial nerve paralysis in hereditary neuropathy with liability to pressure palsy. Presse Med 2000;29:655.
12. Kim KE, Yeom J. Proximal arm weakness is the most common presentation in young Korean soldiers diagnosed as having hereditary neuropathy with liability to pressure palsy (HNPP). J R Army Med Corps 2016;162:352–4.
13. Lorenzoni PJ, Kay CS, Cavalet C, Arndt RC, Werneck LC, Scola RH. Hereditary neuropathy with liability to pressure palsies: a single-center experience in Southern Brazil. Neurol Int 2016;8:6677.
14. Kawaguchi N, Suzuki N, Tateyama M, Takai Y, Misu T, Nakashima I, et al. Two cases of elderly-onset hereditary neuropathy with liability to pressure palsy manifesting bilateral peroneal nerve palsies. Case Rep Neurol 2012;4:149–55.

https://doi.org/10.12701/yujm.2020.00472

Yeungnam University Journal of Medicine
YUJM

Case report
eISSN 2384-0293
Yeungnam Univ J Med 2020;37(4):345-348
https://doi.org/10.12701/yujm.2020.00556

Early surgical intervention for unusually located cardiac fibroelastomas

Eui Suk Chung[1], Jae Hoon Lee[1], Jong Kwon Seo[2], Byung Gyu Kim[2], Gwang Sil Kim[2], Hye Young Lee[2], Young Sup Byun[2], Hyun Jung Kim[3]

[1]Department of Thoracic and Cardiovascular Surgery, Inje University Sanggye Paik Hospital, Inje University School of Medicine, Seoul, Korea
[2]Division of Cardiology, Department of Internal Medicine, Inje University Sanggye Paik Hospital, Inje University School of Medicine, Seoul, Korea
[3]Department of Pathology, Inje University Sanggye Paik Hospital, Inje University School of Medicine, Seoul, Korea

Received: July 6, 2020
Revised: July 10, 2020
Accepted: July 11, 2020

Corresponding author:
Jae Hoon Lee
Department of Thoracic and Cardiovascular Surgery, Inje University Sanggye Paik Hospital, Inje University School of Medicine, 1342 Dongil-ro, Nowon-gu, Seoul 10757, Korea
Tel: +82-2-950-1045
Fax: +82-2-950-1248
E-mail: hoiseljh@hanmail.net

Papillary fibroelastomas are the second most common primary cardiac tumor in adults. Over 80% of fibroelastomas occur on the cardiac valves, usually on the left side of the heart, while the remaining lesions are typically scattered throughout the atria and ventricles. Although the optimal timing for surgery is controversial and depends on tumor size and location, prompt surgical resection is warranted in patients at high risk of embolism. A tumor on the cardiac valve can be removed using the slicing excision technique without leaflet injury. Here we present two cases of papillary fibroelastomas occurring on the ventricular surface of the aortic valve and in the right ventricle.

Keywords: Aortic valve; Embolism; Heart neoplasms; Heart ventricles

Introduction

Cardiac papillary fibroelastoma (PFE), the second most common primary cardiac tumor in adults, has an incidence of 0.02% in every one million autopsies [1]. Its appearance is often likened to sea anemones with frond-like arms emanating from a stalked central core.

In two large studies of PFE patients a mean age of 60 years, the incidence was higher in men (55%); at the time of discovery, the tumors were 2 to 70 mm and the average size was 9 mm [1,2]. Cardiac PFEs usually occur in the heart valve; more than 80% of cases were noted on the left-sided heart valves (aortic, 36%; mitral, 29%; tricuspid, 11%; and pulmonary, 7%), whereas the other lesions were usually scattered throughout the atria and ventricles. Multiple tumors were present in 9% of patients [1,2]. Of PFE cases, 30% were detected accidentally in asymptomatic patients, whereas the other patients presented with stroke, myocardial infarction, and systemic or pulmonary embolic events associated with tumor embolism [1,2]. This case report discusses the ability of early intervention in unusually located PFEs to prevent the occurrence of an embolic event and analyzes whether valve-sparing surgery can be performed safely in cases of valvular involvement in tumors without a risk of recurrence after total excision. Here we present two cases of PFE located at unusual sites.

Cases

This study was approved by the Institutional Review Board (IRB) of Sanggye Paik Hospital (IRB No: SGPAIK 2019-12-008). Written informed consents were obtained from the patients for publication of this case report and accompanying images.

1. Case 1

A 61-year-old woman visited the outpatient clinic for the treatment of a cardiac mass discovered during the workup performed prior to knee arthroplasty surgery. Transthoracic echocardiography showed a 0.8×0.9-cm mobile mass on the ventricular surface of the noncoronary cusp of the aortic valve without valvular dysfunction (Fig. 1A, 1B). Computed tomography also revealed a mass-like lesion between the left ventricular outflow tract and the aortic valve (Fig. 1C). Based on these reports, a PFE was suspected. Surgery was planned immediately because of the hypermobility of the mass at the aortic valve that could potentially cause a fatal cerebral infarction.

The aortic valve was morphologically normal in appearance (Fig. 2A, 2B), and the tumor was removed using the slicing excision technique. After tumor removal, the aortic valve showed normal coaptation without leaflet injury, while postoperative transthoracic echocardiography showed normal function of the aortic valve. The pathologic examination showed findings typical of PFE (Fig. 3). After being discharged from the hospital in a stable condition, the patient was followed up at the outpatient clinic for 1 year without tumor recurrence.

2. Case 2

A 65-year-old man was referred for aortic stenosis with a mass in the right ventricle discovered during the preoperative workup for a right humeral fracture. Transthoracic echocardiography showed severe aortic stenosis with a bicuspid aortic valve and a 1.5-cm hypermobile mass attached to the apex of the right ventricle (Fig. 1D, 1E). Computed tomography showed an aneurysmal change of the ascending aorta (4.7 cm) and a mass lesion in the right ventricle (Fig. 1F).

The tumor was removed concomitantly with replacement of the aortic valve and ascending aorta. The tumor was attached to the myocardial wall at the apex of the right ventricle (Fig. 2C). Immersion of the tumor in water after resection revealed the typical sea anemone appearance (Fig. 2D). After being discharged without complications, the patient was followed up at the outpatient clinic for 18 months without tumor recurrence.

Discussion

Although PFE is the second most common cardiac tumor, its incidence is very low. It is difficult to diagnose before embolic events occur. This study presented two PFE cases that were referred to the medical facility after masses were discovered during preoperative workups for noncardiac surgeries.

In these cases, the tumors were located at unusual sites. In case 1, the tumor was attached to the aortic valve, and the mobile mass

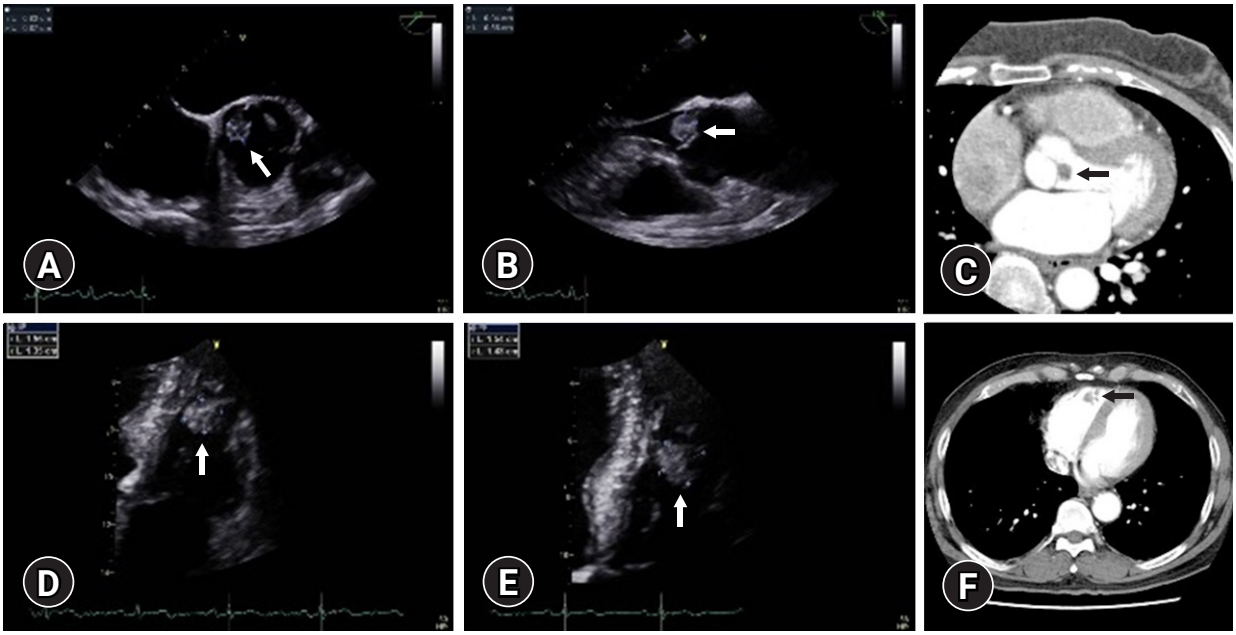


Fig. 1. Radiological findings of case 1 (A–C) and case 2 (D–F). (A, B) Preoperative echocardiograhy shows a mobile mass (arrow) on the ventricular surface of the noncoronary cusp of the aortic valve. (C) Computed tomography image shows a mass lesion (arrow) on the aortic valve. (D, E) Preoperative echocardiography shows a round mass (arrow) in the right ventricle. (F) Computed tomography shows a mass lesion in the right ventricle (arrow).

https://doi.org/10.12701/yujm.2020.00556

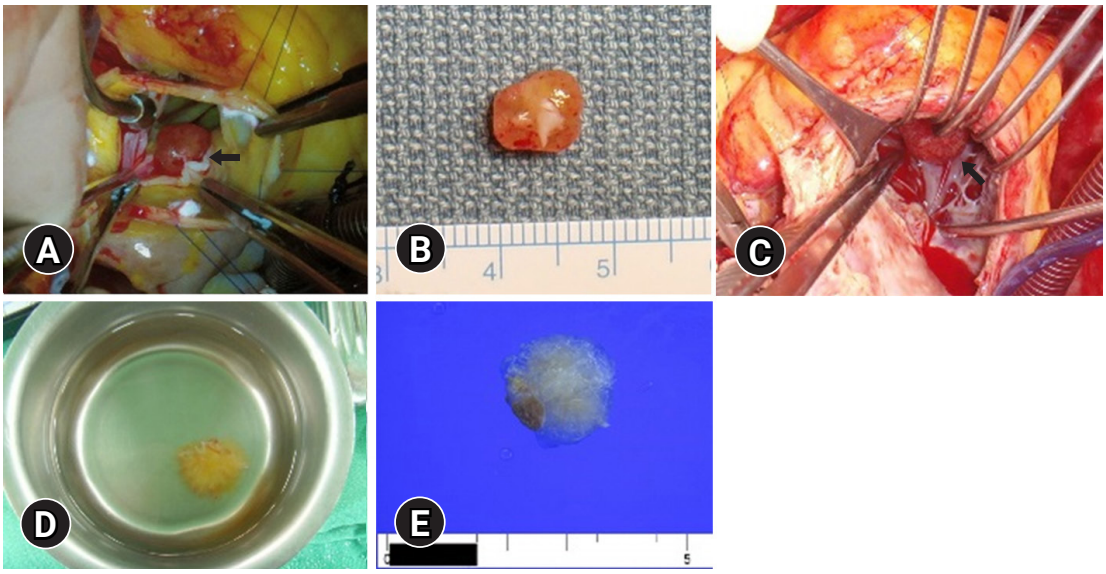


Fig. 2. Operative and gross findings of case 1 (A, B) and case 2 (C–E). (A) The mass is morphologically round and attached to the ventricular surface of the noncoronary cusp of the aortic valve (arrow). (B) A pinkish round mass measures 0.9 cm in the largest dimension. One tip shows a piece of whitish fibrous tissue that might be attached to the aortic valve. (C) The mass is morphologically round and attached to the right ventricular wall (arrow). (D) Immersion in water after resection reveals a typical sea anemone appearance. (E) A whitish papillary mass measures 1.5 cm in the largest dimension. (E) One tip shows a piece of brownish muscular tissue that might be attached to the myocardial wall.

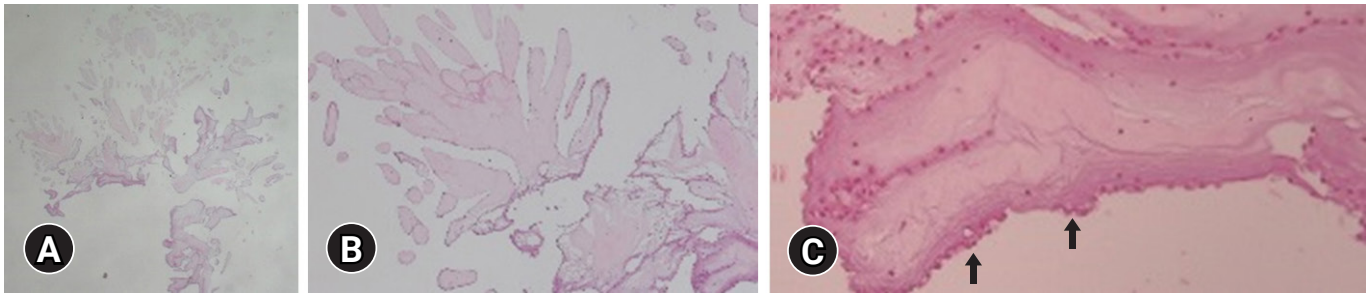


Fig. 3. Histopathological findings. (A) A papillary mass at low power shows numerous arborizing fronds from a common central stalk (hematoxylin and eosin [H&E] stain, ×10). (B) The papillae consist of avascular fronds with hyalinized stroma and partly denuded lining cells (H&E stain, ×40). (C) The fronds are coated by a single endothelial layer (arrows) (H&E stain, ×100).

had grown to 9 mm on the ventricular surface of the leaflet, where it was subjected to high blood pressure and fast blood flow. The tumor in case 2 also occurred at an unusual site, attaching to the endocardium of the right ventricular apex. Although both masses were prone to detachment due to the blood flow, they were discovered before any embolic events occurred.

Echocardiography is a presumptive method for the diagnosis of PFE. However, in both cases, computed tomography showed a clear mass lesion in the heart; these findings might be helpful for screening patients with or without embolic events, and the early detection of PFE is possible through careful consideration of the computed tomography findings.

Decisions regarding the surgical excision of PFE depend on its size, location, and mobility as well as the potential risk of embolism. The excision of an isolated right-sided PFE is indicated only in cases of large mobile tumors that can cause pulmonary embolism. When the tumor is located at the left side of the heart, careful observation is needed if there are no symptoms, the size is less than 1 cm, and the tumor is nonmobile; however, early surgery is required in the case of an embolic event and if the mobile tumor is larger than 1 cm [1,2].

However, some surgeons consider early surgery mandatory because of the potential risk of embolic complications, and valve-sparing surgery can be performed safely in cases of valvular involvement in tumors without a risk of recurrence after total excision [3,4]. According to the results of a comparative study includ-

ing PFE patients split into a surgically treated group and a group that was kept only under observation with aspirin, the incidence of cerebral vascular accident and mortality rates were higher in the latter [5].

In case 1, the stalk on the ventricular surface of the aortic valve was not firmly attached to the normal tissue and could be easily excised using the slicing technique. After tumor excision, there was no significant damage to the remnant leaflet tissue; thus, no valve repair was required. Additional valve repair is required in the case of tissue defects after wide excision, and valve replacement is inevitable when the leaflet is completely excised.

Even when a tumor is benign, if it has a high possibility of recurrence, extensive resection of the area around the stalk is required. However, in the case of PFE, recurrence is unknown. Hence, after excision, the surgeon can distinguish it from other tumors by immersing it in water and observing the typical sea anemone appearance before submitting it for pathological examination. Therefore, aortic valve-sparing procedures can be the first option for treating tumors on the aortic valve.

In these two cases, both tumors were mobile with small stalks and at high risk of detachment due to the blood flow, especially the tumor in case 1. Despite its small size, the early surgical excision of the mobile tumor located in the left side of the heart can prevent the fatal sequelae of cerebral embolism. Tumors larger than 1 cm located in the right side of the heart should also be considered for excision to prevent pulmonary embolism.

PFE is not generally known to recur after excision; however, one case of recurrence was reported recently, so surgeons should be careful about this possibility in the future [6]. However, PFE recurrence is extremely rare compared to other primary cardiac tumors.

In conclusion, PFE is a rare tumor characterized by a small stalk that can be easily detached through blood flow and cause fatal embolism. Its early diagnosis is possible based on a visible shadow on computed tomography followed by echocardiography. Depending on tumor size and location, fatal embolism can be prevented by appropriate early surgical treatment.

Acknowledgments

Conflicts of interest

No potential conflicts of interest relevant to this article are reported.

Author contributions

Conceptualization and Resources: all authors; Formal analysis and Supervision: JHL; Investigation: ESC; Methodology: all authors; Writing-original draft: ESC, JHL; Writing-review & editing: all authors.

ORCID

Eui Suk Chung, https://orcid.org/0000-0003-2942-2322
Jae Hoon Lee, https://orcid.org/0000-0002-2970-8913
Jong Kwon Seo, https://orcid.org/0000-0001-9179-1992
Byung Gyu Kim, https://orcid.org/0000-0001-5780-9642
Gwang Sil Kim, https://orcid.org/0000-0001-5206-8187
Hye Young Lee, https://orcid.org/0000-0003-3187-3667
Young Sup Byun, https://orcid.org/0000-0002-6360-6400
Hyun Jung Kim, https://orcid.org/0000-0002-6617-4578

References

1. Gowda RM, Khan IA, Nair CK, Mehta NJ, Vasavada BC, Sacchi TJ. Cardiac papillary fibroelastoma: a comprehensive analysis of 725 cases. Am Heart J 2003;146:404–10.
2. Sun JP, Asher CR, Yang XS, Cheng GG, Scalia GM, Massed AG, et al. Clinical and echocardiographic characteristics of papillary fibroelastomas: a retrospective and prospective study in 162 patients. Circulation 2001;103:2687–93.
3. Grinda JM, Couetil JP, Chauvaud S, D'Attellis N, Berrebi A, Fabiani JN, et al. Cardiac valve papillary fibroelastoma: surgical excision for revealed or potential embolization. J Thorac Cardiovasc Surg 1999;117:106–10.
4. Ngaage DL, Mullany CJ, Daly RC, Dearani JA, Edwards WD, Tazelaar HD, et al. Surgical treatment of cardiac papillary fibroelastoma: a single center experience with eighty-eight patients. Ann Thorac Surg 2005;80:1712–8.
5. Tamin SS, Maleszewski JJ, Scott CG, Khan SK, Edwards WD, Bruce CJ, et al. Prognostic and bioepidemiologic implications of papillary fibroelastomas. J Am Coll Cardiol 2015;65:2420–9.
6. Díaz-Antón B, González Pinto Á, Parra Jiménez FJ, Cuerpo Caballero G, Pérez Rodríguez F, Solís Martín J. Recurrent cardiac fibroelastoma. Is it really a benign tumor? Rev Esp Cardiol (Engl Ed) 2018;71:685–7.

https://doi.org/10.12701/yujm.2020.00556

Yeungnam University Journal of Medicine
YUJM

Communication
eISSN 2384-0293
Yeungnam Univ J Med 2020;37(4):349-355
https://doi.org/10.12701/yujm.2020.00640

Yeungnam University type drive-through (YU-Thru) coronavirus disease 2019 (COVID-19) screening system: a rapid and safe screening system

Wan Seok Seo[1], Seong Ho Kim[2], Si Youn Song[3], Jian Hur[4], Jun Lee[5], Sunho Choi[6], Yoojung Lee[7], Dai Seg Bai[7]

[1]Department of Psychiatry, Yeungnam University College of Medicine, Daegu, Korea
[2]Department of Neurosurgery, Yeungnam University College of Medicine, Daegu, Korea
[3]Department of Otorhinolaryngology-Head and Neck Surgery, Yeungnam University College of Medicine, Daegu, Korea
[4]Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea
[5]Department of Neurology, Yeungnam University College of Medicine, Daegu, Korea
[6]Department of General Affairs, Yeungnam University Medical Center, Daegu, Korea
[7]Department of Psychiatry, Yeungnam University Hospital, Daegu, Korea

Received: July 16, 2020
Revised: August 24, 2020
Accepted: August 31, 2020

Corresponding author:
Wan Seok Seo
Department of Psychiatry, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-620-3340
Fax: +82-53-629-0256
E-mail: sws3901@ynu.ac.kr

Active and prompt scale-up screening tests are essential to efficiently control the coronavirus disease 2019 (COVID-19) outbreak. The goal of this work was to identify shortcomings in the conventional screening system (CSS) implemented in the beginning of the outbreak. To overcome these shortcomings, we then introduced a novel, independently developed system called the Yeungnam University type drive-through (YU-Thru), and distributed it nationwide in Korea. This system is similar to the drive-throughs utilized by fast food restaurants. YU-Thru system has shortened the time taken to test a single person to 2–4 minutes, by completely eliminating the time required to clean and ventilate the specimen collection room. This time requirement was a major drawback of the CSS. YU-Thru system also reduced the risk of subjects and medical staff infecting one another by using a separate and closed examination system. On average, 50 to 60 tests were conducted per day when using the CSS, while now up to 350 tests per day are conducted with the YU-Thru system. We believe that the YU-Thru system has made an important contribution to the rapid detection of COVID-19 in Daegu, South Korea. Here, we will describe the YU-Thru system in detail so that other countries experiencing COVID-19 outbreaks can take advantage of this system.

Keywords: Conventional screening system; COVID-19; Rapid screening system; YU-Thru system

Introduction

Since the first cases of coronavirus disease 2019 (COVID-19) occurred in Wuhan, China in December 2019, the disease has rapidly spread worldwide [1]. A 35-year-old woman who had visited South Korea from Wuhan, China became the first case in South Korea on January 20, 2020. As of July 31, 2020, a total of 14,305 COVID-19 cases have been reported in South Korea. The vast majority of new cases in this country have occurred in Daegu and the neighboring North Gyeongsang Province. In Daegu, the number of confirmed cases climbed rapidly after the first confirmed cases occurred on February 18, 2020. On March 30, Daegu reported

6,624 cases of COVID-19, and North Gyeongsang Province reported 1,298 cases. Together, these accounted for 82.0% of all COVID-19 cases in South Korea at that time. In Daegu, the number of newly confirmed cases on February 19, 2020 was 15. New cases exceeded 100 and 400 per day, by February 23rd and 27th, respectively, and the highest single-day spike to-date occurred on February 29, with 656 new cases. Since then, the number of new cases per day remained at approximately 400 to 600 and fell below 100 for the first time on March 10. On April 10, 2020, no newly confirmed cases of COVID-19 were reported in Daegu for the first time since the outbreak [2]. Meanwhile, coronavirus is spreading rapidly around the world, with 17,551,097 confirmed cases and 678,317 deaths as of July 31, 2020 [3].

On March 12, 2020, the World Health Organization declared the COVID-19 outbreak a pandemic [4]. In order to contain the spread of infectious diseases, prompt detection of as many cases as possible through active laboratory testing, active quarantine of confirmed patients, systematic classification of patients according to the degree of symptoms, and initiation of step-by-step treatment strategies according to severity are crucial. Screening centers are isolated spaces that are designed to inspect and examine patients with COVID-19 symptoms such as fever and cough without contacting other patients or admitting patients into hospitals, thereby avoiding close contact with medical staff. Therefore, screening centers play a crucial role in preventing transmission by treating suspected COVID-19 patients separately from other patients.

In South Korea, screening centers have been operating throughout the nation since January 24, 2020 [5]. The Yeungnam University Hospital (YU) set up a conventional screening system (CSS) on February 17, 2020, under the guidance of the Korea Centers for Disease Control and Prevention (KCDC).

Brief overview of the conventional screening system and its' limitations

According to the KCDCs' guidelines for screening centers, a screening center should be located outside the hospital. Procedures should be implemented inside negative-pressure rooms/tents that can be separated from other areas [6]. In particular, sample collection should be performed solely in negative-pressure tents. However, the CSS had several limitations. First, a number of patients were exposed to cold weather while they were waiting for their tests. COVID-19 cases were rapidly rising in Daegu in mid-February, and temperatures had dropped to –5°C [7]. Consequently, many people were more likely to have respiratory diseases such as common colds, as well as experience the inconvenience of waiting in long lines. In the CSS, a long line often had people waiting to be tested for up to 5 hours. Second, infectious diseases were communicable to the crowd of individuals waiting in line to be tested. Under the CSS systems' initial testing conditions, the positive case rate in screening centers was approximately 5%, which was quite high [8]. Therefore, it was likely that COVID-19 was transmitted from confirmed patients to other patients who were in close contact. In addition, under the CSS procedures, there was a possibility of medical staff being infected by confirmed COVID-19 patients. Although it was recommended that medical staff wear goggles and maintain a distance of more than 2 m from subjects, as well as use level D clothing and a face shield if they were within 2 m of subjects, the risk of infection could not be ruled out [6]. Third, the amount of time required to clean and ventilate test rooms after sampling was considerable: with the CSS procedure, at least 30 minutes was required to achieve > 99% airborne-contaminant removal efficacy, which is incompatible with the large-scale screening required by COVID-19 [9].

Design and launch of the Yeungnam University type drive-through screening system

Yeungnam University Hospital (YU), one of the major university hospitals in Daegu, operated a CSS beginning on February 17, 2020. However, as the number of newly confirmed patients in Daegu rose, more people visited the screening centers to undergo testing. Once the number of tested subjects exceeded 20 per day, the CSS was unable to meet the testing requirements, and individuals were irritated by the failure of appropriate screening tests. Additionally, early in the COVID-19 outbreak, Daegu underwent a critical medical problem, as well as the inefficient CSS function. At one point, four of five emergency centers of university hospitals in Daegu were closed at the same time due to exposure to COVID-19. From February 19 to 22, YU was also closed three times, for a total of 100 hours of shutdown. We then realized the need for a more efficient screening system.

YU initially solved the CSS problem of subjects being exposed to cold weather. To prevent subjects from contracting infectious respiratory diseases including common colds, and from transmitting diseases to each other, we requested that patients remain in their cars while awaiting testing. Individuals were then notified of their turn through a phone call. Next, we considered the issue of how to decrease the time required to clean and ventilate the negative-pressure tents. The solution we developed was to ensure that individuals did not leave their cars throughout the testing procedure, from the stand-by period to exiting the testing center. We considered a patient's car to be a closed space in which there was no contact

https://doi.org/10.12701/yujm.2020.00640

with other patients, and therefore no risk of infecting other individuals. In addition, there was no need to ventilate and clean the car as tested individuals did not share cars with each other. In addition to these improvements, we also minimized contact between the medical staff and subjects by using shipping containers as medical staff examination rooms. Medical staff and subjects communicated through a two-way microphone and speaker. Upon receiving news from the government concerning system insurance coverage, we launched the Yeungnam University type drive-through (YU-Thru) system. Overall, the YU-Thru system consists of four steps, with details provided below.

The four steps of Yeungnam University type drive-through system with a detailed description of each step

The goal of YU-Thru system was to simplify the testing procedure as much as possible to maximize the number of individuals that could be tested per day. The YU-Thru system process consists of four steps; registration, medical examination, payment, and sample collection. The YU-Thru system occupied approximately 1,527m^2 of parking lot space (Fig. 1). Individuals were requested to drive by themselves and to have one-person-per-car if possible, as having two or more people in one car could encourage transmission between the cars' occupants. However, if the individuals were elderly or could not drive by themselves (e.g., infants, children, or patients with psychiatric disorders such as schizophrenia, severe mania, or depression), caregivers were allowed to drive with them.

Of the four steps, three were performed almost entirely inside the shipping containers. In step 4, sample collection was performed outside the container. The staff and medical personnel involved in steps 1, 3, and 4 were equipped with level D protection, including KF94 or N95 grade face masks and face shields. The doctors in step 2 wore only KF94 or N95 grade face masks.

1. Step 1: registration and creating a hospital number

First, each person to be tested placed their identification (ID) card into the scanner. Then the ID card was scanned into the computer, as shown in Fig. 2. The YU registration number was automatically created when the staff member entered the patient's date of birth and social security number, as displayed on the computer monitor. For non-nationals, the YU registration number was created using the patient's alien registration card; however, the remainder of the process remained the same. For non-nationals who were not registered in South Korea (e.g., tourists or illegal aliens), the YU registration number was created from passport numbers. The staff then recorded the home address and cell phone number of subjects using the two-way microphone and speaker system. It was important to enter the correct cell phone number into the computer as test results were texted. At the same time, a separate staff member used a noncontact forehead thermometer to measure the subject's temperature. Minor exposure to infected patients may have occurred during this procedure. Although two staff members were recommended overall for step 1, it was possible to complete the registration and temperature testing with one staff member performing

Fig. 1. (A) Aerial photography of the Yeungnam University type drive-through (YU-Thru) system. (B) Four steps of the YU-Thru system; ① registration, ② medical examination, ③ payment, and ④ specimen collection.

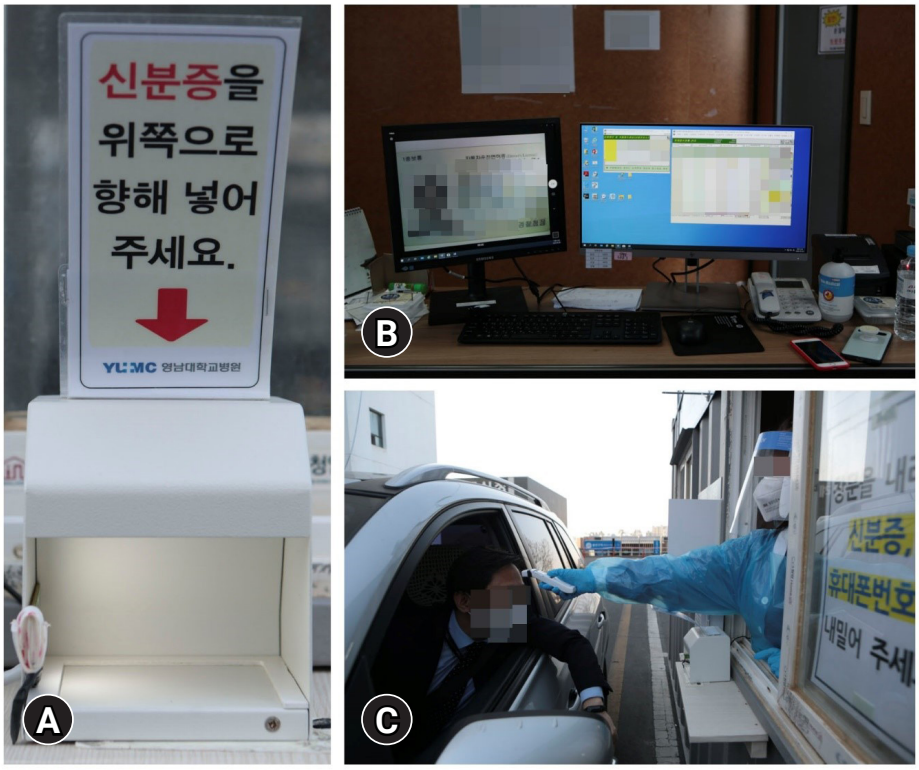


Fig. 2. Step 1. (A) Identification (ID) card scanner (description in Korean: "Please insert the ID card with photo-side up."). (B) A scanned image of the ID card on a computer monitor. (C) A noncontact forehead thermometer was used to measure an individuals' body temperature.

both procedures (Fig. 2).

2. Step 2: medical examination by a physician

For this step in our study, physicians from YU, volunteer doctors in Daegu, and public health doctors in South Korea participated. Physicians thoroughly checked the individuals' symptoms including fever, sore throat, rhinorrhea, nasal congestion, cough, phlegm, and disturbances of smell and taste. They also identified whether the individuals had underlying diseases including lung disease, heart disease, diabetes, hypertension, kidney disease, and cancer. In addition, doctors checked whether there was contact with previously COVID-19 confirmed patients, whether subjects had attended a particular religious meeting, or whether they had visited the hospital located in an infection cluster.

After this screening, the doctors decided whether the individual needed to be tested, whether a nasal and throat or sputum test should be performed, and whether insurance would cover the testing. The test was then prescribed, and if covered by insurance, the physician completed a document called an "infectious patient report" online and sent it to the KCDC. The doctors asked the individuals questions through two-way microphones, and there was no contact between them (Fig. 3). Therefore, the risk of coronavirus contamination was considered to be nonexistent.

Fig. 3. A two-way microphone is used during communication between an individual and a doctor. The doctor and individual view one another through the window and talk via the microphone.

3. Step 3: payment

In this step, the subject paid the registration, examination, and inspection fees. Computers installed with payment systems and card readers were set inside a shipping container. Although paying by

https://doi.org/10.12701/yujm.2020.00640

credit or debit cards was preferred, cash payments were also permitted. Although paying by card is superior in preventing infection, some individuals requested to pay with cash. As some contact was inevitable during this process, there was a risk of contamination by exchanging cards, cash, and/or receipts (Fig. 4).

4. Step 4: sample collection

After the individual paid the required fees sample labels were printed from the computer. Medical staff then brought labeled sample tubes to the individual's car and cross-checked the information. The individual was instructed to stay in the car throughout the process. To obtain a throat swab, the individual lowered their face mask and opened their mouth. To obtain a nasal swab, the individual wore a face mask and kept their mouth closed. To collect sputum samples, the individual produced phlegm by coughing while wearing a face mask, and then spit the phlegm into a tube while the car's windows were closed. The individual then opened the cars' window and gave the tube to the medical staff. This procedure was the greatest source of contamination throughout the process. Medical staff were equipped with level D protection clothing, an N95 grade mask, and face shields, as well as apron gowns (Fig. 5). Apron gowns were replaced between each test.

Results and advantages of the Yeungnam University type drive-through screening system

The YU-Thru system had several advantages over CSS. First, the YU-Thru system allowed us to dramatically reduce the time required to clean and ventilate testing areas. As a result, we were able to perform more tests with the YU-Thru system than with CSS. When operating a CSS, the number of tests performed in a day was 50, which increased to an average of 149 cases per day until March 30. Meanwhile, 339 tests were conducted on March 1, 2020 (Fig. 6). The time required to test a single individual was approximately 30 minutes under the CSS; however, this was reduced to approximately 2 to 4 minutes under the YU-Thru system. The main reason for this improvement was that there was no need to clean and ventilate the examination rooms. As shown in Fig. 6, the number of tests met the demand as the number of confirmed cases in Daegu increased. Since March 14, the number of tests has gradually declined. This likely reflects a decrease in cases in Daegu from 100 per day on March 12, after which a decrease in required testing was observed. Second, the YU-Thru system improved the safety of both the individuals to be tested and the medical staff. A total of 61 doctors and 89 medical and nonmedical hospital staff participated in the system from February 26 to March 30; however, none were confirmed as positive for COVID-19. Although we could not entirely rule out infections using this system, the YU-Thru system utilized segregated spaces including specimen collection rooms, unlike the shared specimen collection rooms in CSS, which posed a risk of infection. As a result, the possibility of transmission from one subject to another was completely eliminated, and we prevented or dramatically reduced the infection of medical staff by tested individuals. Third, YU-Thru system can be readily constructed. Cities without parking lots adjacent to hospitals can be easily modified to become testing sites. If the testing process of YU-Thru system is installed in an underground parking lot or closed space, the lack of ventilation may increase vulnerability to infection, and therefore caution is necessary. Consequently, we recommend installing the YU-Thru process outdoors where natural ventilation is possible. For construction, our test sites required approximately 1,527 m^2 of space, four shipping containers, computers, computer network systems, and several personnel. In addition, flexible expansion was

Fig. 4. Payment using a credit card.

Fig. 5. Throat swab procedure.

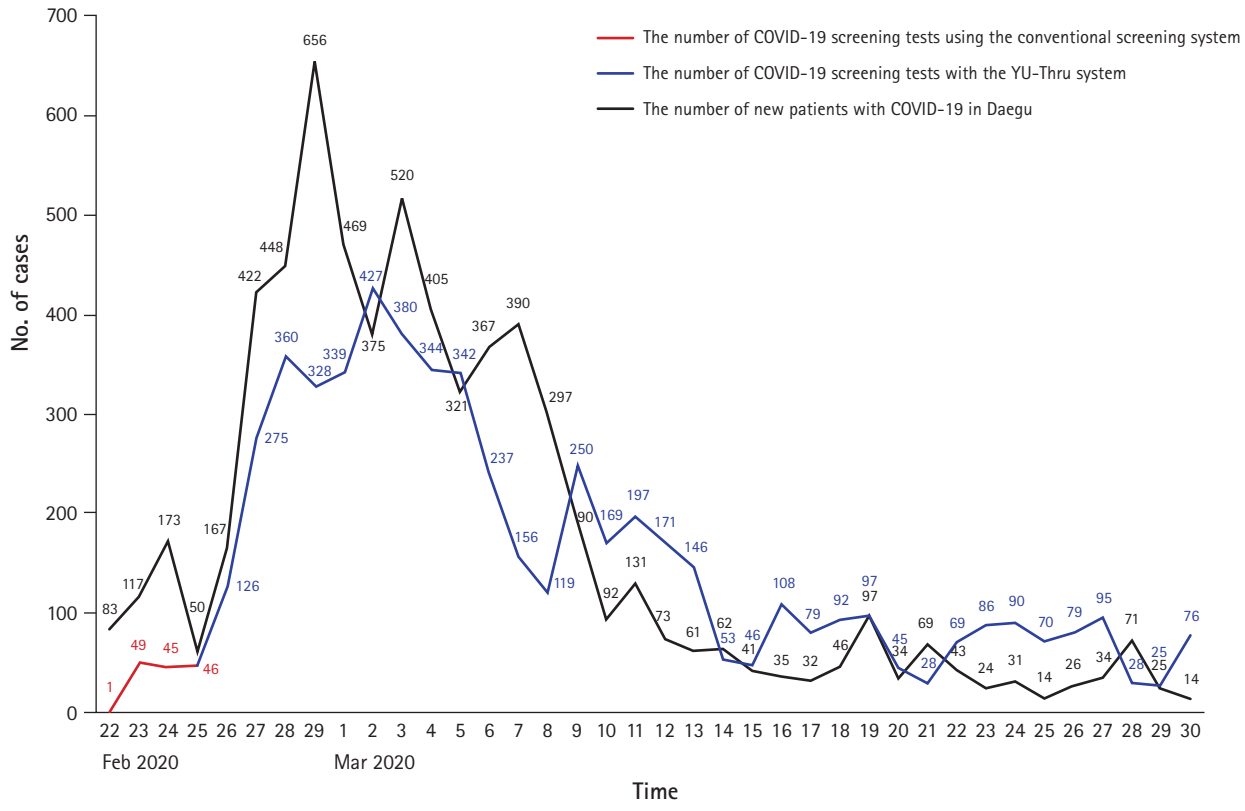


Fig. 6. A comparison of the number of tests achieved using the conventional screening system and the Yeungnam University type drive-through (YU-Thru) system. Red, the number of tests using the conventional screening system; blue, the number of tests using the YU-Thru system; black, the number of newly confirmed cases in Daegu, South Korea. COVID-19, coronavirus disease 2019.

possible depending on the demand. If there was a growing number of newly confirmed cases and the need for screening tests increased, additional YU-Thru system sites were constructed in nearby parking spaces. Moreover, only 1 or 2 days days were required to install the YU-Thru system.

Limitations of the Yeungnam University type drive-through screening system and its' specific concerns

Although the YU-Thru system has enabled faster and safer screening tests compared with the CSS, and none of the staff were confirmed to be COVID-19 positive, additional complementation is necessary to further reduce the chances of infection. First, during the payment step (step 3), if the subject swipes or inserts their own credit card and takes their receipt, the process is completely contactless and the possibility of contamination is zero. Similarly, using noncontact forehead thermometers in step 1 carries a nonexistent risk for infection. Second, it is necessary to find ways to reduce the possibility of infection in passengers sharing the same car with individuals who may be infectious. In this study, most individuals drove by themselves; however, elderly, disabled (e.g., dementia or autism spectrum disorder), or children were often accompanied by caregivers and the possibility of infection transmission could not be ruled out. A system to minimize the risk of infection in these people is necessary.

Conclusion

In order to flatten the curve of the worldwide spread of COVID-19, it is crucial to identify confirmed patients through massive screening, and to initiate preemptive isolation and active treatment measures against positively confirmed patients. To achieve this goal, a safe and efficient screening system such as the YU-Thru system is necessary. We have introduced the YU-Thru system not only to a number of health care facilities and hospitals in South Korea but also to numerous countries around the world [10-13]. We hope that many additional countries will implement and properly utilize the YU-Thru system in the fight against COVID-19.

https://doi.org/10.12701/yujm.2020.00640

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: WSS, SHK, SYS, JH, JL, SC, DSB; Data curation: SHK, SC, DSB; Formal analysis, Methodology, Investigation, and Software: DSB; Resources: SC; Writing-original draft: WSS, JH, YL; Writing-review & editing: WSS, SYS, JH, JL, YL.

ORCID

Wan Seok Seo, https://orcid.org/0000-0002-5122-5360
Si Youn Song, https://orcid.org/0000-0001-6642-8841
Jian Hur, https://orcid.org/0000-0003-3219-8368
Jun Lee, https://orcid.org/0000-0001-8643-0797
Sunho Choi, https://orcid.org/0000-0001-5270-2467
Yoojung Lee, https://orcid.org/0000-0002-7924-0247
Dai Seg Bai, https://orcid.org/0000-0002-6907-6201

References

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet 2020;395:470–3.
2. CoronaBoard. COVID-19 dashboard [Internet]. CoronaBoard; 2020 [cited 2020 Jul 7]. https://coronaboard.kr/.
3. Corona Virus Resource Center, Johns Hopkins University & Medicine. COVID-19 dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) [Interent]. Baltimore (MD): Johns Hopkins University & Medicine; 2020 [cited 2020 Jul 7]. https://coronavirus.jhu.edu/map.html.
4. World Health Organization Regional Office For Europe. WHO announces COVID-19 outbreak a pandemic [Internet]. Copenhagen: WHO Regional Office for Europe; 2020 [cited 2020 Jul 7]. http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic.
5. Korean Society of Infectious Diseases; Korean Society of Pediatric Infectious Diseases; Korean Society of Epidemiology; Korean Society for Antimicrobial Therapy; Korean Society for Healthcare-associated Infection Control and Prevention; Korea Centers for Disease Control and Prevention. Report on the epidemiological features of coronavirus disease 2019 (COVID-19) outbreak in the Republic of Korea from January 19 to March 2, 2020. J Korean Med Sci 2020;35:e112.
6. Central Disaster Management Headquarters, Central Diease Control Headquarters. Guidance for operation of COVID-19 screening centers. Released on February 21, 2020. Sejong (KR): Ministry of Health and Welfare; 2020.
7. AccuWeather. Monthly weather forecast. February 2020 in Daegu, South Korea [Internet]. State College (PA): AccuWeather; 2020 [cited 2020 Jul 7]. https://www.accuweather.com/en/kr/daegu/223347/february-weather/223347.
8. Jung SM, Akhmetzhanov AR, Hayashi K, Linton NM, Yang Y, Yuan B, et al. Real-time estimation of the risk of death from novel coronavirus (COVID-19) infection: inference using exported cases. J Clin Med 2020;9:523.
9. Kohn WG, Collins AS, Cleveland JL, Harte JA, Eklund KJ, Malvitz DM, et al. Guidelines for infection control in dental healthcare settings: 2003. MMWR Recomm Rep 2003;52(RP-17):1–61.
10. Sophie Lewis. CBS News: South Korea is using fast food-style drive-thrus to test for coronavirus [Internet]. New York: CBS Interactive Inc.; March 6, 2020 [cited 2020 Jul 7]. https://www.cbsnews.com/news/coronavirus-south-korea-drive-thru-test-covid-19/.
11. Reuters. South Korea runs 'drive-thru' virus testing in Daegu [Internet]. London: Reuters; March 4, 2020 [cited 2020 Jul 7]. https://uk.reuters.com/video/watch/south-korea-runs-drive-thru-virus-testin-id689445178.
12. Nikkei staff writers. Coronavirus: Week of Mar. 1 to Mar. 7, confirmed cases top 100,000 worldwide [Internet]. Tokyo: Nikkei Asian Review; March 2, 2020 [cited 2020 Jul 7]. https://asia.nikkei.com/Spotlight/Coronavirus/Coronavirus-Free-to-read/Coronavirus-Week-of-Mar.-1-to-Mar.-7-confirmed-cases-top-100-000-worldwide.
13. AFP. COVID-19: China reports fall in cases, South Korea death toll hits 32 [Internet]. Beijing: The Hindu; March 4, 2020 [cited 2020 Jul 7]. https://www.thehindu.com/news/international/covid-19-china-reports-fall-in-cases-south-korea-death-toll-hits-32/article30978782.ece#.

Yeungnam University Journal of Medicine
YUJM

Instructions to authors

Enactment December 30, 1984
First revision April 20, 2011
Second revision May 22, 2012
Third revision July 17, 2013
Fourth revision April 22, 2014
Fifth revised December 23, 2014
Recently revised April 30, 2018

Yeungnam University Journal of Medicine (YUJM) is the official journal of College of Medicine Yeungnam University and is published four times a year (January 31, April 30, July 31, and October 31). The goal of the YUJM is to publish high quality manuscripts dedicated to clinical or basic research. Any authors affiliated with an accredited biomedical institution may submit manuscripts of editorials, review articles, original articles, case reports, and communications. Manuscripts are received with the understanding that they are not under simultaneous consideration by any other publications, and that the authors realize that the identities of the reviewers are kept confidential. The editors reserve the right to make corrections, both literary and technical, to the papers. The agreement of copyright transfer from all the authors should be sent with the manuscript submission. A copyright transfer form is available at the journal homepage.

Editorial policy

The editor assumes that all authors listed in a manuscript have agreed with the following policy of the YUJM on submission of manuscript. Except for the negotiated secondary publication, manuscript submitted to the journal must be previously unpublished and not be under consideration for publication elsewhere.

The purpose of editing is to improve the quality of the paper and to make it possible to convey the topic to readers as briefly as possible. Appropriate peer reviewers are selected to evaluate the creativity and scientific basis of the paper. We also determines the appropriateness of charts and figures. Submitted papers are first reviewed by the editorial committee and rejected if the form is inappropriate or the contents are inadequate.

Anyone who would like to submit a manuscript is advised to carefully read the aims and scope section of this journal. Manuscripts should be prepared for submission according to the Introduction to Authors. For issues not addressed in these instructions, the author is referred to the International Committee of Medical Journal Editors (ICMJE) "Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals" (http://www.icmje.org).

Compliance with ICMJE Recommendations: The journal adheres completely to the ethical guidelines and best practices published by professional organizations, including Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (http://www.icmje.org/icmje-recommendations.pdf) from ICMJE and Principles of Transparency and Best Practice in Scholarly Publishing (joint statement by COPE, DOAJ, WAME, and OASPA; (http://doaj.org/bestpractice).

Ethical considerations

Research ethics

All of the manuscripts should be prepared based on strict observation of research and publication ethics guidelines recommended by the Council of Science Editors (http://www.councilscienceeditors.org), International Committee of Medical Journal Editors (ICMJE, http://www.icmje.org), World Association of Medical Editors (WAME, http://www.wame.org), and the Korean Association of Medical Journal Editors (KAMJE, https://www.kamje.or.kr/en/main_en). All studies involving human subjects or human data must be reviewed and approved by a responsible Institutional Review Board (IRB). Please refer to the principles embodied in the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) for all investigations involving human materials. Animal experiments also should be reviewed by an appropriate committee (IACUC) for the care and use of animals. Also studies with pathogens requiring a high degree of biosafety should pass review of a relevant committee (IBC). The approval should be described in the Methods section. For studies of humans including case reports, state whether informed consents were obtained from the study participants. The editor of YUJM may request submission of copies of informed consents from human subjects in clinical studies or IRB approval documents. The YUJM will follow the guidelines by the Committee on Publication Ethics (COPE, http://publicationethics.org) for settlement of any misconduct.

Conflicts of interest

The corresponding author of an article is asked to inform the Editor of the authors' potential conflicts of interest possibly influencing the research or interpretation of data. A potential conflicts of interest should be disclosed in the cover letter even when the authors are confident that their judgments have not been influenced in preparing the manuscript. Such conflicts may include financial support or private connections to pharmaceutical companies, political pressure from interest groups, or academic problems. Disclosure form shall be same with ICMJE Uniform Disclosure Form for Potential Conflicts of Interest (http://www.icmje.org/coi_disclosure.pdf). The Editor will decide whether the information on the conflicts should be included in the published paper. In particular, all sources of funding for a study should be explicitly stated. The YUJM asks referees to let its editor know of any conflicts of interest before reviewing a particular manuscript.

Authorship

Each author is expected to have made substantial contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; or have drafted the work or substantively revised it; AND to have approved the submitted version (and any substantially modified version that involves the author's contribution to the study); AND to have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Those who do not meet the above criteria should be acknowledged as contributors instead of authors. The corresponding author is responsible for completing this information at submission, and it is expected that all authors will have reviewed, discussed, and agreed to their individual contribution ahead of this time.

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. When submitting a manuscript authored by a group, the corresponding author should clearly indicate the preferred citation and identify all individual authors as well as the group name. Journals generally list other members of the group in the Acknowledgements. Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship.

Contributor Roles Taxonomy (CRediT)

- Conceptualization
- Data curation
- Formal analysis
- Funding acquisition
- Investigation
- Methodology
- Project administration
- Resources
- Software
- Supervision
- Validation
- Visualization
- Writing - original draft
- Writing - review & editing

Redundant publication and plagiarism

Redundant publication is defined as "reporting (publishing or attempting to publish) substantially the same work more than once, without attribution of the original source(s)". Characteristics of reports that are substantially similar include the following: (a) "at least one of the authors must be common to all reports (if there are no common authors, it is more likely plagiarism than redundant publication)," (b) "the subjects or study populations are the same or overlapped," (c) "the methodology is typically identical or nearly so," and (d) "the results and their interpretation generally vary little, if at all."

When submitting a manuscript, authors should include a letter informing the editor of any potential overlap with other already published material or material being evaluated for publication and should also state how the manuscript submitted to YUJM differs substantially from other materials. If all or part of your patient population was previously reported, this should be mentioned in the Methods, with citation of the appropriate reference(s).

The duplication will be checked through crosscheck (https://app.ithenticate.com) or eTBLAST (https://helioblast.heliotext.com) before submission. If duplicate publication related to the papers of this journal is detected, the manuscripts may be rejected, the authors will be announced in the journal, and their institutes will be informed. There will also be penalties for the authors.

Secondary publication

It is possible to republish manuscripts if the manuscripts satisfy the condition of secondary publication of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by International Committee of Medical Journal Editors (ICMJE), available from http://www.icmje.org. These are:

- The authors have received approval from the editors of both journals (the editor concerned with the secondary publication

must have access to the primary version).

- The priority for the primary publication is respected by a publication interval negotiated by editors of both journals and the authors.
- The paper for secondary publication is intended for a different group of readers; an abbreviated version could be sufficient.
- The secondary version faithfully reflects the data and interpretations of the primary version.
- The secondary version informs readers, peers, and documenting agencies that the paper has been published in whole or in part elsewhere—for example, with a note that might read, "This article is based on a study first reported in the (journal title, with full reference)"—and the secondary version cites the primary reference.
- The title of the secondary publication should indicate that it is a secondary publication (complete or abridged republication or translation) of a primary publication. Of note, the United States National Library of Medicine (NLM) does not consider translations as "republications" and does not cite or index them when the original article was published in a journal that is indexed in MEDLINE.

Registration of the clinical trial research

Clinical trial defined as "any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome" should be registered to the primary registry to be prior publication. YUJM accepts the registration in any of the primary registries that participate in the WHO International Clinical Trials Portal (http://www.who.int/ictrp/en/), NIH ClinicalTrials.gov (http://www.clinicaltrials.gov), ISRCTN Resister (www.ISRCTN.org), or the Clinical Research Information Service (CRIS), Korea CDC (https://cris.nih.go.kr/cris/index.jsp). The clinical trial registration number shall be published at the end of the abstract.

Data sharing statement

YUJM accepts the ICMJE Recommendations for data sharing statement policy (http://icmje.org/icmje-recommendations.pdf). All manuscripts reporting clinical trial results should submit a data sharing statement following the ICMJE guidelines from 1 July 2018. Authors may refer to the editorial, "Data Sharing statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors," in JKMS Vol. 32, No. 7: 1051-1053 (http://crossmark.crossref.org/dialog/?doi=10.3346/jkms.2017.32.7.1051&domain=pdf&date_stamp=2017-06-05).

Process to manage the research and publication misconduct

When the Journal faces suspected cases of research and publication misconduct such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem discovered with the submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and other issues, the resolving process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board of YUJM will discuss the suspected cases and reach a decision. YUJM will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

For the policies on research and publication ethics not stated in the Instructions, Guidelines on Good Publication (http://publicationethics.org) or Good Publication Practice Guidelines for Medical Journals (http://kamje.or.kr) can be applied.

Categories of publications

YUJM publishes editorials, review articles, original articles, case reports, and communications. Editorials are invited perspectives on an area of medical science, dealing with very active fields of research, current medical interests, fresh insights and debates. Review articles provide a concise review of a subject of importance to medical researchers written by an invited expert in medical science. Original articles are papers reporting the results of basic and clinical investigations that are sufficiently well documented to be acceptable to critical readers. Case reports deal with clinical cases of medical interest or innovation. Communications are interesting and instructive information for readers.

Manuscript submission

The main document with manuscript text and tables should be prepared with a Microsoft Word program. Authors should submit manuscripts via the online submission system (https://submit.e-yujm.org/). Please log in first as a member of the system and follow the directions. Manuscripts should be submitted by the corresponding author, who should indicate the address and phone number for correspondence in the title page of the manuscript. If available, a fax number and e-mail address would be helpful. The revised manuscript should be submitted through the same web system under the same identification numbers. Items pertaining to manuscripts submitted for publication, as well as letters or other forms of communication regarding the editorial management of YUJM, all correspondences and business communications should

be sent to:

Joon Hyuk Choi, M.D., Ph.D., Editor-in-Chief
Yeungnam University Journal of Medicine
Yeungnam University College of Medicine
170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-640-6832, Fax: +82-53-651-0394
E-mail: yujm@yu.ac.kr
Homepage: https://www.e-yujm.org

Peer review process

YUJM reviews all manuscripts received. A manuscript is previewed for its format and academic relevancy, and then rejected or sent to the 2 (or more) relevant investigators available for review of the contents. The editor selects peer referees by recommendation of the editorial board members or from the board's specialist database. The identities of the reviewers and authors will not be revealed (double blinded review). All the radiologic images and pathologic (microscopic) images are reviewed by radiologist or pathologist for appropriateness. A manuscript containing statistical analysis will be reviewed by a statistical editor.

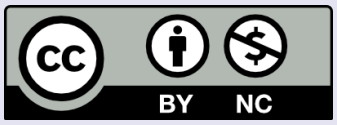
Upon completion of the review, authors will receive notification of the Editor's decision by e-mail with comments offered by the reviewers. Revised manuscripts must be submitted within 3 months of the date on the decision letter.

Acceptance of manuscripts is based on many factors, including the importance, originality, and priority of the research. Acceptance of the manuscript is decided based on the critiques and recommended decision of the referees. A referee may recommend "accept", "minor revision", "major revision," or "reject". If there is a marked discrepancy in the decisions between two referees or between the opinions of the author and referee(s), the editor may send the manuscript to another referee for additional comments and a recommended decision. The reviewed manuscripts are returned back to the corresponding author with comments and recommended revisions. Names and decisions of the referees are masked. A final editor's decision on acceptance or rejection for publication is forwarded to the corresponding author from the editorial office.

The usual reasons for rejection are topics that are too specific and target audience that is too limited, insufficient originality, serious scientific flaws, poor quality of illustrations, or absence of a message that might be important to readers. Rarity of a disease condition is itself not an acceptable justification for a case report. The peer review process takes usually 2–4 weeks after the manuscript submission.

Revisions are usually requested to take account of criticisms and comments made by referees. The revised manuscript should be resubmitted via the web system. Failure to resubmit the revised manuscript within 2 months without any notice from the corresponding author is regarded as a withdrawal. The corresponding author must indicate clearly what alterations have been made in response to the referee's comments point by point. Acceptable reasons should be given for noncompliance with any recommendation of the referees.

Copyrights and creative commons attribution license



Manuscript preparation

Review article

Review articles are usually solicited by the Editor-in-Chief. However, unsolicited Reviews will be also considered. Authors should contact the Editor-in-Chief in advance to determine the appropriateness of their review articles for publication. All Review articles will undergo peer review. An abstract is required whereas Materials and methods section and a Results section are not required. The length of review articles is limited to 5,000-8,000 words with a maximum of 100 references. Also, there should be no more than 3 authors.

Original article

Original articles should begin with the title page followed by an abstract; a list of key words; an Introduction, Materials and methods, Results, Discussion, References (no more than 30), and tables and/or illustrations.

1) Title page

The tile page should contain the following information: (1) title (less than 150 characters, including spaces); (2) author list

(first name, middle name, and last name); (3) name of the institutions at which the work was performed; (4) acknowledgement of research support; (5) name, address, telephone, fax number, and e-mail address of the corresponding author; (6) running title (less than 50 characters, including spaces).

2) *Abstract*

Abstract must be organized and formatted according to the following headings: Background, Methods, Results, and Conclusion. The abstract length is typically no more than 250 words.

3) *Keywords*

List 3-6 keywords from the list provided in Index Medicus under "Medical Subject Heading (MeSH)."

4) *Text*

The text of manuscripts must have the following sections: Introduction, Materials and methods, Results, and Discussion. The body of the manuscript should be written as concisely as possible. All pages of the manuscript should be numbered.

Introduction

This should provide a context or background for the study and states the specific purpose or research objective of or hypothesis tested by the study. This may include mention of papers most closely related to the article, and of the problem.

Materials and methods

Explanation of the experimental methods should be concise but sufficient to allow other workers to reproduce the results. This provides the technical information, apparatus (the manufacturer's name and brief address) and procedures. Give references and brief descriptions for the methods that have been published. Describe statistical methods with enough detail to enable a reader with access to the original data to verify the reported results. Define statistical terms, abbreviations, and most symbols.

Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex or gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance.

Results

This should include a concise textual description of the data presented in tables and figures.

Discussion

This section includes the new and important aspects of the study and the conclusions. The data should be interpreted concisely. Speculation is permitted, but it must be supported by the data presented by the authors.

References

References should be numbered consecutively in the order in which they are first mentioned in the text, with numbers in square brackets before any closing punctuation. They should be listed on a separate document under the heading "References," and double-spaced. Reference format should conform to that set forth in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals. 5th ed." (JAMA 1997;277:927-34). Titles of journals should be abbreviated according to the Index Medicus style.

Reference style:

Journal articles

List all authors when six or less; when seven or more, list the first six and add et al.

Vega KJ, Pina I. Heart transplantation is associated with an increased risk for pancreatobiliary disease. Ann Intern Med 1996;124:980-3.

Verbalis JG. Renal physiology of nocturia. Neurourol Urodyn 2014;33(Suppl 1):S6-9.

Book

Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996.

Luzikov VN. Mitochondrial biogenesis and breakdown. Galkin AV, translator; Roodyn DB, editor. New York: Consultants Bureau; 1985. p. 362

Book chapter

Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78.

Web resources

Polgreen PM, Diekema DJ, Vandeberg J, Wiblin RT, Chen YY, David S, et al. Risk factors for groin wound infection after fem-

oral artery catheterization: a case-control study. Infect Control Hosp Epidemiol [Internet]. 2006 [cited 2007 Jan 5];27:34-7. http://www.journals.uchicago.edu/ICHE/journal/issues/v27n1/2004069/2004069.web.pdf

Testa J. The Thomson Reuters journal selection process [Internet]. Philadelphia: Thomson Reuters; 2012 [cited 2013 Sep 30]. http://wokinfo.com/essays/journal-selection-process

5) Tables

Tables should fit within a single page. The Table's legend may include any pertinent notes and must include definitions of all abbreviations and acronyms that have been used in the Table. For footnotes, the following symbols should be used in this sequence: a), b), c), d), e), f), g), h), etc. Authors are obligated to indicate the significance of their observations by appropriate statistical analysis.

6) Illustrations

Figures must be cited consecutively using Arabic numerals. Authors must submit illustrations as electronic files. Acceptable figure file formats are JPEG, TIFF, and PPT/PPTX. Each figure needs to be prepared in a resolution higher than 300 dpi with good contrast and sharpness. The file size of each submitted figure should not exceed 10 MB per figure. If the patient's photograph is presented in a paper, it should be manipulated to make it difficult to recognize. Patients introduced in the manuscripts should be informed and aware that their photographs, videotapes, and other images (imaging records) will be released by the authors, and the authors should attach the Authorization and Release Form available at the YUJM website (https://www.e-yujm.org/authors/ethics.php) including each patient's signature. If the patient is a minor, a written consent of the guardian must be submitted.

7) Legends for tables and illustrations

Typed legends that use double-spacing should start on a separate page with Arabic numerals corresponding to the Tables or Illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the Tables or Illustrations, they should be individually identified and explained clearly in the legend.

8) Abbreviations

Authors should limit the use of abbreviations to an absolute minimum. Abbreviations are not to be used in titles. Abstracts may contain abbreviations for terms mentioned many times in the abstract section, but each term must be identified the first time it is mentioned.

9) Unit of measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples. Temperature should be in degrees Celsius. Authors must consult the information for authors for the particular journal and should report laboratory information in both the local and International System of Units (SI).

Case report

Case reports should consist of an Abstract, Keywords, Introduction, Case, Discussion, and References (no more than 20). Case reports should have fewer than nine authors. The abstract should be concisely written (no more than 250 words).

Permission

If any portion of a manuscript has been previously published, the original source must be acknowledged, and the written permission from the copyright holder to reproduce the material must be submitted. It is the responsibility of the author to request permission from the publisher for any material that is being reproduced. This requirement applies to text, illustrations, and tables.

Article processing charges

Manuscripts that have accepted will be charged 200,000 won. The surcharge for color figures is none.

Author change

If the addition or deletion of authors or changes in the order of authorship is required, the correspondent author must complete the authorship change form and submit it to the editorial board with the signature of all existing authors and new authors. When there is a request for change by the author, the editorial committee convenes an ethics committee and judges whether it is appropriate. If a new author should be added or an author should be deleted after the submission, it is the responsibility of the corresponding author to ensure that all of the authors concerned are aware of and agree to the change in authorship. The YUJM has no responsibility for such changes.

Yeungnam University Journal of Medicine
YUJM

Research and publication ethics

Research ethics

All of the manuscripts should be prepared based on strict observation of research and publication ethics guidelines recommended by the Council of Science Editors (http://www.councilscienceeditors.org), International Committee of Medical Journal Editors (ICMJE, http://www.icmje.org), World Association of Medical Editors (WAME, http://www.wame.org), and the Korean Association of Medical Journal Editors (KAMJE, https://www.kamje.or.kr/en/main_en). All studies involving human subjects or human data must be reviewed and approved by a responsible Institutional Review Board (IRB). Please refer to the principles embodied in the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) for all investigations involving human materials. Animal experiments also should be reviewed by an appropriate committee (IACUC) for the care and use of animals. Also studies with pathogens requiring a high degree of biosafety should pass review of a relevant committee (IBC). The approval should be described in the Methods section. For studies of humans including case reports, state whether informed consents were obtained from the study participants. The editor of YUJM may request submission of copies of informed consents from human subjects in clinical studies or IRB approval documents. The YUJM will follow the guidelines by the Committee on Publication Ethics (COPE, http://publicationethics.org) for settlement of any misconduct.

Conflicts of interest

The corresponding author of an article is asked to inform the Editor of the authors' potential conflicts of interest possibly influencing the research or interpretation of data. A potential conflicts of interest should be disclosed in the cover letter even when the authors are confident that their judgments have not been influenced in preparing the manuscript. Such conflicts may include financial support or private connections to pharmaceutical companies, political pressure from interest groups, or academic problems. Disclosure form shall be same with ICMJE Uniform Disclosure Form for Potential Conflicts of Interest (http://www.icmje.org/coi_disclosure.pdf). The Editor will decide whether the information on the conflicts should be included in the published paper. In particular, all sources of funding for a study should be explicitly stated. The YUJM asks referees to let its editor know of any conflicts of interest before reviewing a particular manuscript.

Authorship

Each author is expected to have made substantial contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; or have drafted the work or substantively revised it; AND to have approved the submitted version (and any substantially modified version that involves the author's contribution to the study); AND to have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Those who do not meet the above criteria should be acknowledged as contributors instead of authors. The corresponding author is responsible for completing this information at submission, and it is expected that all authors will have reviewed, discussed, and agreed to their individual contribution ahead of this time.

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. When submitting a manuscript authored by a group, the corresponding author should clearly indicate the preferred citation and identify all individual authors as well as the group name. Journals generally list other members of the group in the Acknowledgements. Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship.

Contributor Roles Taxonomy (CRediT)

- Conceptualization
- Data curation
- Formal analysis
- Funding acquisition
- Investigation
- Methodology
- Project administration
- Resources
- Software
- Supervision

- Validation
- Visualization
- Writing - original draft
- Writing - review & editing

Redundant publication and plagiarism

Redundant publication is defined as "reporting (publishing or attempting to publish) substantially the same work more than once, without attribution of the original source(s)". Characteristics of reports that are substantially similar include the following: (a) "at least one of the authors must be common to all reports (if there are no common authors, it is more likely plagiarism than redundant publication)," (b) "the subjects or study populations are the same or overlapped," (c) "the methodology is typically identical or nearly so," and (d) "the results and their interpretation generally vary little, if at all."

When submitting a manuscript, authors should include a letter informing the editor of any potential overlap with other already published material or material being evaluated for publication and should also state how the manuscript submitted to YUJM differs substantially from other materials. If all or part of your patient population was previously reported, this should be mentioned in the Methods, with citation of the appropriate reference(s).

The duplication will be checked through crosscheck (https://app.ithenticate.com) or eTBLAST (https://helioblast.heliotext.com) before submission. If duplicate publication related to the papers of this journal is detected, the manuscripts may be rejected, the authors will be announced in the journal, and their institutes will be informed. There will also be penalties for the authors.

Secondary publication

It is possible to republish manuscripts if the manuscripts satisfy the condition of secondary publication of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by International Committee of Medical Journal Editors (ICMJE), available from http://www.icmje.org. These are:

- The authors have received approval from the editors of both journals (the editor concerned with the secondary publication must have access to the primary version).
- The priority for the primary publication is respected by a publication interval negotiated by editors of both journals and the authors.
- The paper for secondary publication is intended for a different group of readers; an abbreviated version could be sufficient.
- The secondary version faithfully reflects the data and interpretations of the primary version.
- The secondary version informs readers, peers, and documenting agencies that the paper has been published in whole or in part elsewhere—for example, with a note that might read, "This article is based on a study first reported in the (journal title, with full reference)"—and the secondary version cites the primary reference.
- The title of the secondary publication should indicate that it is a secondary publication (complete or abridged republication or translation) of a primary publication. Of note, the United States National Library of Medicine (NLM) does not consider translations as "republications" and does not cite or index them when the original article was published in a journal that is indexed in MEDLINE.

Registration of the clinical trial research

Clinical trial defined as "any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome" should be registered to the primary registry to be prior publication. YUJM accepts the registration in any of the primary registries that participate in the WHO International Clinical Trials Portal (http://www.who.int/ictrp/en/), NIH ClinicalTrials.gov (http://www.clinicaltrials.gov), ISRCTN Resister (www.ISRCTN.org), or the Clinical Research Information Service (CRIS), Korea CDC (https://cris.nih.go.kr/cris/index.jsp). The clinical trial registration number shall be published at the end of the abstract.

Data sharing statement

YUJM accepts the ICMJE Recommendations for data sharing statement policy (http://icmje.org/icmje-recommendations.pdf). All manuscripts reporting clinical trial results should submit a data sharing statement following the ICMJE guidelines from 1 July 2018. Authors may refer to the editorial, "Data Sharing statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors," in JKMS Vol. 32, No. 7:1051-1053 (http://crossmark.crossref.org/dialog/?doi=10.3346/jkms.2017.32.7.1051&domain=pdf&date_stamp=2017-06-05).

Process to manage the research and publication misconduct

When the Journal faces suspected cases of research and publication

misconduct such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem discovered with the submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and other issues, the resolving process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board of YUJM will discuss the suspected cases and reach a decision. YUJM will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

For the policies on research and publication ethics not stated in the Instructions, Guidelines on Good Publication (http://publicationethics.org) or Good Publication Practice Guidelines for Medical Journals (http://kamje.or.kr) can be applied.

Yeungnam University Journal of Medicine
YUJM

Research and publication ethics form

Affiliation: _____

Author's name (please print): _____

Manuscript title: _____

All authors pledges that we follow the basic standards of research and publication ethics in the submission process to Yeungnam University Journal of Medicine

Check Yes if Research subject, research object and size, setting of controls, and the methods of data collection are suitable for the research ethics.	☐ ***Yes*** ☐***No***
Check Yes if Authors should ensure that their submitted manuscripts are not against publication ethics such as fabrication, falsification or plagiarism.	☐ ***Yes*** ☐***No***
Check Yes if In clinical research involving human, informed consent from patient should be conducted and written in the method section of the manuscript.	☐ ***Yes*** ☐***No***
Check Yes if All clinical research involving human and animal subjects to be approved by the author's Institutional Review Board (IRB) or equivalent committees.	☐ ***Yes*** ☐***No***
Check Yes if This study is conducted in compliance with the Declaration of Helsinki and this comment is written in the method section of the manuscript.	☐ ***Yes*** ☐***No***
Check Yes if All Authors must disclose all relationships that could be viewed as potential conflicts of interest. This relationship also includes any potential conflicts of interest with all material, products, and companies in the manuscript.	☐ ***Yes*** ☐***No***
Check Yes if Authors should confirm that the submitted work is not under consideration or accepted for publications elsewhere, and would not be submitted in any other journals after acceptance.	☐ ***Yes*** ☐***No***
Check Yes if Duplicate publication, which includes 'imalas publication', 'plagiarism', and 'salami publication', is strictly not conducted.	☐ ***Yes*** ☐***No***

If the rationale provided by the authors remains unsatisfactory in the judgment of the editors, the manuscript will be rejected or retracted. The authors will not be allowed to subsequently submit their research to Yeungnam University Journal of Medicine. The authors should keep the above mentioned disadvantages in mind.

Date: _____

Corresponding author's name: _____

Yeungnam University Journal of Medicine
YUJM

Copyright transfer agreement

The author(s) submit manuscript with the following title

_____

_____

In consideration of editors and publisher's effort in reviewing and editing our/my Article, the undersigned authors hereby transfer, convey, and assign all copyrights in the Article to the Editorial Board of the Yeungnam University Journal of Medicine (YUJM). The copyright transfer covers the right to print, publish, distribute and sell throughout the world the said contribution and parts thereof, including all revisions or versions and future editions, in all forms and media.

The authors certify that I have participated in the intellectual content, the analysis of data, and the writing of the Article, to take public responsibility for it The authors reviewed the final version of the Article, believe it represents valid work and approve it for publication The authors certify that none of the material in the manuscript has been published previously, is included in another manuscript The authors also certify that the Article has not been accepted for publication elsewhere, nor have they assigned any right or interest in the Article to any third party. The authors will obtain and include with the manuscript written permission from any respective copyright owners for the use of any text, figures, and tables that have been previously published. The authors agree that it is their responsibility to pay fees charged for permissions.

Author's name	**Signature**
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

Yeungnam University Journal of Medicine
YUJM

Patient photographic and videographic consent, authorization and release form

I am informed and aware of photographs, videotapes and other images (imaging records) taken by Dr. _____ or his designee(s) of myself or any parts of my body regarding surgical procedures carried out by Dr. _____ . I understand and consent that such imaging records may and will be used by Dr. _____ as reference in diagnosing and treating other patients in the future. I further consent to the release and transfer of copyright ownership by Dr. to Yeungnam University Journal of Medicine of such imaging records.

I understand that by consenting on release of my imaging records, these may and will be used in upcoming issue or issues of the journal, as well as on the journal website, or any other print or electronic media for the purpose of informing medical professionals or other readers about surgical methods. I understand that when these imaging records are included in any articles, medical information regarding sex, age, operative date and treatment results may and will be included together. But I, nor any member of my family, will be identied by name in any publication, and any information that may aid in identifying me or my family will not be exposed. (In case of facial photographs, the photo is cropped to only necessary parts in order to make individual identication impossible.) I understand that whether I consent on this form or not, it bears no consequences whatsoever on any future actions, and that there will be no eect on the medical treatment I receive from Dr. _____ or any subordinates.

I grant this consent as a voluntary contribution in the interest of public education, and certify that I have read the above Consent, Authorization and Release form and fully understand its terms. I understand that, if I do not revoke this authorization, it will expire ten years from the date written below.

I hereby transfer in above-mentioned terms, the copyright of my imaging records to

Dr. _____ .

20 . . .

Name: _____ **Signature:** _____

Hospital: _____ **Department:** _____

Designated Doctor: _____ **Signature:** _____