Prevalence of depression and its associated factors in bronchiectasis: findings from KMBARC registry

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Abstract

**Background:** With the emergence of bronchiectasis as a common respiratory disease, epidemiological data have accumulated. However, the prevalence and impact of psychological comorbidities were not sufficiently evaluated. The present study examined the prevalence of depression and its associated factors in patients with bronchiectasis.

**Methods:** This study involved a multicenter cohort of bronchiectasis patients recruited from 33 pulmonary specialist hospitals. The baseline characteristics and bronchiectasis-related factors at enrollment were analyzed. Depressive symptoms were assessed using the Patient Health Questionnaire (PHQ-9).

**Results:** Of the 810 patients enrolled in the study, 168 (20.7%) patients had relevant depression (PHQ-9 score ≥ 10), and only 20 (11.9%) patients had a diagnosis of depression. Significant differences were noted in the depressive symptoms with disease severity, which was assessed using the Bronchiectasis Severity Index and E-FACED (all \(p < 0.001\)). Depressive symptoms inversely correlated with quality-of-life (\(r = -0.704, p < 0.001\)) and positively correlated with fatigue severity score (\(r = 0.712, p < 0.001\)). Multivariate analysis showed that depression was significantly associated with the modified Medical Research Council dyspnea scale ≥ 2 (OR 2.960, 95% CI 1.907–4.588, \(p = <0.001\)) and high number of exacerbations (≥ 3) in the previous year (OR 1.596, 95% CI 1.012–2.482, \(p = 0.041\)).

**Conclusions:** Depression is common, but its association with bronchiectasis was underrecognized. It negatively affected quality-of-life and presented with fatigue symptoms. Among the bronchiectasis-related factors, dyspnea and exacerbation were closely associated with depression. Therefore, active screening for depression is necessary to optimize the treatment of bronchiectasis.

**Trial registration:** The study was registered at Clinical Research Information Service (CRIS), Republic of Korea (KCT0003088). The date of registration was June 19th, 2018.

**Keywords:** Bronchiectasis, Depression, Dyspnea, mMRC, Exacerbation
In one or more lobes. Patients with cystic fibrosis and secondary traction bronchiectasis were excluded. All baseline data at the time of enrollment were collected when patients were stable for 4 weeks. Data on age, body mass index (BMI), pulmonary function tests, modified Medical Research Council (mMRC) dyspnea scale, exacerbation, etiology determined by physicians, microbiological results, and CT findings were collected at baseline. Further information on the protocol was recently published [12]. The patients were enrolled between August 2018 and November 2020 from 33 pulmonary specialist hospitals. Baseline data were extracted during the enrollment of the cohort, and analyses were performed.

The Institutional Review Board of Wonju Severance Christian Hospital (CR318139) and the institutional review boards of all participating institutions approved the study, and it adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients at the time of study enrollment.

**Methods**

**Study design**

The data source of this study was the Korean Multicenter Bronchiectasis Audit and Research Collaboration (KMBARC) registry. The KMBARC was an observational cohort study that examined the clinical characteristics, disease burden, etiology, risk factors for exacerbation, and prognosis in Korean patients with bronchiectasis. Patients were included if they were aged ≥ 18 years and had bronchiectasis confirmed by computed tomography in one or more lobes. Patients with cystic fibrosis and secondary traction bronchiectasis were excluded. All baseline data at the time of enrollment were collected when patients were stable for 4 weeks. Data on age, body mass index (BMI), pulmonary function tests, modified Medical Research Council (mMRC) dyspnea scale score, exacerbation, etiology determined by physicians, microbiological results, and CT findings were collected at baseline. Further information on the protocol was recently published [12]. The patients were enrolled between August 2018 and November 2020 from 33 pulmonary specialist hospitals. Baseline data were extracted during the enrollment of the cohort, and analyses were performed.

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**Definition of study variables**

Exacerbation of bronchiectasis was defined as an aggravation of three or more symptoms, including cough, sputum volume and/or consistency, sputum purulence, dyspnea and/or exercise intolerance, fatigue and/or malaise, and hemoptysis, for at least 48 h that necessitated a change in treatment [13]. Exacerbations were assessed using information obtained via history taking and reviews of antibiotic prescription records and medical charts. The number of exacerbations and rate of hospital admissions within the previous 12 months before enrollment in the study were recorded.

The severity of bronchiectasis was evaluated using validated scoring systems, such as the Bronchiectasis Severity Index (BSI), FACED, and E-FACED. BSI takes into account age, BMI, predicted value of forced expiratory volume in the first second (FEV₁%), number of admissions and exacerbations, mMRC dyspnea scale, *Pseudomonas aeruginosa* (PA) colonization, and bronchiectasis involving 3 or more lobes or the presence of cystic bronchiectasis. According to the BSI, the severity of bronchiectasis was categorized into mild (0–4), moderate (5–8), and severe (≥ 9) [14]. FACED stands for FEV₁% (F), age (A), colonization with PA (C), extension of bronchiectasis (E), and dyspnea score for mMRC (D). FACED was categorized into mild (0–2), moderate (3–4), and severe (5–7) [15]. Exacerbation was added to the FACED in E-FACED, and it was classified into mild (0–3), moderate (4–6), and severe (7–9) [16].

The first coronavirus disease 2019 (COVID-19) occurred on January 20, 2020, in our country. The COVID-19 pandemic developed from March 2020. Therefore, all participants were classified into pre-pandemic (until February 2020) and pandemic (from March 2020) groups according to the enrollment date to determine whether COVID-19 affected the prevalence of depression.

**Patient-reported outcomes**

This study used three patient health-related questionnaires. The Bronchiectasis Health Questionnaire (BHQ) was developed to measure bronchiectasis-specific quality-of-life and health status. The BHQ is comprised of 10 items, with higher scores indicating a better quality-of-life [17]. A Korean version of the BHQ that was validated in Korean patients with bronchiectasis was used [18]. Fatigue was assessed using the Korean version of the Fatigue Severity Score (FSS) [19]. The FSS is comprised
of 9 items. Higher FSS indicates more severe fatigue symptoms.

The Patient Health Questionnaire 9 (PHQ-9) was used to assess depressive symptoms. The PHQ-9 contains 9 items. Each item is evaluated on a 4-point scale: 0, “not at all”; 1, “several days”; 2, “more than half of the days”; and 3, “nearly every day.” Higher scores on the PHQ-9 indicate more severe depressive symptoms. A Korean version of the PHQ-9 was validated for screening major depression [20]. Patients with a PHQ-9 score of 10 or greater were considered to have depression. All three questionnaires were administered in the outpatient department after the patients were stable for at least 4 weeks.

**Statistical analysis**

Continuous variables are presented as the means ± standard deviations, and categorical variables are presented as the number of patients and percentages. The baseline clinical characteristics of patients with and without depression were compared using an independent t-test for continuous variables, and a chi-squared test was used for categorical variables. PHQ-9 scores for the degrees of severity assessed by the BSI, FACED, and E-FACED were compared using a one-way analysis of variance with post hoc testing using the Bonferroni test. Correlations were compared using a one-way analysis of variance with the Bonferroni test. Statistical analyses were performed and the figures were prepared using R software (ver. 4.0.3; R Development Core Team, Vienna, Austria). Statistical significance was set at \( p < 0.05 \).

**Results**

**Baseline characteristics**

Among 848 patients in a registry, patients lacking demographics or missing data for critical values for analysis were excluded. A total of 810 patients with bronchiectasis were ultimately included for this study (Table 1). The mean age was 64.3 ± 9.3 years, and 452 (55.8%) of the participants were female. There were 168 (20.7%) patients with depression (PHQ-9 ≥ 10), and only 20 (11.9%) patients had a diagnosis of depression. The number of recruited patients was 665 in the pre-pandemic group and 145 in the COVID-19 pandemic group. The prevalence of depression was 21.7% (144/665) pre-pandemic and 16.6% (24/145) pandemic. A significant difference was not found between these groups (\( p = 0.208 \)). The baseline characteristics of patients with and without depression were compared. Patients with depression had a lower BMI than patients without depression (22.5 ± 3.9 versus 23.3 ± 6.9, \( p = 0.049 \)). Lung function was significantly lower in patients with depression without depression. \( \text{FEV}_1 \) was 60.4 ± 20.8% and 65.8 ± 20.8% for patients with and without depression, respectively (\( p = 0.005 \)). FVC was 68.4 ± 17.1% and 74.1 ± 17.5% for patients with and without depression, respectively (\( p < 0.001 \)). The number of exacerbations and rates of hospital admission within the previous 12 months were significantly higher for patients with depression than patients without depression (number of exacerbations: 2.0 ± 1.9 versus 1.2 ± 1.9, \( p < 0.001 \); admission rate: 25.0% versus 15.4%, \( p = 0.005 \)). The number of patients treated with long-term oxygen therapy (LTOT) or noninvasive ventilation (NIV) were 11 (6.5%) and 8 (1.2%) patients with and without depression, respectively (\( p < 0.001 \)). The number of patients admitted to the intensive care unit

| Variable | Nondepressed (PHQ-9 < 10) \( n = 642 \) | Depressed (PHQ-9 ≥ 10) \( n = 168 \) | p value |
|----------|----------------------------------------|------------------------------------------|--------|
| Age (years) | 66.4 ± 9.1 | 63.3 ± 10.2 | 0.140 |
| Sex (female) | 355 (55.3) | 97 (57.7) | 0.631 |
| Bronchiectasis duration (years) | 3.2 ± 1.6 | 3.3 ± 1.7 | 0.432 |
| Ever smoker | 216 (33.7) | 56 (33.3) | 1.000 |
| BMI | 23.3 ± 6.9 | 22.5 ± 3.9 | 0.049 |
| FEV1 (%) | 65.8 ± 20.8 | 60.4 ± 20.8 | 0.005 |
| FVC (%) | 74.1 ± 17.5 | 68.4 ± 17.1 | 0.001 |
| FVC (L) | 2.7 ± 0.8 | 2.4 ± 0.8 | < 0.001 |
| Asthma or COPD | 294 (45.8) | 80 (47.6) | 0.737 |
| Number of exacerbations in the previous year | 1.2 ± 1.9 | 2.0 ± 3.7 | < 0.001 |
| Hospitalization | 99 (15.4) | 42 (25.0) | 0.005 |
| Tuberculosis history | 219 (35.8) | 51 (31.7) | 0.372 |
| NTM history | 65 (10.64) | 14 (8.70) | 0.564 |
| Depression history | 15 (2.3) | 20 (11.9) | < 0.001 |
| LTOT or NIV | 8 (1.2) | 11 (6.5) | < 0.001 |
| ICU or MV | 4 (0.6) | 3 (1.8) | 0.326 |
| Etiology | | | |
| Post-infectious | 249 (43.7) | 60 (38.5) | 0.281 |
| Idiopathic | 229 (40.2) | 66 (42.3) | 0.698 |
| PA colonization | 46 (7.3) | 16 (9.6) | 0.412 |
| Sputum volume (≥ 30 cc/day) | 253 (39.4) | 64 (38.1) | 0.825 |
| Radiological extent (≥ 3 lobes) | 342 (53.3) | 96 (57.1) | 0.418 |

Values are presented as the means ± standard deviation or number (%)

BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; NTM, nontuberculosis mycobacterium; LTOT, long term oxygen therapy; NIV, noninvasive ventilation; ICU, intensive care unit; MV, mechanical ventilation; PA, Pseudomonas aeruginosa
or treated with mechanical ventilation for the management of bronchiectasis exacerbations were 3 (1.8%) for patients with depression and 4 (0.6%) for patients without depression ($p = 0.326$).

The severity of bronchiectasis and patient-reported outcomes were compared between patients with and without depression (Table 2). The mean BSI and E-FACED scores were significantly higher for patients with depression than patients without depression (BSI: $8.0 \pm 4.7$ versus $6.6 \pm 3.4$, $p = 0.001$; E-FACED: $2.8 \pm 2.3$ versus $2.3 \pm 1.8$, $p = 0.014$). However, the severity estimated by FACED did not differ ($p = 0.425$). The quality-of-life score assessed using the BHQ was $41.4 \pm 9.5$ for patients with depression, which was lower than $54.8 \pm 7.4$ for patients without depression ($p < 0.001$). The fatigue score estimated by the FSS was $39.7 \pm 13.6$ for patients with depression, which was higher than $20.0 \pm 11.1$ for patients without depression ($p < 0.001$).

**Depressive symptoms across the severity of bronchiectasis**

The PHQ-9 scores were compared according to the grade of severity. The PHQ-9 scores were $4.8 \pm 5.6$, $4.8 \pm 5.0$, and $6.9 \pm 6.7$ for the mild, moderate, and severe groups based on the BSI, respectively ($p < 0.001$). The post hoc analysis showed that the PHQ-9 scores for the mild versus severe and moderate versus severe groups were significantly different (all $p < 0.001$) (Fig. 1a). PHQ-9 scores for the E-FACED were $4.9 \pm 5.4$ for the mild group, $6.2 \pm 6.4$ for the moderate group, and $11.1 \pm 6.9$ for the severe group ($p < 0.001$). The post hoc analysis showed that the PHQ-9 scores for the mild versus moderate, mild versus severe, and moderate versus severe groups were significantly different ($p = 0.039$, $p < 0.001$, and $p < 0.001$, respectively) (Fig. 1b).

**Relevant factors underlying depression in bronchiectasis**

PHQ-9 scores inversely correlated with BHQ ($r = -0.704$, $p < 0.001$) and positively correlated with FSS ($r = 0.712$, $p < 0.001$) (Fig. 2a, b), and these scores showed a weak positive correlation with BSI ($r = 0.214$, $p < 0.001$) and E-FACED scores ($r = 0.145$, $p < 0.001$) and a weak negative correlation with FEV1% ($r = -0.134$, $p < 0.001$).

The univariate analysis showed that FEV1% was negatively associated with depression (odds ratio [OR] = 0.985, 95% confidence interval [CI]: 0.976–0.994, $p = 0.001$). The mMRC dyspnea scale was associated with an elevated risk of depression (OR = 2.031, 95% CI 1.659–2.500, $p < 0.001$). The number of exacerbations and presence of hospital admission were significantly related to depression (exacerbations: OR = 1.140, 95% CI 1.064–1.228, $p < 0.001$; admission: OR = 1.828, 95% CI

### Table 2 Comparison of severity index and patient-reported outcomes between patients with and without depression

| Variable  | Nondepressed | Depressed   | $p$ value |
|-----------|--------------|-------------|-----------|
| BSI       | $6.6 \pm 3.4$ | $8.0 \pm 4.7$ | 0.001     |
| FACED     | $2.3 \pm 1.6$ | $2.4 \pm 1.7$ | 0.425     |
| E-FACED   | $2.3 \pm 1.8$ | $2.8 \pm 2.3$ | 0.014     |
| BHQ       | $54.8 \pm 7.4$ | $41.4 \pm 9.5$ | <0.001   |
| FSS       | $20.0 \pm 11.1$ | $39.7 \pm 13.6$ | <0.001   |

Values are presented as the means ± standard deviation.

BSI, bronchiectasis severity index; BHQ, Bronchiectasis Health Questionnaire; FSS, Fatigue Severity Score.

**Fig. 1** Comparison of PHQ-9 scores according to the severity classified by BSI (a) and E-FACED (b). The number at the top of the figure indicates the $p$ value from the Bonferroni post hoc test. PHQ-9, Patient Health Questionnaire 9; BSI, bronchiectasis severity index.
1.205–2.740, \( p = 0.004 \)). LTOT or NIV was significantly associated with depression (OR = 5.553, 95% CI 2.211–14.562, \( p < 0.001 \)) (Table 3).

The multivariate analysis showed that the mMRC dyspnea scale was significantly associated with depression (OR = 2.137, 95% CI 1.671–2.752, \( p < 0.001 \)). The number of exacerbations in the previous year and LTOT or NIV were not significantly associated with depression (number of exacerbations: OR = 1.085, 95% CI 0.997–1.178, \( p = 0.052 \); LTOT or NIV: OR = 1.899, 95% CI 0.642–5.673, \( p = 0.243 \)). A multivariate analysis of the categorical variables was also performed, and mMRC \( \geq 2 \) and a high number of exacerbations (\( \geq 3 \)) were significantly related to depression (mMRC: OR = 2.960, 95% CI 1.907–4.588, \( p < 0.001 \); exacerbation: OR = 1.596, 95% CI 1.012–2.482, \( p = 0.041 \)) (Fig. 3). LTOT or NIV was not significantly associated with depression (OR = 2.641, 95% CI 0.961–7.500, \( p = 0.060 \)). Hospitalization was excluded from the multivariate analysis because exacerbation and admission substantially overlapped and interfered with each other.

**Discussion**

This multicenter study found a 20.7% prevalence of depression in patients with bronchiectasis. The depressive symptoms were aggravated as bronchiectasis worsened and strongly correlated with quality-of-life and fatigue symptoms. Dyspnea and frequent exacerbations were identified as clinical factors associated with depression.

The prevalence of depression using the Hospital Anxiety and Depression Scale (HADS) was 22.8% in 93 bronchiectasis patients in a cross-sectional study [11]. Other studies using HADS reported a prevalence of 21.1% in 133 patients [21] and 30.1% in 163 patients [22]. A study of depression using the Beck Depression Inventory (BDI) found a prevalence of 33.8% in 74 patients [23]. Previous studies used the HADS or BDI as a screening tool, but our study used the PHQ-9 to assess depressive symptoms. The BDI is comprised of 21 items, and it takes time

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**Table 3**  Factors associated with depression in logistic regression analysis

| Factors                               | Univariate analysis | Multivariate analysis |
|---------------------------------------|---------------------|-----------------------|
|                                       | OR (95% CI) \( p \) | OR (95% CI) \( p \)  |
| Age                                   | 0.986 (0.968–1.004) | 0.980 (0.960–1.000)  |
| Sex (female)                          | 1.105 (0.785–1.561) | 1.019 (0.692–1.506)  |
| BMI                                   | 0.952 (0.904–1.002) | 0.971 (0.919–1.024)  |
| FEV1 (%)                              | 0.985 (0.976–0.994) | 1.001 (0.991–1.012)  |
| FVC (%)                               | 0.983 (0.972–0.992) | < 0.001 – –           |
| mMRC                                  | 2.031 (1.659–2.500) | 2.137 (1.671–2.752)  |
| Number of exacerbations in the previous year | 1.140 (1.064–1.228) | 1.085 (0.997–1.178)  |
| Hospitalization                       | 1.828 (1.205–2.740) | < 0.001 – –           |
| LTOT or NIV                           | 5.553 (2.211–14.562) | 1.899 (0.642–5.673)  |

BMI, body mass index; FEV\(_1\), forced expiratory volume in 1 s; FVC, forced vital capacity; mMRC, Modified Medical Research Council; LTOT, long term oxygen therapy; NIV, noninvasive ventilation; OR, odds ratio; CI, confidence interval
to complete. The HADS has a low diagnostic accuracy for identifying depression in COPD [24]. The PHQ-9 is comprised of 9 questions that correspond to the diagnostic criteria of depressive disorder and was an accurate screening tool for depression in a recent meta-analysis with a sensitivity of 88% and specificity of 85% [25]. Because this study involved a large number of patients and used practical and accurate screening tools, it strengthens the findings of previous studies that reported depression as common in bronchiectasis patients.

A Korean population-based study on bronchiectasis-associated comorbidities reported that the prevalence of depression was 4.3%, but the diagnostic code was used to define comorbidities [6]. Only 4.3% of patients (35/810) in the present study reported a history of depression. These data suggest that comorbidities based on patient self-reports or administrative databases may not reflect the true prevalence of depression. Therefore, we suggest the PHQ-9 for evaluating depression in a baseline study of bronchiectasis.

Differences in depressive symptoms based on bronchiectasis severity were rarely studied. Gao et al. reported that depressive symptoms assessed using HADS did not significantly differ from the degree of severity determined by the BSI and FACED [22]. However, depressive symptoms significantly differed with severity based on the BSI and E-FACED but not FACED in our study. The inconsistency in the results may be attributed to the differences in patient characteristics and depression measurement tools. The E-FACED includes exacerbation, and FACED does not [15, 16]. Our study results showed that exacerbation was a significant factor associated with depression. Therefore, it was hypothesized that the depressive symptoms did not differ with severity based on FACED because there were no items reflecting exacerbation.

The predictive factors for depression in other studies were FEV1%, hemoptysis, admission to an emergency department, living with a partner, and sleep disturbance [10, 21, 22]. However, each study included different variables. Some studies collected information on socioeconomic and educational status, but we did not [21, 22]. One study included a separate questionnaire for sleep quality, and questions for sleep disturbance were confined to only one item in the BHQ and PHQ-9 in the present study [22]. Therefore, a comparison between our study and previous studies is not feasible.

Dyspnea and a high number of exacerbations were significant predictors of depression in our study. Depression was not related to lung function and obstructive lung diseases. Therefore, bronchiectasis-specific factors may be associated with the deterioration of symptoms and the development of depression. The association between dyspnea and depression seems complex [26]. Depression can affect the perception of dyspnea, and dyspnea can lead to the worsening of depression [27]. Dyspnea is often associated with a decrease in physical activity, which can cause psychological symptoms [26]. However, an association with physical activity was not determined in our study because it was not measured. Depressive symptoms are closely related to frequent exacerbations and poor control of disease in COPD [28]. Similar to COPD, frequent exacerbations of bronchiectasis were associated with poor control of disease.
Therefore, the use of inhaled or long-term macrolide antibiotics for the prevention of exacerbation and the management of depression should be considered, as suggested by bronchiectasis guidelines [29]. Patients with chronic diseases showed a higher risk of depression, and patients with depression had poorer clinical outcomes than patients without depression [30, 31]. Although bronchiectasis is the third most common chronic airway disease, the impact of comorbidities was rarely studied [2]. A European observational cohort study suggested the Bronchiectasis Aetiology Comorbidity Index (BACI) [7]. The BACI includes 13 comorbidities that independently predict 5-year mortality. Depression was the tenth most common comorbidity. However, it did not correlate with increased mortality. Some studies reported that depressive symptoms correlated with poor quality-of-life [11, 22]. However, another study did not find a relationship between these two factors [23]. The findings from our study are consistent with a previous finding that depression was closely linked with quality-of-life. Depression was strongly correlated with fatigue symptoms. Fatigue is a common symptom in chronic airway disease, including bronchiectasis, and negatively affects exercise tolerance [32]. Physical inactivity is a risk factor for depression [33]. Depression and fatigue were associated with chronic inflammation, which may lead to changes in brain structure or function [34]. Therefore, depression and fatigue commonly manifest simultaneously in chronic inflammatory disease [35]. A meta-analysis showed that fatigue was strongly associated with quality-of-life in bronchiectasis [36]. Therefore, a thorough investigation of patient-reported outcomes for identifying factors affecting quality-of-life is warranted.

The strength of the present study is the large sample size. Most studies included a few patients recruited at a single center [22, 33]. To the best of our knowledge, our study is the first study to demonstrate the prevalence of depression, its clinical relevance, and associated factors based on data obtained from a national multicenter cohort of patients with bronchiectasis. Therefore, our study results are relatively generalizable. This study had several limitations. First, we used different tools to identify depression and included different variables. This difference limits the direct comparison of our results with other studies. Second, although significance of LTOT or NIV was not identified in the multivariate analysis, we could not rule out the significance of that because small proportion of patients treated with LTOT or NIV was included in this study. Third, our study could not explain the causality between depression and bronchiectasis because the results were not based on a prospective study. A prospective study on the impact of depression and the clinical course of bronchiectasis is warranted.

**Conclusion**

Depression is common and negatively affects the quality-of-life, but it is underrecognized in bronchiectasis. Active screening for depression is necessary to optimize the treatment of bronchiectasis, especially in patients with risk factors, such as dyspnea and exacerbation.

**Abbreviations**

COVID-19: Coronavirus disease 2019; BHQ: Bronchiectasis Health Questionnaire; BMI: Body mass index; BSJ: Bronchiectasis Severity Index; COPD: Chronic obstructive pulmonary disease; FEV1: Forced expiratory volume in the first second; FSS: Fatigue Severity Score; FVC: Forced vital capacity; mMRC: Modified Medical Research Council; NTM: Nontuberculosis mycobacterium; LTOT: Long-term oxygen therapy; NIV: Noninvasive ventilation; ICU: Intensive care unit; MV: Mechanical ventilation; *P. aeruginosa*; PHQ-9: Patient Health Questionnaire 9.
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Conceptualization: LJH. Acquisition of data: KWI, LCY, SS, KY, and JIY. Data curation: LJH. Formal analysis: LJH. Methodology: LWY and YSJ. Supervision: KSH. Conceptualization: LJH. Acquisition of data: KWJ, LCY, SS, KY, and JJY. Data curation: KSH, SS, and JJY. All authors read and approved the final manuscript.

Availability of data and materials
Data are available from the KMBARC committee upon reasonable request.

Declarations

Ethics approval and consent to participate
The Institutional Review Board of Wonju Severance Christian Hospital approved this study (CR318139). Written informed consent was obtained from all patients at the time of study enrollment.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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