Aims and scope
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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.

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

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Introduction

Since the introduction of the flexible fiberoptic bronroscope 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-
loss is 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.

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...
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].

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 (hypoechoic 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].
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.

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**Conflicts of interest**

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Biological treatments for severe asthma

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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].

Severe asthma patients comprise about 3% to 13% of all asthmatic 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
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 peristin 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 pathophysiology is 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

<table>
<thead>
<tr>
<th>Biologics (trade name)</th>
<th>Mechanism of action</th>
<th>Indication</th>
<th>Dose and route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab (Xolair)</td>
<td>Anti-IgE; prevents IgE from binding to its receptor on mast cells and basophils</td>
<td>≥ 6 yr old; positive allergy testing (allergic asthma); IgE, 30–700 IU/mL</td>
<td>0.016 mg/kg per IU of IgE SC every 2–4 wk</td>
</tr>
<tr>
<td>Mepolizumab (Nucala)</td>
<td>Anti–IL-5; binds to IL-5 ligand; prevents IL-5 from binding to its receptor</td>
<td>≥ 18 yr old; AEC ≥ 150 cells/μL or ≥300 cells/μL at least once a year</td>
<td>100 mg SC every 4 wk</td>
</tr>
<tr>
<td>Reslizumab (Cinqair)</td>
<td>Anti–IL-5; binds to IL-5 ligand; prevents IL-5 from binding to its receptor</td>
<td>≥ 18 yr old; AEC ≥ 400 cells/μL</td>
<td>Weight-based dosing of 3 mg/kg IV every 4 wk</td>
</tr>
<tr>
<td>Benralizumab (Fasenra)</td>
<td>Anti–IL-5; binds to IL-5 receptor α; causes apoptosis of eosinophils and basophils</td>
<td>≥ 18 yr old; severe eosinophilic asthma</td>
<td>30 mg SC every 4 wk for 3 doses; followed by every 8 wk subsequently</td>
</tr>
<tr>
<td>Dupilumab (Dupixent)</td>
<td>Anti–IL-4R; binds to IL-4 receptor α2; blocks signaling of IL-4 and IL-13</td>
<td>≥ 12 yr old; AEC ≥ 150 cells/μL or FeNO ≥ 25 ppb with OCS-dependent</td>
<td>400–600 mg SC loading dose followed by 200 or 300 mg SC every 2 wk</td>
</tr>
</tbody>
</table>

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.
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-
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-4Ra) 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, co-morbidities, 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 for 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.

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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...
Kim S et al. Kinase inhibitor for idiopathic pulmonary fibrosis

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 irreversible 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 trial 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 VEGFR and also binds to PDGFR in fibroblasts, subsequently stimulating cellular proliferation [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
TNF-α, interferon-γ, and interleukin-13, have been conducted with no significant impact in patients with IPF (NCT02277145, 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 αvβ1 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 is key

<table>
<thead>
<tr>
<th>Target molecule</th>
<th>Compound (type)</th>
<th>Mode of action</th>
<th>NCT ID (phase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple receptor kinases</td>
<td>Nintedanib&lt;sup&gt;a&lt;/sup&gt; (small-molecule)</td>
<td>Inhibit receptor kinases including PDGFR, FGFR, and VEGFR</td>
<td>Completed</td>
</tr>
<tr>
<td>TGF-β</td>
<td>BGG00011 (IgG antibody)</td>
<td>Inhibit the activation of latent TGF-β via targeting integrin αvβ6</td>
<td>NCT01371305 (2)</td>
</tr>
<tr>
<td>TGF-β</td>
<td>PLN-74809 (small-molecule)</td>
<td>Inhibit the activation of latent TGF-β via targeting αvβ1 and αvβ6</td>
<td>NCT04396756 (2)</td>
</tr>
<tr>
<td>TGF-β</td>
<td>TRK-250 (nucleic acid)</td>
<td>Interfere the expression of TGF-β mRNA</td>
<td>NCT03727802 (1)</td>
</tr>
<tr>
<td>TGF-β receptor</td>
<td>TD139 (small-molecule)</td>
<td>Suppress the expression of TGF via targeting galectin-3</td>
<td>NCT03832946 (2)</td>
</tr>
<tr>
<td>CTGF</td>
<td>Pamrevlumab (IgG antibody)</td>
<td>Interfere CTGF bioavailability and subsequent receptor signaling</td>
<td>NCT03955146 (3)</td>
</tr>
<tr>
<td>ROCK</td>
<td>KD025 (small-molecule)</td>
<td>Inhibit ROCK</td>
<td>NCT02688647 (2)</td>
</tr>
<tr>
<td>JNK</td>
<td>CC-90001 (small-molecule)</td>
<td>Inhibit JNK</td>
<td>NCT03142191 (2)</td>
</tr>
</tbody>
</table>

<sup>a</sup>U.S. Food and Drug Administration approved.

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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-

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**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.
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-β1-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.

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**Introduction**

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.

**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].

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**Keywords:** Diagnosis; Multidrug-resistant tuberculosis; Treatment
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 $10^{-7}$ 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 an- ti-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 MTB-DRplus 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 (MTBDRplus version 1, version 2, and Nipro NTM+MTBDR [NIPRO Corp., Osaka, Japan]) for detecting MTB.
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 MTBDRplus 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 rpoB gene for rifampicin resistance and in the katG gene and the inhA promoter region for isoniazid resistance [20,21]. Although MTBDRplus 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 MTBDRsl (Hain Lifescience GmbH) that was developed to detect resistance to ethambutol (mutation in embB), fluoroquinolones (mutations in gyrA and gyrB), 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 rifapicin 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-
According 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 MDR-TB regimen unless contraindicated. Clofazimine and either cycloserine or terizidone are included in group B. These drugs can be used when an adequate regimen cannot be formulated 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 gyrA and gyrB genes [38]. Fluoroquinolone resistance in MTB is usually caused by mutations in the gyrA 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].

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

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

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

### 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 gyrA and gyrB genes [38]. Fluoroquinolone resistance in MTB is usually caused by mutations in the gyrA 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].
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 C, 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>
<thead>
<tr>
<th>Group</th>
<th>Medicine</th>
</tr>
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</table>
| A     | Levofloxacin or moxifloxacin  
Bedaquiline  
Linezolid |
| B     | Clofazimine  
Cycloserine |
| C     | Amikacin (streptomycin)  
Ethambutol  
Imipenem or meropenem  
Para-aminosalicylic acid  
Prothionamide  
Pyrazinamide  
Delamanid |

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. Aminoglycosides are preferred over streptomycin. Kanamycin can be used as a substitute for amikacin.  
- b) Delamanid can be used as a substitute for bedaquiline.
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... 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].

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 Bangladeshi 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.
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.

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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.

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Novel respiratory infectious diseases in Korea

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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 health-care 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 virus 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
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

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Year first recognized</td>
<td>2002</td>
<td>2012</td>
<td>2019</td>
</tr>
<tr>
<td>Causative virus</td>
<td>SARS-CoV</td>
<td>MERS-CoV</td>
<td>SARS-CoV</td>
</tr>
<tr>
<td>Intermediate host</td>
<td>Palm civets</td>
<td>Dromedary camels</td>
<td>Pangolins</td>
</tr>
<tr>
<td>Nosocomial infection</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Healthcare worker infection (%)</td>
<td>21.0</td>
<td>18.6</td>
<td>3.8</td>
</tr>
<tr>
<td>Incubation period (day)</td>
<td>2–11</td>
<td>2–13</td>
<td>3–6</td>
</tr>
<tr>
<td>Treatment</td>
<td>Supportive care</td>
<td>Supportive care</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Vaccination</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total case (global)</td>
<td>8,096</td>
<td>2,229</td>
<td>12,964,809+</td>
</tr>
<tr>
<td>Total death (global)</td>
<td>774</td>
<td>791</td>
<td>570,288+</td>
</tr>
<tr>
<td>CFR (%)</td>
<td>9.6</td>
<td>34.4</td>
<td>3.5</td>
</tr>
<tr>
<td>CFR with comorbidities (%)</td>
<td>46.0</td>
<td>60.0</td>
<td>73.3</td>
</tr>
</tbody>
</table>

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

https://doi.org/10.12701/yujm.2020.00633
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 (SpO₂ ≤ 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
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.

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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 of postoperative complications than young adults. This risk is associated with the physiologic decline observed 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.

Definition of frailty

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

### 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 non-specific, 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 1. FRAIL scale

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

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

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

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

### Table 3. Modified frailty index

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

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.
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 data-set of 23,000 patients who underwent RARP. An mFI score of \( \geq 3 \) 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.

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6. Townsend NT, Robinson TN. Surgical risk and comorbidity in...

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

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²Department of Radiology, Kyungpook National University Chilgok Hospital, School of Medicine, Kyungpook National University, Daegu, Korea
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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-

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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 by 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

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

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

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.
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

<table>
<thead>
<tr>
<th>Table 2. The diagnostic accuracy for determination of central lymph node (LN) metastasis by surgeon using inspection and palpation (n=127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Suspicious for metastatic LN determined by surgeon (n = 28)</td>
</tr>
<tr>
<td>Normal LN determined by surgeon (n = 99)</td>
</tr>
</tbody>
</table>
Values are presented as number (%).

<table>
<thead>
<tr>
<th>Table 3. The diagnostic accuracy for determination of central lymph node (LN) metastasis by surgeon in cases without thyroiditis (n=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Suspicious for metastatic LN determined by surgeon (n = 12)</td>
</tr>
<tr>
<td>Normal LN determined by surgeon (n = 65)</td>
</tr>
</tbody>
</table>
Values are presented as number (%).
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 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.

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9. Kim WW, Park HY, Jung JH. Surgical extent of central lymph
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 hysterec-

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Table 1: The choice of surgery 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.

### 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/m² (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)

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>53.4 (30–88)</td>
</tr>
<tr>
<td>Gravidity (no. of times)</td>
<td>3.8 (0–15)</td>
</tr>
<tr>
<td>Parity (no. of times)</td>
<td>2.2 (0–8)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.6 (16.4–40.4)</td>
</tr>
<tr>
<td>History of abdominopelvic surgery</td>
<td>304 (37.6)</td>
</tr>
<tr>
<td>Chief complaints</td>
<td></td>
</tr>
<tr>
<td>No symptom</td>
<td>200 (24.7)</td>
</tr>
<tr>
<td>Abnormal uterine bleeding</td>
<td>232 (28.7)</td>
</tr>
<tr>
<td>Protruding prolapse of pelvic organs</td>
<td>143 (17.7)</td>
</tr>
<tr>
<td>Abdominal pain or discomfort</td>
<td>130 (16.1)</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>47 (5.8)</td>
</tr>
<tr>
<td>Palpable pelvic mass</td>
<td>21 (2.6)</td>
</tr>
<tr>
<td>Urinary symptoms</td>
<td>19 (2.3)</td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td>9 (1.1)</td>
</tr>
<tr>
<td>Others</td>
<td>8 (1.0)</td>
</tr>
<tr>
<td>Surgical indications&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Uterine leiomyoma</td>
<td>384 (47.5)</td>
</tr>
<tr>
<td>Pelvic organ prolapse</td>
<td>143 (17.7)</td>
</tr>
<tr>
<td>Adenomyosis or adenomyoma</td>
<td>108 (13.3)</td>
</tr>
<tr>
<td>Cervical intraepithelial neoplasia</td>
<td>71 (8.8)</td>
</tr>
<tr>
<td>Adnexal lesion</td>
<td>62 (7.7)</td>
</tr>
<tr>
<td>Endometrial hyperplasia or polyp</td>
<td>20 (2.5)</td>
</tr>
<tr>
<td>Postpartum uterine atony</td>
<td>7 (0.9)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Hematometra or hydrometra</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Placenta accreta, increta</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Abnormal uterine bleeding</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Pelvic actinomycosis</td>
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<tr>
<td>Pelvic endometriosis</td>
<td>2 (0.2)</td>
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<tr>
<td>Hydatidiform mole</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Tubo-ovarian abscess</td>
<td>1 (0.1)</td>
</tr>
</tbody>
</table>

Values are presented as mean (range) or number (%).
<sup>a</sup> Main diagnosis that was assumed clinically before hysterectomy was described.

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%).

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

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

<sup>a</sup> Main diagnosis that was assumed clinically before hysterectomy was described.
<sup>b</sup> Denominators are the number of the total case of laparoscopic and robotic surgery.

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
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/m²) or obese (BMI, ≥ 25 kg/m²).

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-

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

<table>
<thead>
<tr>
<th>Surgical outcome</th>
<th>Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative time (min)</td>
<td></td>
</tr>
<tr>
<td>TAH</td>
<td>137.1 (65−290)</td>
</tr>
<tr>
<td>LAVH</td>
<td></td>
</tr>
<tr>
<td>Single-port</td>
<td>89.5 (70−125)</td>
</tr>
<tr>
<td>Multi-port</td>
<td>181.2 (80−495)</td>
</tr>
<tr>
<td>TLH</td>
<td>105.0 (60−250)</td>
</tr>
<tr>
<td>Robot</td>
<td></td>
</tr>
<tr>
<td>Single-port</td>
<td>133.8 (75−240)</td>
</tr>
<tr>
<td>Multi-port</td>
<td>273.8 (215−325)</td>
</tr>
<tr>
<td>Vaginal hysterectomy</td>
<td>96.8 (60−170)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemoglobin drop after surgery (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAH</td>
</tr>
<tr>
<td>LAVH</td>
</tr>
<tr>
<td>Single-port</td>
</tr>
<tr>
<td>Multi-port</td>
</tr>
<tr>
<td>TLH</td>
</tr>
<tr>
<td>Robot</td>
</tr>
<tr>
<td>Single-port</td>
</tr>
<tr>
<td>Multi-port</td>
</tr>
<tr>
<td>Vaginal hysterectomy</td>
</tr>
</tbody>
</table>

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

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

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

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.
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 occurred 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

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**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.

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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.

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References
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-
Everyday 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 m², which was calculated using the Modification of Diet in Renal Disease formula: 186 × (creatinine)⁻¹.154 × (age)⁻⁰.²⁰³ × (0.742, 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 categorical 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

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

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.

<sup>a</sup>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).
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-

Table 2. Major risk factors of amputation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-amputation (n = 181)</th>
<th>Amputation (n = 170)</th>
<th>p-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteomyelitis</td>
<td>77 (42.5)</td>
<td>142 (83.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Lesion on percutaneous transluminal angioplasty</td>
<td>10 (5.5)</td>
<td>30 (17.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diabetic peripheral polyneuropathy</td>
<td>120 (66.2)</td>
<td>97 (57.0)</td>
<td>0.095</td>
</tr>
<tr>
<td>Chronic kidney disease (eGFR &lt; 60 mL/min/1.73 m²)</td>
<td>49 (27.0)</td>
<td>66 (36.4)</td>
<td>0.019</td>
</tr>
<tr>
<td>ABI decreased (ABI &lt; 0.9)</td>
<td>26 (n = 126, 20.6)</td>
<td>46 (n = 126, 36.5)</td>
<td>0.005</td>
</tr>
<tr>
<td>Previous amputation history</td>
<td>12 (6.6)</td>
<td>22 (12.9)</td>
<td>0.046</td>
</tr>
<tr>
<td>Hypertension</td>
<td>113 (62.4)</td>
<td>103 (60.6)</td>
<td>0.723</td>
</tr>
<tr>
<td>Smoking</td>
<td>79 (43.6)</td>
<td>82 (48.2)</td>
<td>0.358</td>
</tr>
<tr>
<td>Alcohol</td>
<td>60 (33.1)</td>
<td>70 (41.2)</td>
<td>0.108</td>
</tr>
<tr>
<td>Wagner classification</td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>Grade 0–1</td>
<td>72 (39.7)</td>
<td>30 (17.6)</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>47 (26.0)</td>
<td>31 (18.2)</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>36 (19.9)</td>
<td>52 (30.6)</td>
<td></td>
</tr>
<tr>
<td>Grade 4–5</td>
<td>26 (14.4)</td>
<td>57 (33.5)</td>
<td></td>
</tr>
<tr>
<td>Ulcer location</td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Forefoot</td>
<td>110 (60.8)</td>
<td>129 (75.9)</td>
<td></td>
</tr>
<tr>
<td>Midfoot</td>
<td>61 (33.7)</td>
<td>37 (21.8)</td>
<td></td>
</tr>
<tr>
<td>Hindfoot</td>
<td>10 (5.5)</td>
<td>4 (2.3)</td>
<td></td>
</tr>
</tbody>
</table>

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

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

Cl, 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 pri-
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, where-in 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.
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.

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References


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

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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 CHA2DS2-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 CHA2DS2-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-
Interrupted anticoagulation in non-cardiac surgery

The demographic and clinical characteristics of the patients are shown in Table 1. The mean age was 73 ± 8 years; 127 males (58.8%) were included. The mean body weight was 78 ± 33 kg; furthermore, 52 patients (24.1%) had a history of hypertension, diabetes mellitus, and smoking. The mean left atrial anteroposterior diameter (mm) and left ventricular ejection fraction (LVEF, %) were measured using two-dimensional echocardiography. Regarding laboratory data, the mean estimated glomerular filtration rate was 78 ± 33 mL/min; furthermore, 52 patients (24.1%) had a history of hypertension and diabetes mellitus.

Materials and methods

The study was approved 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 non-valvular AF (NVAF) who consulted the Department of Cardiology for suspending their 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 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 CHA2DS2-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 peroperative 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 peroperative 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 of hypertension and diabetes mellitus.
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$_2$DS$_2$-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$_2$DS$_2$-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$_2$DS$_2$-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$_2$DS$_2$-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$_2$DS$_2$-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$_2$DS$_2$-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 1. Surgery type according to the bleeding risk (n=216)

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

EMR, endoscopic mucosal resection; ERCP, endoscopic retrograde cholangiopancreatography.
*Neck lymph node core needle biopsy, subclavicular lymph node excisional biopsy, etc.

of chronic kidney disease. The mean CHA$_2$DS$_2$-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, 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$_2$DS$_2$-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$_2$DS$_2$-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$_2$DS$_2$-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$_2$DS$_2$-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$_2$DS$_2$-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$_2$DS$_2$-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$_2$DS$_2$-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.

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

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 216)</th>
<th>NOACs (n = 138)</th>
<th>Warfarin (n = 78)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>72.9 ± 7.7</td>
<td>73.2 ± 7.6</td>
<td>72.3 ± 8.1</td>
<td>0.418</td>
</tr>
<tr>
<td>Male sex</td>
<td>127 (58.8)</td>
<td>74 (53.6)</td>
<td>53 (67.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>63.0 ± 11.5</td>
<td>62.2 ± 12.2</td>
<td>64.2 ± 10.2</td>
<td>0.232</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>127 (58.8)</td>
<td>89 (64.5)</td>
<td>38 (48.7)</td>
<td>0.024</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>66 (30.6)</td>
<td>43 (31.2)</td>
<td>23 (29.5)</td>
<td>0.798</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>24 (11.1)</td>
<td>15 (10.9)</td>
<td>9 (11.5)</td>
<td>0.881</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>46 (21.3)</td>
<td>25 (18.1)</td>
<td>21 (26.9)</td>
<td>0.129</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>16 (7.4)</td>
<td>11 (8.0)</td>
<td>5 (6.4)</td>
<td>0.674</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>18 (8.3)</td>
<td>10 (7.2)</td>
<td>8 (10.3)</td>
<td>0.442</td>
</tr>
<tr>
<td>CHA(_2)DS(_2)-VASc score</td>
<td>3.3 ± 1.5</td>
<td>3.3 ± 1.4</td>
<td>3.1 ± 1.8</td>
<td>0.41</td>
</tr>
<tr>
<td>HAS-BLED score</td>
<td>1.9 ± 1.0</td>
<td>1.9 ± 0.9</td>
<td>2.0 ± 1.1</td>
<td>0.519</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>52 (24.1)</td>
<td>28 (20.3)</td>
<td>24 (30.8)</td>
<td>0.084</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>55.1 ± 9.2</td>
<td>56.0 ± 9.2</td>
<td>53.6 ± 9.1</td>
<td>0.078</td>
</tr>
<tr>
<td>Left atrium size, AP diameter (mm)</td>
<td>47.7 ± 7.7</td>
<td>47.0 ± 7.9</td>
<td>48.9 ± 7.8</td>
<td>0.081</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.1 ± 0.8</td>
<td>0.9 ± 0.3</td>
<td>1.3 ± 1.3</td>
<td>0.008</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>77.8 ± 32.7</td>
<td>80.0 ± 29.1</td>
<td>74.0 ± 38.1</td>
<td>0.23</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12.7 ± 1.8</td>
<td>12.7 ± 1.7</td>
<td>12.9 ± 1.9</td>
<td>0.412</td>
</tr>
<tr>
<td>Platelet (× 10(^3)/µL)</td>
<td>205.9 ± 77.0</td>
<td>206.5 ± 66.1</td>
<td>204.8 ± 93.7</td>
<td>0.874</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant antiplatelet agents</td>
<td>26 (12.0)</td>
<td>15 (10.9)</td>
<td>11 (14.1)</td>
<td>0.495</td>
</tr>
<tr>
<td>Heparin bridging therapy</td>
<td>54 (25.0)</td>
<td>15 (10.9)</td>
<td>39 (50.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type of NOACs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>-</td>
<td>33 (23.9)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>-</td>
<td>21 (15.2)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Edoxaban</td>
<td>-</td>
<td>27 (19.6)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>-</td>
<td>57 (41.3)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Surgical bleeding risk</td>
<td></td>
<td></td>
<td></td>
<td>0.395</td>
</tr>
<tr>
<td>Not necessarily requiring discontinuation</td>
<td>44 (20.4)</td>
<td>30 (21.7)</td>
<td>14 (17.9)</td>
<td></td>
</tr>
<tr>
<td>Low bleeding risk</td>
<td>3 (1.4)</td>
<td>3 (2.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>High bleeding risk</td>
<td>169 (78.2)</td>
<td>105 (76.1)</td>
<td>64 (82.1)</td>
<td></td>
</tr>
</tbody>
</table>

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.
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 excess-

![Fig. 1. Duration of perioperative anticoagulant discontinuation according to anticoagulant type (non-vitamin K antagonist oral anticoagulants [NOACS] vs. warfarin).](https://doi.org/10.12701/yujm.2020.00353)

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 216)</th>
<th>Low/high bleeding risk patients (n = 172)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events (+) (n = 7)</td>
<td>Events (-) (n = 209)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>74.4 ± 5.4</td>
<td>72.8 ± 7.8</td>
</tr>
<tr>
<td>Male sex</td>
<td>4 (57.1)</td>
<td>123 (58.9)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>65.0 ± 10.3</td>
<td>62.9 ± 11.6</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (100)</td>
<td>120 (57.4)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (42.9)</td>
<td>63 (30.1)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1 (14.3)</td>
<td>23 (11.0)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>3 (42.9)</td>
<td>43 (20.6)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2 (28.6)</td>
<td>14 (6.7)</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>2 (28.6)</td>
<td>16 (7.7)</td>
</tr>
<tr>
<td>CHA2DS2-VASc score</td>
<td>4.9 ± 2.0</td>
<td>3.2 ± 1.5</td>
</tr>
<tr>
<td>HAS-BLED score</td>
<td>3.6 ± 1.1</td>
<td>1.8 ± 0.9</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>3 (42.9)</td>
<td>49 (23.4)</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>52.9 ± 12.8</td>
<td>55.2 ± 9.1</td>
</tr>
<tr>
<td>Left atrium size, AP diameter (mm)</td>
<td>46.6 ± 7.7</td>
<td>47.7 ± 7.7</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.9 ± 0.3</td>
<td>1.1 ± 0.8</td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td>76.4 ± 25.2</td>
<td>77.8 ± 33.0</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.6 ± 1.8</td>
<td>12.8 ± 1.8</td>
</tr>
<tr>
<td>Platelet (× 10^5)/µL</td>
<td>225.7 ± 33.8</td>
<td>205.2 ± 78.0</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant antiplatelet agents</td>
<td>2 (28.6)</td>
<td>24 (11.5)</td>
</tr>
<tr>
<td>Heparin bridging therapy</td>
<td>4 (57.1)</td>
<td>50 (23.9)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOACs</td>
<td>4 (57.1)</td>
<td>134 (64.1)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>3 (42.9)</td>
<td>75 (35.9)</td>
</tr>
<tr>
<td>High bleeding risk surgery</td>
<td>6 (85.7)</td>
<td>163 (78.0)</td>
</tr>
<tr>
<td>Discontinuation duration (day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>4.4 ± 2.1</td>
<td>2.9 ± 1.8</td>
</tr>
<tr>
<td>After surgery</td>
<td>1.8 ± 4.4</td>
<td>2.8 ± 3.4</td>
</tr>
<tr>
<td>Total</td>
<td>5.7 ± 2.6</td>
<td>5.7 ± 4.2</td>
</tr>
</tbody>
</table>

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.
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\(_2\)DS\(_2\)-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\(_2\)DS\(_2\)-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-

---

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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Name of surgery</th>
<th>CHA(_2)DS(_2)-VASc score</th>
<th>HAS-BLED score</th>
<th>Anticoagulant</th>
<th>INR at event</th>
<th>Discontinuation duration (day)</th>
<th>Heparin bridging therapy</th>
<th>Perioperative event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>74</td>
<td>Craniotomy/aneurysm clipping</td>
<td>5</td>
<td>4</td>
<td>Rivaroxaban 20 mg</td>
<td>–</td>
<td>9 (7/2)</td>
<td>–</td>
<td>Stroke</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>78</td>
<td>Femur fracture(^a)</td>
<td>8</td>
<td>4</td>
<td>Warfarin 2.1</td>
<td>8 (6/2)</td>
<td>+</td>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>75</td>
<td>Total hysterectomy</td>
<td>7</td>
<td>5</td>
<td>Warfarin 2.49</td>
<td>7 (5/2)</td>
<td>+</td>
<td>Major bleeding</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>75</td>
<td>Planned tooth extraction</td>
<td>4</td>
<td>2</td>
<td>Apixaban 5 mg</td>
<td>–</td>
<td>3 (3/0)</td>
<td>–</td>
<td>Systemic embolism</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>76</td>
<td>Femur fracture(^b)</td>
<td>3</td>
<td>4</td>
<td>Warfarin 2.68</td>
<td>5 (3/2)</td>
<td>+</td>
<td>Major bleeding</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>63</td>
<td>Planned gastric EMR</td>
<td>3</td>
<td>2</td>
<td>Edoxaban 60 mg</td>
<td>–</td>
<td>6 (6/0)</td>
<td>–</td>
<td>Stroke</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>80</td>
<td>Acetabular fracture(^c)</td>
<td>4</td>
<td>4</td>
<td>Rivaroxaban 10 mg</td>
<td>–</td>
<td>2 (1/1)</td>
<td>+</td>
<td>Major bleeding</td>
</tr>
</tbody>
</table>

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\(_2\)DS\(_2\)-VASc scores and duration of preoperative anticoagulant discontinuation for predicting perioperative events. AUC, area under the curve.
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<sub>2</sub>DS<sub>2</sub>-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.


Negative myoclonus associated with tramadol use

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Negative myoclonus (NM) is a brief involuntary jerky 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 for 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.
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References
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 (PCDAI < 10) with 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.

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
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.

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

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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.

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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-
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).

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).

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-
The sciatic notch is divided into the greater and lesser sciatic foramina. 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 ‘curlieque 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.

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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.

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

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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 23-year-old male presented to our emergency department with weakness in the left arm after wrist drop in his right hand 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.

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 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.
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**

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

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.

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

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

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References
Early surgical intervention for unusually located cardiac fibroelastomas

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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 papillary fibroelastomas occurring on the ventricular surface of the aortic valve and in the right ventricle.

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

Readership

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.
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 echocardiography 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).
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.

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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.

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References

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

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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 in long lines. In the CSS, a long line often had people wait-

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...
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 1,527m² 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...
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.

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
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 m² of space, four shipping containers, computers, computer network systems, and several personnel. In addition, flexible expansion was
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 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.

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**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.

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

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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. (In case of facial photographs, the photo is cropped to only necessary parts in order to make individual identification 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 effect 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: ___________________________