Gastro-oesophageal reflux disease increases healthcare use and medical costs in patients with bronchiectasis: a Korean nationwide population-based study

Jai Hoon Yoon*, Sang Hyuk Kim*, Jiin Ryu*, Sung Jun Chung, Youlim Kim, Chang Ki Yoon, Seung Won Ra, Yeon Mok Oh, Hayoung Choi† and Hyun Lee† (ID)

Abstract

Background: Gastro-oesophageal reflux disease (GORD) is not only a common aetiology but also accompanying comorbidity of non-cystic fibrosis bronchiectasis (bronchiectasis). However, the association between GORD and the disease burden of bronchiectasis has not been well evaluated. Our study aimed to evaluate whether GORD is associated with increased healthcare use and medical costs in patients with bronchiectasis.

Methods: We analyzed the data from 44,119 patients with bronchiectasis using a large representative Korean population-based claim database between 2009 and 2017. We compared the healthcare use [outpatient department (OPD) visits and emergency room (ER) visits/hospitalizations] and medical costs in patients with bronchiectasis according to the presence or absence of GORD.

Results: The prevalence of GORD in patients with bronchiectasis tended to increase during the study period, especially in the 50s and older population. GORD was associated with increased use of all investigated healthcare resources in patients with bronchiectasis. Healthcare use including OPD visits (mean 47.6/person/year *versus* 30.0/person/year), ER visits/hospitalizations (mean 1.7/person/year *versus* 1.1/person/year), and medical costs (mean 3564.5 Euro/person/year *versus* 2198.7 Euro/person/year) were significantly higher in bronchiectasis patients with GORD than in those without GORD ($p < 0.001$ for all). In multivariable analysis, bronchiectasis patients with GORD showed 1.44-fold (95% confidence interval = 1.37–1.50) and 1.26-fold (95% confidence interval = 1.19–1.33) increased all-cause and respiratory-related ER visits/hospitalizations relative to those without GORD, respectively. After adjusting for potential confounders, the estimated total medical costs (mean 4337.3 *versus* 3397.4 Euro/person/year) and respiratory disease-related medical costs (mean 920.7 *versus* 720.2 Euro/person/year) were significantly higher in bronchiectasis patients with GORD than in those without GORD ($p < 0.001$ for both).

Conclusion: In patients with bronchiectasis, GORD was associated with increased healthcare use and medical costs. Strategies to reduce the disease burden associated with GORD are needed in patients with bronchiectasis.

Keywords: bronchiectasis, gastrointestinal tract, gastro-oesophageal reflux disease, health economics

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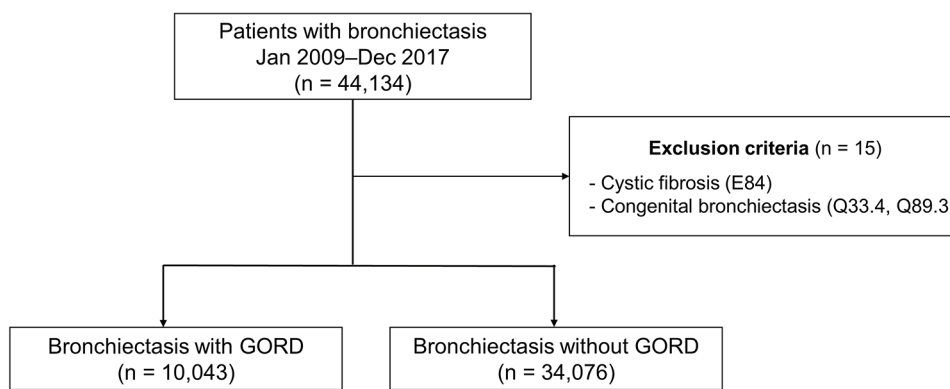
Figure 1. Flow chart of the study.
GORD, gastro-oesophageal reflux.

Introduction

The disease burden of non-cystic fibrosis bronchiectasis (hereafter referred to as bronchiectasis) is substantial, with an increasing prevalence and incidence worldwide.[1–3] Furthermore, disease burden in terms of healthcare use and mortality is significantly higher in patients with bronchiectasis than those without bronchiectasis.[4–6] Accordingly, studies evaluating factors associated with increased disease burden in bronchiectasis are urgently needed.

Bronchiectasis-related comorbidities are contributors to increased disease burdens in patients with bronchiectasis; thus, appropriate management of bronchiectasis-related comorbidities is required to help reduce these burdens.[7,8] Gastro-oesophageal reflux disease (GORD) is a common comorbidity of bronchiectasis, affecting 19–79% of patients with bronchiectasis.[9–12] GORD is associated with more symptoms, such as cough and sputum amount, reduced lung function, disease severity, and radiologic severity, as well as increased risk of exacerbation.[10,12,13]

However, few studies have evaluated the association between GORD and healthcare use and medical costs in patients with bronchiectasis.[12] South Korea provides universal health coverage for almost all Korean citizens. This method of coverage has the advantage of relatively easy assessment of healthcare use and associated medical costs.[14] We hypothesized that the disease burden, assessed by healthcare use, and medical costs would be higher in bronchiectasis patients with GORD than in those without GORD.

To evaluate our hypothesis, we used a large representative population-based claims database from Korea, the Health Insurance Review and Assessment Service-National Patient Sample (HIRA-NPS), in this study.

Methods

Study population

The HIRA-NPS is nationally representative and open to the public for research purposes.[15] The data are cross-sectional and composed of health insurance claims records in each year. The database includes approximately 1,400,000 data each year drawn by 3% stratified random sampling by age and sex from the entire population who had claims records for each year. More detailed information on HIRA-NPS was described in previous studies.[11,16] We initially included 44,134 patients with bronchiectasis from January 2009 to December 2017 using the International Classification of Diseases, 10th revision (ICD-10) diagnosis code J47. Of the 44,134 patients, we excluded 15 patients with cystic fibrosis (E84) or congenital bronchiectasis (Q33.4 and Q89.3). Consequently, 44,119 patients with bronchiectasis were included in the final analysis (Figure 1).

Exposure

The exposure of this study was the presence of GORD. GORD was defined when the following criteria were met: (1) ICD-10 code for GORD (K21) and (2) prescription of proton pump inhibitors for at least 2 weeks.[17]

Outcomes

The outcomes were healthcare uses [outpatient department (OPD) visits, emergency room (ER) visits, or hospitalizations] and medical costs. The medical cost (patient out-of-pocket costs and payer costs) consisted of expenses associated with diagnostic tests, procedures, and treatments (e.g. examination, diagnostic tests, procedures, prescriptions, infection, and operation) covered by National Health Insurance.[18] Respiratory-related healthcare uses were defined as healthcare uses under ICD codes for respiratory diseases (J00–J99).

Covariables

We used the ICD-10 codes to define comorbidities. Pulmonary comorbidities consisted of chronic obstructive pulmonary disease [COPD; J42–J44, except J43.0 (unilateral emphysema)], asthma (J45–J46), pulmonary tuberculosis (TB; A15–A19), non-tuberculous mycobacterial pulmonary disease (NTM-PD; A31.0, A31.8, and A31.9), and lung cancer (C33–C34). Extrapulmonary comorbidities consisted of cerebrovascular disease (G45–G46, I60-I69, and H34.0), hypertension (I10–I15), angina or myocardial infarction (MI; I20, I21, I22, and I25.2), congestive heart failure (I43, I50, I09.9, I11.0, I25.5, I13.0, I13.2, I42.0, I42.5–I42.9, and P29.0), inflammatory bowel disease (K50–K51), diabetes mellitus (E10–E14), chronic kidney disease (N18), and connective tissue disease (M05, M06, M315, M32, M33, M34, M351, M353, and M360). Charlson comorbidity index (CCI) was calculated using a modified version consisting of 17 comorbidities.[19]

Statistical analyses

We calculated the age-adjusted prevalence of GORD among patients with bronchiectasis by dividing the number of events by 100,000 persons/year. In addition, we compared healthcare uses and medical costs between bronchiectasis patients with GORD and those without GORD. All variables were categorized and compared using Pearson's chi-square tests. Regarding medical costs, we provided real medical costs as well as estimated medical costs adjusted for potential confounders (age, sex, type of insurance, and CCI) using analysis of covariance (ANCOVA). A multivariable logistic regression model was used to assess the association between GORD and ER visits or hospitalizations among patients with bronchiectasis, with adjustment for age, sex, type of insurance, and CCI. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). All tests were two-tailed, and p-values < 0.05 were considered statistically significant.
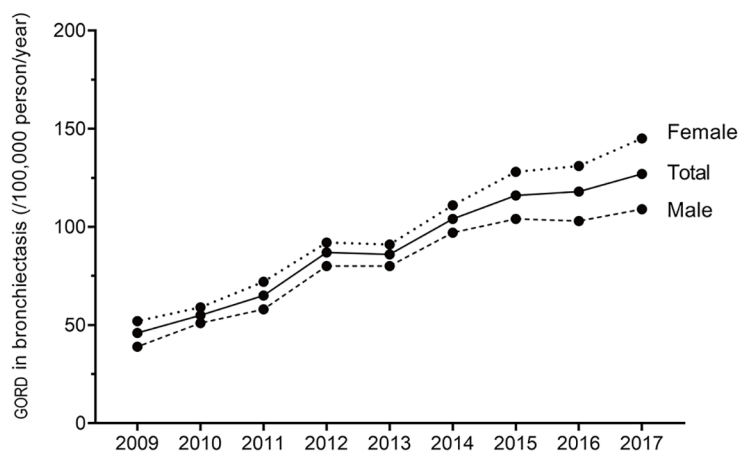
Results

Prevalence of GORD in patients with bronchiectasis

Of 44,119 patients with bronchiectasis, 29.5% had GORD. The age-adjusted prevalence of GORD in patients with bronchiectasis from 2009 to 2017 is described in Figure 2. The total prevalence of GORD in patients with bronchiectasis increased from 46/100,000 persons/year in 2009 to 127/100,000 persons/year in 2017. This prevalence of bronchiectasis in patients aged under 50 years of age was similar over the study periods. However, the prevalence of bronchiectasis showed an increasing trend in the 50s or older populations. The prevalence of bronchiectasis was substantially higher in females than in males over the study periods ($p < 0.001$ for each year).

Characteristics of the population

The baseline characteristics of the study population are summarized in Table 1. The proportions of patients over 70 years (33.9% *versus* 30.5%, $p < 0.001$), female (56.5% *versus* 54.8%, $p = 0.003$), and those under medical aid (10.3% *versus* 7.0%, $p < 0.001$) were higher in bronchiectasis patients with GORD than in those without GORD. Among pulmonary comorbidities, the proportions of COPD (44.1% *versus* 35.7%), asthma (52.2% *versus* 42.1%), and lung cancer (4.5% *versus* 3.4%) were significantly higher in bronchiectasis patients with GORD than in those without GORD ($p < 0.001$ for all). However, there was no significant intergroup difference in the proportions of pulmonary TB (7.5% *versus* 7.3%, $p = 0.433$) and NTM-PD (4.0% *versus* 3.7%, $p = 0.081$). All extrapulmonary comorbidities were more frequent in the bronchiectasis patients with GORD than in those without GORD. The proportion of patients with CCI ≥ 2 was also higher in bronchiectasis patients with GORD than in those without GORD (86.3% *versus* 68.6%, $p < 0.001$).

Figure 2. Age-adjusted prevalence of gastro-oesophageal reflux in patients with bronchiectasis. Data are expressed as numbers per 100,000 persons/year.
GORD, gastro-oesophageal reflux.

Healthcare use and medical costs according to the presence or absence of bronchiectasis

As shown in Table 2, bronchiectasis patients with GORD showed increased healthcare use compared with those without GORD. The numbers of all-cause OPD visits (47.6 ± 38.6 *versus* 30.0 ± 28.6/person/year), respiratory disease-related OPD visits (8.6 ± 10.6 *versus* 6.8 ± 8.5 person/year), all-cause ER visits or hospitalizations (1.7 ± 3.3 *versus* 1.1 ± 2.8/person/year), and respiratory disease-related ER visits or hospitalizations (0.4 ± 1.4 *versus* 0.3 ± 0.9/person/year) were all increased ($p < 0.001$ for all).

In addition, total medical costs (3564.5 ± 6372.6 *versus* 2198.7 ± 4477.4 Euro/person/year, $p < 0.001$) and respiratory disease-related medical costs (773.9 ± 2717.1 *versus* 500.3 ± 1759.7 Euro/person/year, $p < 0.001$) were significantly higher in bronchiectasis patients with GORD than in those without GORD.

Association between GORD and increased healthcare use and medical costs

As shown in Table 3, both all-cause (adjusted odds ratio = 1.44, 95% confidence interval = 1.37–1.50) and respiratory disease-related (adjusted odds ratio = 1.26, 95% confidence interval = 1.19–1.33) healthcare use were significantly higher in bronchiectasis patients with GORD than in those without GORD.

These differences persisted even after adjusting for potential confounders. The adjusted total medical costs (4337.3 ± 13,662.4 *versus* 3397.4 ± 24,001.4 Euro/person/year, $p < 0.001$) and adjusted respiratory disease-related medical costs (920.7 ± 5665.6 *versus* 720.2 ± 9953.0 Euro/person/year, $p < 0.001$) were significantly higher in bronchiectasis patients with GORD than in those without GORD (Table 4).

Discussion

In this study, using a large representative population-based database, we evaluated the prevalence of GORD and its impact on healthcare use and medical costs in patients with bronchiectasis. We found that the prevalence of GORD has increased over the 9-year study period, especially in the population aged 50 years or older. GORD in patients with bronchiectasis was substantially associated with increased OPD visits, ER visits or hospitalizations, and medical costs.

The prevalence of GORD in patients with bronchiectasis is highly variable depending on study methods but has been demonstrated to be up to 79% in patients with bronchiectasis.[12] Consistent with previous findings, our study found that a considerable number of patients with bronchiectasis (about 30% in our study) have GORD and, surprisingly, the prevalence of GORD has been increasing during the study period. To the best of our knowledge, this is the first study showing the increasing prevalence of GORD, which indicates the importance of this comorbidity in patients with bronchiectasis.

Interestingly, while the prevalence of bronchiectasis in patients aged under 50 years was stable,

Table 1. Baseline characteristics of the study population.

	Total (N = 44,119)	BE with GORD (n = 10,043)	BE without GORD (n = 34,076)	*p*-value
Age, mean				<0.001
20–29 years	728 (1.7)	66 (0.7)	662 (1.9)	
30–39 years	1715 (3.9)	178 (1.8)	1537 (4.5)	
40–49 years	4354 (9.9)	638 (6.4)	3716 (10.9)	
50–59 years	10,707 (24.3)	2402 (23.9)	8305 (24.4)	
60–69 years	12,810 (29.0)	3350 (33.4)	9460 (27.8)	
≥70 years	13,805 (31.3)	3409 (33.9)	10,396 (30.5)	
Sex				0.003
Male	19,766 (44.8)	4371 (43.5)	15,395 (45.2)	
Female	24,353 (55.2)	5672 (56.5)	18,681 (54.8)	
Type of insurance				<0.001
Self-employed health insurance	40,484 (91.8)	8936 (89.0)	31,548 (92.6)	
Medical aid	3406 (7.7)	1030 (10.3)	2376 (7.0)	
Others	229 (0.5)	77 (0.8)	152 (0.5)	
Pulmonary comorbidities				
COPD	16,600 (37.6)	4432 (44.1)	12,168 (35.7)	<0.001
Asthma	19,591 (44.4)	5239 (52.2)	14,352 (42.1)	<0.001
Pulmonary TB	3229 (7.3)	753 (7.5)	2476 (7.3)	0.433
NTM-PD	1651 (3.7)	405 (4.0)	1246 (3.7)	0.081
Lung cancer	1618 (3.7)	450 (4.5)	1168 (3.4)	<0.001
Extrapulmonary comorbidities				
Cerebrovascular disease	6137 (13.9)	1846 (18.4)	4291 (12.6)	<0.001
Hypertension	19,899 (45.1)	5373 (53.5)	14,526 (42.6)	<0.001
Angina or MI	6580 (14.9)	2159 (21.5)	4421 (13.0)	<0.001
Congestive heart failure	4002 (9.1)	1269 (12.6)	2733 (8.0)	<0.001
Inflammatory bowel disease	160 (0.4)	56 (0.6)	104 (0.3)	<0.001
Diabetes mellitus	12,899 (29.2)	3801 (37.9)	9098 (26.7)	<0.001
Chronic kidney disease	979 (2.2)	308 (3.1)	671 (2.0)	<0.001
Connective tissue disease	3060 (6.9)	1064 (10.6)	1996 (5.9)	<0.001
Charlson comorbidities index				<0.001
0 or 1	12,083 (27.4)	1372 (13.7)	10,711 (31.4)	
2 or more	32,036 (72.6)	8671 (86.3)	23,365 (68.6)	

BE, bronchiectasis; COPD, chronic obstructive pulmonary disease; GORD, gastro-oesophageal reflux; MI, myocardial infarction; NTM-PD, non-tuberculous mycobacteria pulmonary disease; TB, tuberculosis.
Data are presented as number (%) or mean (standard deviation).

Table 2. Comparison of healthcare use and medical costs.

	Total (*N* = 44,119)	BE with GORD (*n* = 10,043)	BE without GORD (*n* = 34,076)	*p*-value
Healthcare use				
Number of all-cause OPD visits (/person/year)	34.0 ± 32.0	47.6 ± 38.6	30.0 ± 28.6	<0.001
Number of respiratory disease-related OPD visits (/person/year)	7.2 ± 9.0	8.6 ± 10.6	6.8 ± 8.5	<0.001
Number of all-cause ER visits or hospitalizations (/person/year)	1.2 ± 3.0	1.7 ± 3.3	1.1 ± 2.8	<0.001
Number of respiratory disease-related ER visits or hospitalizations (/person/year)	0.3 ± 1.1	0.4 ± 1.4	0.3 ± 0.9	<0.001
Medical costs				
Total medical costs (Euro[a]/person/year)	2509.6 ± 5005.5	3564.5 ± 6372.6	2198.7 ± 4477.4	<0.001
Respiratory disease-related medical costs (Euro[a]/person/year)	562.6 ± 2021.2	773.9 ± 2717.1	500.3 ± 1759.7	<0.001

BE, bronchiectasis; ER, emergency room; GORD, gastro-oesophageal reflux; OPD, outpatient department.
Data are presented as mean ± standard deviation.
[a]One Euro = 1341.9 Won (27 April 2021).

Table 3. Odds ratios and 95% confidence intervals of GORD for healthcare use in patients with bronchiectasis.

	Model	Emergency room visits or hospitalizations	
		All-cause	**Respiratory-related**
Without GORD		Reference	Reference
With GORD	Unadjusted	1.69 (1.62–1.77)	1.41 (1.34–1.49)
	Adjusted	1.44 (1.37–1.50)	1.26 (1.19–1.33)

GORD, gastro-oesophageal reflux.
Adjusted values were adjusted for age, sex, type of insurance, and Charlson comorbidity index.

Table 4. Comparison of estimated medical costs after adjusting for potential confounders.

	Total (*N* = 44,119)	BE with GORD (*n* = 10,043)	BE without GORD (*n* = 34,076)	*p*-value
Estimated total medical costs (Euro[a]/person/year)[b]	3613.1 ± 27,264.8	4337.3 ± 13,662.4	3397.4 ± 24,001.4	<0.001
Estimated respiratory disease-related medical costs (Euro[a]/person/year)[b]	766.2 ± 9913.1	920.7 ± 5665.6	720.2 ± 9953.0	<0.001

BE, bronchiectasis; GORD, gastro-oesophageal reflux.
Data are presented as mean ± standard deviation.
[a]One Euro = 1341.9 Won (27 April 2021).
[b]Adjusted for age, sex, type of insurance, and Charlson comorbidity index.

there was a strikingly increased prevalence among the 50s and older population. The reasons are not clear as our study did not aim to evaluate this association. However, we suggest a few possible explanations for this finding. Previous studies showed that aging is a risk factor of GORD, and risk factors for GORD increase with age (e.g. delayed gastric emptying).[20–22] In addition, aging is associated with increased symptoms of bronchiectasis such as coughing and sputum production. As coughing and sputum production naturally increase abdominal pressure, reflux symptoms may occur in patients with bronchiectasis. Although our study could not provide a detailed explanation or mechanism, our study results do suggest that the burden of GORD is increased in older age groups.

The most important finding of our study is that GORD is associated with increased healthcare use and medical costs in patients with bronchiectasis. All-cause and respiratory disease-related OPD visits and ER visits or hospitalizations were significantly higher in bronchiectasis patients with GORD, which might lead to an increase in medical expense. To some extent, the increased healthcare burden in this population can be attributable to the clinical characteristics of bronchiectasis patients with GORD, including older age, lower socioeconomic status, and higher number of comorbidities, compared to those without GORD. However, importantly, after adjusting these factors, the disease burden was still substantially higher in bronchiectasis patients with GORD compared with those without GORD, indicating that GORD is an important contributor to this phenomenon.

The reasons for the increased healthcare burden in bronchiectasis patients with GORD can be explained by the interactive bidirectional relationship between GORD and bronchiectasis, which leads to worsening conditions of both diseases. Patients with bronchiectasis often have hyperinflated lungs with the descent diaphragm that predisposes the patient to reflux by lowering the resting pressure of the lower oesophageal sphincter.[23] In addition, chronic respiratory symptoms, such as cough and sputum production, can lead to a recurrent sudden increase in intra-abdominal pressure, predisposing reflux.[23] Also, refluxate, whether acidic, nonacidic, or gaseous mistic,[24] can be proinflammatory and cause lung damage, aggravating the bronchiectasis.[23] This will cause a vicious cycle of worsened GORD and bronchiectasis. Our study results are meaningful in terms of providing evidence supporting the theoretical link between bronchiectasis and GORD in increasing healthcare costs.

Despite the close association between GORD and bronchiectasis, whether appropriate management of GORD may help improve treatment outcomes in patients with bronchiectasis remains unclear. A case series showed that anti-reflux surgery substantially improved bronchiectasis.[25] Regarding medical treatment, there have been no randomized controlled trials that demonstrate the effectiveness of proton pump inhibitor use in improving the treatment outcomes in bronchiectasis patients with GORD. While airway clearance technique in sitting position is recommended in bronchiectasis patients with GORD to minimize reflux,[26] the usefulness of this technique has not been demonstrated. Although the clinical efficacy of current treatment of GORD has not been demonstrated, clinicians should assess comorbid GORD in patients with bronchiectasis who are hampered by frequent exacerbations.[13] We also suggest that collaborative work between pulmonologists and gastroenterologists may be beneficial for the control of both diseases. Also, clinical studies are urgently needed to test whether controlling GORD can improve the treatment outcomes of bronchiectasis and vice versa.

The strength of this study is that our findings were obtained from a large national dataset, which represents the entire population. We used the largest number of bronchiectasis patients with GORD in our evaluation. However, there are some potential limitations. First, we used the ICD-10 code with medication to define both GORD and bronchiectasis since the HIRA-NPS database does not provide objective test results for diagnosing GORD (e.g. ambulatory pH monitoring) and bronchiectasis (e.g. computed tomography scan of the chest). Thus, both diseases might be over- or under-diagnosed. Second, GORD is generally considered to be more common in patients with severe bronchiectasis,[27] which could be a confounding factor for increased medical care costs or medical utilization in this study. However, as pulmonary function tests and computed tomography findings are not available in the HIRA-NPS database, we could not adjust for the severity of bronchiectasis. Future studies considering the severity of bronchiectasis are

needed to address this issue. Third, our study was conducted in the Korean population; to generalize our study findings, studies from other countries are needed. Finally, a causal relationship between GORD and bronchiectasis has not been established due to the cross-sectional nature of the study. However, we achieved our study aim, and future studies using longitudinal databases are needed to confirm and expand upon our results.

Conclusion

In patients with bronchiectasis, the presence of GORD increases healthcare use and medical costs. Early recognition and appropriate management of this comorbidity should be helpful in reducing bronchiectasis disease burden.

Author contributions

HC and HL are guarantors of the manuscript. JHY, SHK, JR, HC, and HL designed the study; JR and CKY performed data analysis. JHY, SHK, HC, and HL wrote the initial draft of the manuscript, and all authors were involved at all stages of critical revision of the manuscript. All of the authors read and approved the final manuscript. All authors meet the criteria for authorship as recommended by the International Committee of Medical Journal Editors.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

The Institutional Review Board of the Hanyang University Hospital approved the study and waived the requirement for informed consent because the HIRA-NPS data were de-identified (application no. HYUH 2021-04-018).

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Patient consent for publication

Not required.

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Data availability statement

Data of our study are available upon reasonable request.

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