THERAPEUTIC ADVANCES in
Respiratory Disease

Original Research

Cardiovascular and cerebrovascular–associated mortality in patients with preceding bronchiectasis exacerbation

Ther Adv Respir Dis

2022, Vol. 16: 1–15

DOI: 10.1177/17534666221144206

Sang Chul Lee*, **Kang Ju Son***, **Chang Hoon Han**, **Seon Cheol Park**† and **Ji Ye Jung**†

Abstract

Background: Bronchiectasis is associated with an increased incidence of atherosclerotic cardiovascular disease (ASCaVD) and atherosclerotic cerebrovascular disease (ASCeVD). Its effect on associated mortality is unclear.

Objectives: This study investigated the effects of bronchiectasis exacerbation prior to ASCaVD or ASCeVD events on mortality in patients with bronchiectasis using a large population–based database.

Methods: A retrospective cohort of patients with bronchiectasis who experienced ASCaVD ($n = 1066$) or ASCeVD ($n = 825$) was studied for the first time using a nationwide population–based database (National Health Insurance Service-National Sample Cohort, Korea, 2002–2015). We classified each cohort according to the presence of moderate bronchiectasis exacerbation within 1 year before the ASCaVD or ASCeVD event. We evaluated 90-day, 1-year, and all-cause mortalities risk.

Results: Within 1 year before the index ASCaVD or ASCeVD event, 149 (13.9%) and 112 (13.6%) patients with bronchiectasis experienced moderate exacerbation(s), respectively. Mild exacerbations did not different in frequency between the survivors and nonsurvivors. In both cohorts, more nonsurvivors experienced moderate exacerbations than survivors. The odds ratios of 90-day and 1-year mortalities and hazard ratios of all-cause mortalities on experiencing moderate exacerbations were 2.27 [95% confidence interval (CI) = 1.26–4.10], 3.30 (95% CI = 2.03–5.38), and 1.78 (95% CI = 1.35–2.34) in the bronchiectasis-ASCaVD cohort and 1.73 (95% CI = 0.94–3.19), 1.79 (95% CI = 1.07–3.00), and 1.47 (95% CI = 1.10–1.95), in the bronchiectasis-ASCeVD cohort.

Conclusion: Hospitalization or emergency room visit for bronchiectasis exacerbation within 1 year before ASCaVD or ASCeVD is associated with an increased ASCaVD- or ASCeVD-associated mortality.

Keywords: atherosclerotic cardiovascular disease, atherosclerotic cerebrovascular disease, bronchiectasis, exacerbation, mortality

Received: 5 September 2022; revised manuscript accepted: 23 November 2022.

Correspondence to:
Seon Cheol Park
Division of Pulmonology, Department of Internal Medicine, National Health Insurance Service Ilsan Hospital, 100 Ilsan-ro, Ilsandong-gu, Goyang 10444, Gyeonggi-do, Republic of Korea.
parksc@nhimc.or.kr

Ji Ye Jung
Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea.
stopyes@yuhs.ac

Sang Chul Lee
Chang Hoon Han
Division of Pulmonology, Department of Internal Medicine, National Health Insurance Service Ilsan Hospital, Goyang, Republic of Korea

Kang Ju Son
Department of Research and Analysis, National Health Insurance Service Ilsan Hospital, Goyang, Republic of Korea

*Sang Chul Lee and Kang Ju Son contributed equally as first authors.

†Ji Ye Jung and Seon Cheol Park jointly supervised this work as corresponding authors.

Kang Ju Son is also affiliated to Department of Biostatistics and Computing, Yonsei University Graduate School, Seoul, Republic of Korea

Introduction

Bronchiectasis is a respiratory disease with increased incidence, resulting in a significant burden on public health including increased healthcare costs, hospital admission, and mortality.[1–3] Moreover, various comorbidities are common in bronchiectasis and significantly contribute to disease burden and mortality.[4]

Previous studies have established the relationship between bronchiectasis and increased risk of atherosclerotic cardiovascular and cerebrovascular disease (ASCCVD).[5,6] Hypoxia and systemic inflammation are common risk factors for both bronchiectasis and ASCCVD.[7] Moreover, it has been suggested that repeated lower respiratory tract infections result in an acute phase response

and increased systemic inflammation, contributing to the increased risk of ASCCVD.[6] Increased prevalence of bronchiectasis as age increases may also elevate the risk of ASCCVD.[8]

Exacerbations in bronchiectasis are important events in the natural history of bronchiectasis.[9] It is one of the assessment factors for the bronchiectasis severity index (BSI) and also an important predictor of prognosis.[10] Exacerbations leading to hospitalization or admission to the intensive care unit (ICU) have been associated with high mortality of 30–40%.[11,12]

It is, however, unclear whether exacerbations affect the prognosis of atherosclerotic cardiovascular disease (ASCaVD) or atherosclerotic cerebrovascular disease (ASCeVD) for a patient with bronchiectasis. Previous studies have shown the risk factors of ASCCVD morbidity and all-cause mortality associated with bronchiectasis exacerbation, while the effects of exacerbation on the mortality of ASCCVD have not been completely evaluated.

The aim of this study was to investigate the effects of bronchiectasis exacerbation prior to hospitalization owing to ASCaVD or ASCeVD on mortality in patients with bronchiectasis using a large population–based database. The study results establish the importance of preventing exacerbation in patients with bronchiectasis to reduce the following ASCCVD-related mortalities.

Methods

Study design and participants

This retrospective cohort study was conducted using nationwide data from National Health Insurance Service–National Sample Cohort (NHIS-NSC).[13] This study consisted of two separate cohorts of patients, namely, those with bronchiectasis experiencing first-time ASCaVD ($n = 1066$) and those with bronchiectasis experiencing first-time ASCeVD ($n = 825$) between 1 January 2004 and 31 December 2014 (Figure 1).

NHIS-NSC is a population-based sample cohort that provides representative, useful health insurance, and health examination data to public health researchers and policymakers. Data from 1,025,340 participants (2.2% of the total eligible population) were randomly sampled from the 2002 Korean nationwide health insurance database to obtain baseline data for NHIS-NSC. Cohort participants were followed until 2015. The cohort data comprise insurance eligibility, medical treatments, medical care institutions, and general health examinations. The medical treatment database consists of information about the 10th revision of the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) codes and medical and pharmacy bills of participants claimed by medical service providers in Korea.

In each cohort, patients were categorized into exacerbators and non-exacerbators according to the presence of moderate bronchiectasis exacerbation(s) within 1 year prior to the index ASCaVD and ASCeVD event.

Definitions

Bronchiectasis (J47), ASCaVD, and ASCeVD were defined using the ICD-10 codes. ASCaVD includes acute myocardial infarction (I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22.0, I22.1, I22.8, I22.9, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.8, I24.1, I25.2), angina (I20.0, I20.1, I20.8, I20.9), and coronary revascularization (see Online Supplement Table S1). ASCeVD includes ischemic stroke (I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9) and transient ischemic attack (G45.0, G45.1, G45.2, G45.3, G45.8, G45.9, G46.0, G46.1, G46.2).[14]

Bronchiectasis exacerbations were categorized into mild and moderate exacerbations. Mild and moderate bronchiectasis exacerbations were defined as outpatient clinic visits and emergency room visits/hospitalizations, respectively, under the following conditions: (1) diagnostic code for bronchiectasis (J47) and antibiotic administration and (2) diagnostic codes J12.x–J17.x (pneumonia), J20.x (acute bronchitis), J21.x (acute bronchiolitis), R06.0 (dyspnoea), J80 (acute respiratory distress syndrome), R09.3 (abnormal sputum), or R04.2 (blood-tinged sputum) and antibiotic administration.[8]

The data concerning baseline characteristics and comorbidities were collected 1 year prior to the admission date of each index event in ASCaVD and ASCeVD cohorts.

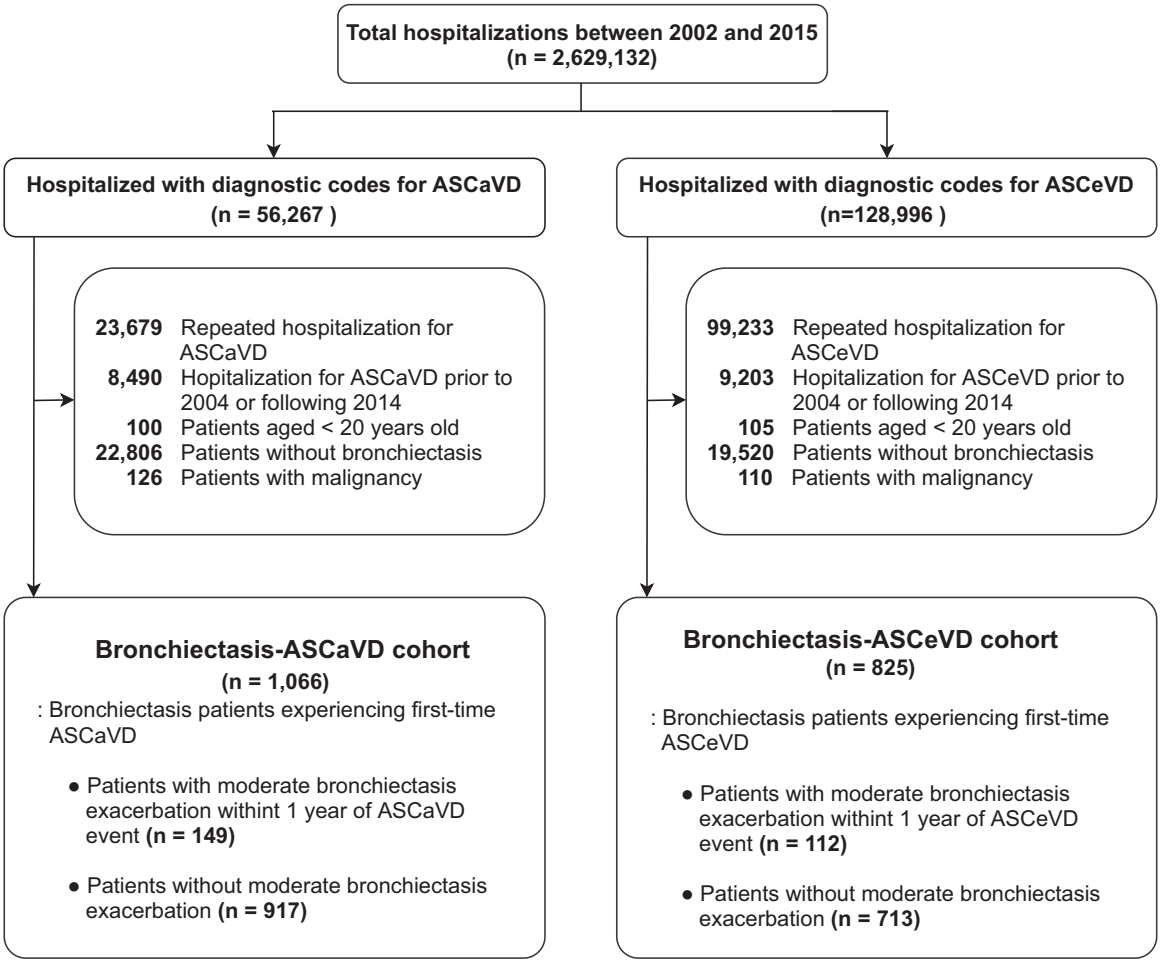

Figure 1. Flowchart of the study population.
ASCaVD, atherosclerotic cardiovascular disease; ASCeVD, atherosclerotic cerebrovascular disease.

Primary outcomes

Primary outcomes were all-cause mortalities including 90-day, 1-year, and all-cause mortalities. From the admission date of index events, all the patients were followed up until death or 31 December 2015, whichever came first.

Statistical analyses

We compared exacerbators and non-exacerbators and survivors and nonsurvivors using the chi-square test for categorical variables and Student's *t*-test for continuous variables. Multivariate logistic regression analysis was conducted to estimate the risk of all-cause 90-day and 1-year mortality associated with moderate bronchiectasis exacerbation. Risk factors are reported as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Multivariate Cox regression analysis was performed to evaluate the risk of all-cause mortality associated with moderate bronchiectasis exacerbation. Risk factors are reported as adjusted hazard ratios (HRs) with 95% CIs. Kaplan–Meier analysis with the log-rank test was used to compare survival between exacerbators and non-exacerbators for 90-days, 1-year, and overall survival outcomes. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed with SAS, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics of participants

The baseline characteristics of bronchiectasis-ASCaVD ($n=1066$) and bronchiectasis-ASCeVD ($n=825$) patients are summarized in Tables 1 and 2, respectively. In each cohort, 149 (13.9%)

Table 1. Baseline characteristics of the atherosclerotic cardiovascular disease cohort.

Characteristics	Total (*n* = 1066)	Non-exacerbators (*n* = 917)	Exacerbators (*n* = 149)	*p*-value
Age, years				
20–49	63 (5.9)	54 (5.9)	9 (6.0)	0.013
50–59	171 (16.0)	154 (16.8)	17 (11.4)	
60–69	306 (28.7)	274 (29.9)	32 (21.5)	
70–79	357 (33.5)	301 (32.8)	56 (37.6)	
80+	169 (15.9)	134 (14.6)	35 (23.5)	
Sex				
Male	535 (50.2)	459 (50.1)	76 (51.0)	0.829
Female	531 (49.8)	458 (49.9)	73 (49.0)	
BMI[a], kg/m^2	24.1 ± 3.4	24.2 ± 3.4	22.7 ± 3.4	<0.001
Underweight	34 (4.7)	26 (4.1)	8 (10.0)	0.001
Normal	214 (29.8)	183 (28.7)	31 (38.7)	
Overweight	199 (27.8)	174 (27.3)	25 (31.3)	
Obese	270 (37.7)	254 (39.9)	16 (20.0)	
Comorbidities				
Heart disease	461 (43.3)	363 (39.6)	98 (65.8)	<0.001
Myocardial infarction	300 (28.1)	223 (24.3)	77 (51.7)	<0.001
Heart failure	234 (22.0)	199 (21.7)	35 (23.5)	0.625
CAOD	802 (75.2)	718 (78.3)	84 (56.4)	<0.001
PAOD	107 (10.0)	94 (10.3)	13 (8.7)	0.565
Cerebral infarction	138 (13.0)	119 (12.9)	19 (12.8)	0.939
Hypertension	867 (81.3)	755 (82.3)	112 (75.2)	0.037
Diabetes mellitus	528 (49.5)	445 (48.5)	83 (55.7)	0.104
Dyslipidemia	744 (69.8)	660 (72.0)	84 (56.4)	0.000
Chronic kidney disease	44 (4.1)	38 (4.1)	6 (4.03)	0.947
Dementia	7 (0.7)	7 (0.76)	0 (0)	0.285
Parkinson's disease	20 (1.9)	15 (1.6)	5 (3.4)	0.151
Atrial fibrillation	118 (11.1)	104 (11.3)	14 (9.4)	0.483
Asthma	261 (24.5)	208 (22.7)	53 (35.6)	0.001
COPD	175 (16.4)	129 (14.1)	46 (30.9)	<0.001

(Continued)

Table 1. (Continued)

Characteristics	Total (*n* = 1066)	Non-exacerbators (*n* = 917)	Exacerbators (*n* = 149)	*p*-value
CCI				<0.001
0–1	128 (12.0)	126 (13.7)	2 (1.3)	
2	190 (17.8)	179 (19.5)	11 (7.4)	
3	193 (18.1)	162 (17.7)	31 (20.8)	
4+	555 (52.1)	450 (49.1)	105 (70.5)	
Registration year				0.044
2004	33 (3.1)	24 (2.6)	9 (6.0)	
2005	57 (5.3)	48 (5.2)	9 (6.0)	
2006	70 (6.6)	54 (5.9)	16 (10.8)	
2007	102 (9.6)	85 (9.3)	17 (11.4)	
2008	98 (9.2)	89 (9.7)	9 (6.0)	
2009	92 (8.6)	74 (8.1)	18 (12.1)	
2010	92 (8.6)	80 (8.7)	12 (8.1)	
2011	115 (10.8)	104 (11.3)	11 (7.4)	
2012	133 (12.5)	120 (13.1)	13 (8.7)	
2013	129 (12.1)	112 (12.2)	17 (11.4)	
2014	145 (13.6)	127 (13.9)	18 (12.1)	
Total follow-up duration, years	4.1 ± 3.0	4.1 ± 2.9	3.8 ± 3.3	0.201
All-cause mortality				
90-days	70 (6.6)	49 (5.3)	21 (14.1)	<0.001
1-year	124 (11.6)	84 (9.2)	40 (26.9)	<0.001
All-cause	291 (27.3)	215 (23.5)	76 (51.0)	<0.001
Bronchiectasis acute exacerbation				
Total				<0.001
0	617 (57.9)	617 (67.3)	0 (0)	
1	300 (28.1)	207 (22.6)	93 (62.4)	
2	84 (7.9)	57 (6.2)	27 (18.1)	
⩾3	65 (6.1)	36 (3.9)	29 (19.5)	
Mild[b]				0.010
0	717 (67.3)	617 (67.3)	100 (67.1)	

(Continued)

Table 1. (Continued)

Characteristics	Total (*n* = 1066)	Non-exacerbators (*n* = 917)	Exacerbators (*n* = 149)	*p*-value
1	230 (21.6)	207 (22.6)	23 (15.4)	
⩾2	119 (11.1)	93 (10.1)	26 (17.5)	
Moderate[b]				<0.001
0	0 (0)	0 (0)	0 (0)	
1	133 (89.3)	0 (0)	133 (89.3)	
⩾2	16 (10.7)	0 (0)	16 (10.7)	

BMI, body mass index; CAOD, coronary artery occlusive disease; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; PAOD, peripheral arterial occlusive disease.
[a]Data on BMI were available only for 717 patients [non-exacerbators (*n* = 637) and exacerbators (*n* = 80)].
[b]Mild and moderate bronchiectasis exacerbations were defined as outpatient clinic visits and emergency room visits/hospitalizations, respectively, under the following conditions: (1) diagnostic code for bronchiectasis and antibiotic administration and (2) diagnostic codes J12.x–J17.x (pneumonia), J20.x (acute bronchitis), J21.x (acute bronchiolitis), R06.0 (dyspnoea), J80 (acute respiratory distress syndrome), R09.3 (abnormal sputum), or R04.2 (blood-tinged sputum) and antibiotic administration.

and 112 (13.6%) patients with bronchiectasis experienced moderate exacerbation(s) within 1 year prior to the index ASCaVD and ASCeVD event, respectively. The mean follow-up duration was 4.1 years and 3.4 years in ASCaVD and ASCeVD cohorts, respectively. More proportion of older individuals was observed in exacerbators than in non-exacerbators in the ASCaVD cohort. In both cohorts, the proportions of males and females were not different between exacerbators and non-exacerbators, but exacerbators showed lower body mass index (BMI), more chronic airway diseases such as asthma and chronic obstructive pulmonary disease (COPD), and more comorbidities according to the Charlson comorbidity index (CCI).

All-cause 90-day mortality (14.1% *versus* 5.3%, $p < 0.001$), 1-year mortality (26.9% *versus* 9.2%, $p < 0.001$), and all-cause mortality (51.0% *versus* 23.5%, $p < 0.001$) were higher in exacerbators than in non-exacerbators in the ASCaVD cohort. In the ASCeVD cohort, all-cause 1-year mortality (25.0% *versus* 16.0%, $p = 0.019$) and all-cause mortality (53.6% *versus* 35.3%, $p < 0.001$) were higher in exacerbators than in non-exacerbators, while 90-day mortality was higher in exacerbators than in non-exacerbators without statistical significance (15.2% *versus* 9.4%; $p = 0.060$).

Comparison between survivors and nonsurvivors

A comparison of baseline characteristics between survivors and nonsurvivors is presented in Online Supplement Tables S2 and S3. In both cohorts, nonsurvivors showed a higher proportion of older individuals, more comorbidities, and lower BMI than survivors. More nonsurvivors experienced total exacerbations than survivors in both cohorts (50.2% *versus* 39.1%, $p = 0.007$ in the ASCaVD cohort; 44.2% *versus* 33.1%, $p = 0.015$ in the ASCeVD cohort). In subgroup analysis, according to the different degrees of bronchiectasis, the frequency of mild exacerbations was not different between the groups. More nonsurvivors, however, experienced moderate exacerbations than survivors in both cohorts (26.1% *versus* 9.4%, $p < 0.001$ in the ASCaVD cohort; 19.2% *versus* 10.2%, $p < 0.001$ in the ASCeVD cohort).

Moderate exacerbation and risk of all-cause mortality

The risk of all-cause mortality was evaluated for 90-day mortality, 1-year mortality, and all-cause mortality after a cardiovascular and cerebrovascular event in the ASCaVD and ASCeVD cohorts, respectively (Tables 3 and 4). In the ASCaVD cohort, moderate bronchiectasis exacerbation

Table 2. Baseline characteristics of atherosclerotic cerebrovascular disease cohort.

Characteristics	Total (*n* = 825)	Non-exacerbators (*n* = 713)	Exacerbators (*n* = 112)	*p*-value
Age, years				
20–49	31 (3.8)	24 (3.4)	7 (6.2)	0.387
50–59	74 (8.9)	68 (9.5)	6 (5.4)	
60–69	184 (22.3)	158 (22.1)	26 (23.2)	
70–79	323 (39.2)	280 (39.3)	43 (38.4)	
80+	213 (25.8)	183 (25.7)	30 (26.8)	
Sex, male				
Male	394 (47.8)	345 (48.4)	49 (43.8)	0.361
Female	431 (52.2)	368 (51.6)	63 (56.2)	
BMI[a], kg/m^2	23.7 ± 3.6	23.8 ± 3.6	22.7 ± 3.5	0.031
Underweight	37 (6.9)	29 (6.2)	8 (13.8)	0.057
Normal	181 (34.2)	159 (33.7)	22 (37.9)	
Overweight	128 (24.2)	113 (23.9)	15 (25.9)	
Obese	184 (42.7)	171 (36.2)	13 (22.4)	
Comorbidities				
Heart disease	151 (18.3)	129 (18.1)	22 (19.6)	0.693
Myocardial infarction	37 (4.5)	32 (4.5)	5 (4.5)	0.991
Heart failure	125 (15.2)	106 (14.9)	19 (17.0)	0.565
CAOD	247 (29.9)	208 (29.2)	39 (34.8)	0.225
PAOD	79 (9.6)	72 (10.1)	7 (6.2)	0.198
Cerebral infarction	646 (78.3)	560 (78.5)	86 (76.8)	0.675
Hypertension	607 (73.6)	518 (72.7)	89 (79.5)	0.128
Diabetes mellitus	407 (49.3)	358 (50.2)	49 (43.8)	0.204
Dyslipidemia	487 (59.0)	435 (61.0)	52 (46.4)	0.004
Chronic kidney disease	46 (5.6)	38 (5.3)	8 (7.1)	0.437
Dementia	13 (1.6)	13 (1.8)	0 (0)	0.150
Parkinson's disease	32 (3.9)	30 (4.2)	2 (1.8)	0.217
Atrial fibrillation	85 (10.3)	74 (10.7)	11 (9.8)	0.857
Asthma	166 (20.1)	136 (19.1)	30 (26.8)	0.058
COPD	123 (14.9)	99 (13.9)	24 (21.4)	0.037

(Continued)

Table 2. (Continued)

Characteristics	Total (*n* = 825)	Non-exacerbators (*n* = 713)	Exacerbators (*n* = 112)	*p*-value
CCI				
0–1	44 (5.3)	44 (6.2)	0 (0)	0.004
2	98 (11.9)	91 (12.8)	7 (6.2)	
3	176 (21.3)	145 (20.3)	31 (27.7)	
4+	507 (61.5)	433 (60.7)	74 (66.1)	
Registration year				
2004	21 (2.5)	17 (2.4)	4 (3.6)	0.013
2005	29 (3.5)	23 (3.2)	6 (5.4)	
2006	50 (6.1)	40 (5.6)	10 (8.9)	
2007	60 (7.3)	50 (7.0)	10 (8.9)	
2008	61 (7.4)	53 (7.5)	8 (7.1)	
2009	78 (9.5)	62 (8.7)	16 (14.4)	
2010	84 (10.2)	80 (11.2)	4 (3.6)	
2011	114 (13.8)	92 (12.9)	22 (19.6)	
2012	110 (13.3)	95 (13.3)	15 (13.4)	
2013	114 (13.8)	104 (14.6)	10 (8.9)	
2014	104 (12.6)	97 (13.6)	7 (6.2)	
Total follow-up duration, years	3.4 ± 2.8	3.4 ± 2.8	3.3 ± 2.9	0.512
All-cause mortality				
90-days	84 (10.2)	67 (9.4)	17 (15.2)	0.060
1-year	142 (17.2)	114 (16.0)	28 (25.0)	0.019
All-cause	312 (37.8)	252 (35.3)	60 (53.6)	<0.001
Bronchiectasis acute exacerbation				
Total				
0	517 (62.7)	517 (72.5)	0 (0)	<0.001
1	194 (23.5)	128 (18.0)	66 (58.9)	
2	66 (8.0)	40 (5.6)	26 (23.2)	
⩾3	48 (5.8)	28 (3.9)	20 (17.9)	
Mild[b]				
0	592 (71.8)	517 (72.5)	75 (67.0)	0.368

(Continued)

Table 2. (Continued)

Characteristics	Total	Non-exacerbators	Exacerbators	*p*-value
	(*n* = 825)	(*n* = 713)	(*n* = 112)	
1	150 (18.2)	128 (18.0)	22 (19.6)	
⩾2	83 (10.0)	68 (9.5)	15 (13.4)	
Moderate[b]				
0	0 (0)	0 (0)	0 (0)	<0.001
1	94 (83.9)	0 (0)	94 (83.9)	
⩾2	18 (6.1)	0 (0)	18 (6.1)	

BMI, body mass index; CAOD, coronary artery occlusive disease; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; PAOD, peripheral arterial occlusive disease.
[a]Data on BMI were available only for 530 patients [non-exacerbators (*n* = 472) and exacerbators (*n* = 58)].
[b]Mild and moderate bronchiectasis exacerbations were defined as outpatient clinic visits and emergency room visits/hospitalizations, respectively, under the following conditions: (1) diagnostic code for bronchiectasis and antibiotic administration and (2) diagnostic codes J12.x–J17.x (pneumonia), J20.x (acute bronchitis), J21.x (acute bronchiolitis), R06.0 (dyspnoea), J80 (acute respiratory distress syndrome), R09.3 (abnormal sputum), or R04.2 (blood-tinged sputum) and antibiotic administration.

Table 3. Odds ratios of 90-day and 1-year mortalities and hazard ratios of all-cause mortality after the cardiovascular event with recent moderate bronchiectasis exacerbation within 1 year prior to ASCaVD in ASCaVD cohort.

Risk factors	90-days			1-year			All-cause		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	HR	95% CI	*p*-value
Sex, male (*versus* female)	1.34	0.78–2.29	0.287	1.33	0.86–2.05	0.206	1.47	1.15–1.87	0.002
Age, years	1.10	1.06–1.13	<0.001	1.11	1.08–1.14	<0.001	1.10	1.08–1.11	<0.001
CCI	1.24	1.06–1.44	0.007	1.19	1.04–1.35	0.009	1.20	1.11–1.28	<0.001
Registration year	1.04	0.95–1.14	0.447	1.11	1.03–1.20	0.007	1.03	0.98–1.08	0.209
Cerebral infarction	1.71	0.90–3.24	0.100	1.56	0.91–2.68	0.110	1.03	0.75–1.39	0.878
Hypertension	1.16	0.51–2.62	0.730	1.56	0.80–3.05	0.192	1.13	0.79–1.63	0.505
Diabetes mellitus	0.64	0.35–1.18	0.155	0.63	0.38–1.05	0.075	0.77	0.58–1.02	0.063
Chronic kidney disease	1.59	0.57–4.43	0.376	2.02	0.87–4.74	0.104	2.01	1.26–3.19	0.003
Asthma	1.14	0.61–2.14	0.678	0.84	0.50–1.42	0.518	1.03	0.78–1.37	0.820
COPD	1.31	0.65–2.64	0.451	1.73	0.98–3.05	0.059	1.34	0.99–1.81	0.054
Bronchiectasis exacerbation, moderate[a]	2.27	1.26–4.10	0.007	3.30	2.03–5.38	<0.001	1.78	1.35–2.34	<0.001

ASCaVD, atherosclerotic cardiovascular disease; CCI, Charlson comorbidity index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; OR, odds ratio.
[a]Moderate bronchiectasis exacerbations were defined as emergency room visits/hospitalizations under the following conditions: (1) diagnostic code for bronchiectasis and antibiotic administration and (2) diagnostic codes J12.x–J17.x (pneumonia), J20.x (acute bronchitis), J21.x (acute bronchiolitis), R06.0 (dyspnoea), J80 (acute respiratory distress syndrome), R09.3 (abnormal sputum), or R04.2 (blood-tinged sputum) and antibiotic administration.

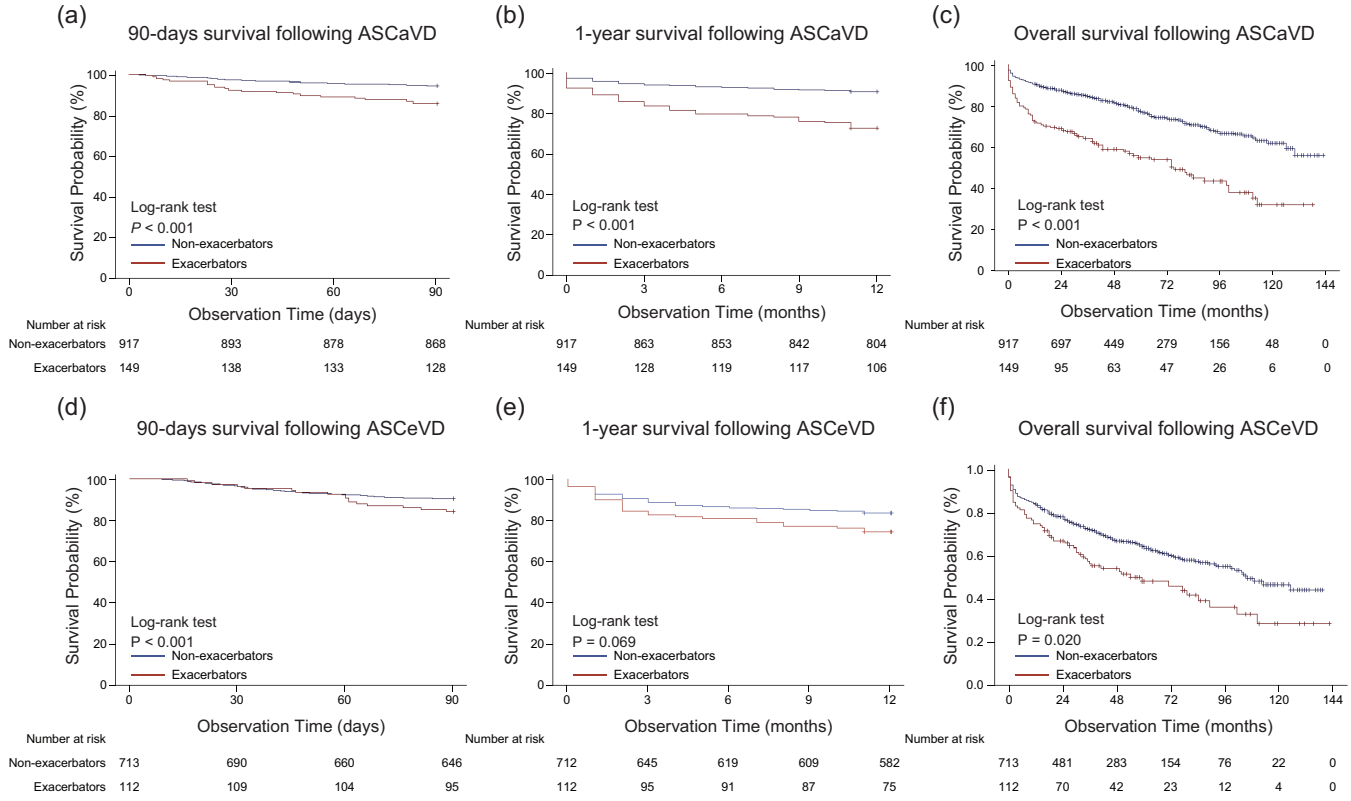

Figure 2. Kaplan–Meier survival curves for the bronchiectasis-ASCaVD cohort and bronchiectasis-ASCeVD cohort, depending on exacerbation experience. Kaplan–Meier survival curves for 90-day, 1-year, and all-cause survival following ASCaVD or ASCeVD events were compared between exacerbators and non-exacerbators. Exacerbators showed decreased survival compared with that in non-exacerbators in all periods in the bronchiectasis-ASCaVD cohort: (a) 90-days survival following ASCaVD ($p < 0.001$), (b) 1-year survival following ASCaVD ($p < 0.001$), and (c) all-cause survival following ASCaVD ($p < 0.001$). Exacerbators showed decreased survival compared with that in non-exacerbators in all periods except 1-year survival in the bronchiectasis-ASCeVD cohort: (d) 90-days survival following ASCeVD ($p < 0.001$), (e) 1-year survival following ASCeVD ($p = 0.069$), and (f) all-cause survival following ASCeVD ($p = 0.020$).
ASCaVD, atherosclerotic cardiovascular disease; ASCeVD, atherosclerotic cerebrovascular disease.

independently increased the risk of 90-day mortality (OR = 2.27, 95% CI = 1.26–4.10, $p = 0.007$), 1-year mortality (OR = 3.30, 95% CI = 2.03–5.38, $p < 0.001$), and all-cause mortality (HR = 1.78, 95% CI = 1.35–2.34, $p < 0.001$) (Table 3). Age and CCI were also significant risk factors for 90-day, 1-year, and all-cause mortalities. COPD tended to increase the risk of 1-year mortality and all-cause mortality, without statistical significance. In the ASCeVD cohort, moderate bronchiectasis exacerbation significantly increased the risk of 1-year mortality (OR = 1.79, 95% CI = 1.07–3.00, $p = 0.027$) and all-cause mortality (HR = 1.47, 95% CI = 1.10–1.95, $p = 0.009$) (Table 4). Age was also a significant risk factor for all types of mortalities.

Figure 2 shows the Kaplan–Meier curves of 90-day, 1-year, and all-cause survival following ASCaVD or ASCeVD events based on moderate bronchiectasis exacerbation within 1 year prior to the events. Exacerbators showed decreased survival compared with that of non-exacerbators in all the analyses except for 90-day survival in the ASCeVD cohort.

Risk of all-cause mortality after BMI adjustment

Online Supplement Tables S4 and S5 show the risk of all-cause mortality including BMI as a co-variate in subgroups of the ASCaVD ($n = 717$) and ASCeVD ($n = 530$) cohorts. In the ASCaVD cohort, moderate bronchiectasis exacerbation significantly increased the risk of 1-year mortality (OR = 3.85, 95% CI = 1.94–7.63, $p < 0.001$) and all-cause mortality (HR = 2.30, 95% CI = 1.55–3.43, $p < 0.001$) (see Online Supplement Table S4). In the ASCeVD

Table 4. Odds ratios of 90-day and 1-year mortalities and hazard ratios of all-cause mortality after cerebrovascular event with recent moderate bronchiectasis exacerbation within 1 year prior to ASCeVD in ASCeVD cohort.

Risk factors	90-days			1-year			All-cause		
	OR	95% CI	*p* value	OR	95% CI	*p*-value	HR	95% CI	*p*-value
Sex, male (*versus* female)	1.02	0.62–1.68	0.929	1.18	0.79–1.77	0.427	1.26	1.00–1.59	0.049
Age, years	1.08	1.05–1.12	<0.001	1.08	1.05–1.11	<0.001	1.08	1.06–1.09	<0.001
CCI	0.99	0.84–1.16	0.858	1.09	0.96–1.24	0.185	1.04	0.96–1.12	0.366
Registration year	1.04	0.94–1.14	0.461	1.04	0.96–1.12	0.320	0.99	0.94–1.03	0.597
CAOD	1.16	0.69–1.97	0.577	1.01	0.66–1.56	0.951	1.25	0.97–1.61	0.083
Hypertension	1.30	0.67–2.52	0.447	1.97	1.11–3.49	0.021	1.18	0.88–1.59	0.273
Diabetes mellitus	0.98	0.54–1.76	0.940	0.91	0.56–1.46	0.686	0.95	0.71–1.25	0.694
Chronic kidney disease	2.28	0.92–5.65	0.075	2.01	0.94–4.29	0.070	1.67	1.06–2.63	0.028
Asthma	1.26	0.67–2.35	0.475	0.85	0.49–1.45	0.548	1.16	0.87–1.54	0.320
COPD	1.33	0.68–2.61	0.407	1.16	0.65–2.06	0.622	1.13	0.83–1.56	0.437
Bronchiectasis exacerbation, moderate[a]	1.73	0.94–3.19	0.079	1.79	1.07–3.00	0.027	1.47	1.10–1.95	0.009

ASCeVD, atherosclerotic cerebrovascular disease; CAOD, coronary artery occlusive disease; CCI, Charlson comorbidity index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; OR, odds ratio.
[a]Moderate bronchiectasis exacerbations were defined as emergency room visit/hospitalization under the following conditions: (1) diagnostic code for bronchiectasis and antibiotic administration and (2) diagnostic codes J12.x–J17.x (pneumonia), J20.x (acute bronchitis), J21.x (acute bronchiolitis), R06.0 (dyspnoea), J80 (acute respiratory distress syndrome), R09.3 (abnormal sputum), or R04.2 (blood-tinged sputum) and antibiotic administration.

cohort, moderate bronchiectasis exacerbation increased the risk of 1-year mortality (OR = 2.38, 95% CI = 1.12–5.08, $p = 0.024$) and all-cause mortality without statistical significance (HR = 1.47, 95% CI = 0.96–2.25, $p = 0.080$) (see Online Supplement Table S5). In both cohorts, age and BMI were also significant risk factors for 90-day, 1-year, and all-cause mortalities.

Discussion

This study revealed the association between preceding hospitalization or emergency room visit for bronchiectasis exacerbation and mortality due to ASCaVD or ASCeVD in patients with bronchiectasis using a nationally representative, population-based sample cohort. To date, a few studies have shown the association between bronchiectasis exacerbation and risk of ASCCVD, but the effects of bronchiectasis exacerbation on mortality after ASCCVD events have not been completely studied. Moderate bronchiectasis exacerbation within 1 year before ASCaVD or ASCeVD increased all-cause 90-day, 1-year, and all-cause mortalities.

ASCCVD is more prevalent and the associated mortality is higher in patients with bronchiectasis than in the general population. According to the Health Insurance Review and Assessment Service, National Patient Sample in Korea, the prevalence of cerebrovascular disease, angina pectoris, heart failure, and myocardial infarction in patients with bronchiectasis is 7.6%, 5.8%, 2.9%, and 0.8%, respectively.[8] Although the prevalence of cardiovascular diseases was relatively low compared with that in European bronchiectasis patients in which the prevalence of myocardial infarction, congestive heart failure, and the cerebrovascular accident was 11.7%, 10%, and 6.1%, respectively, cardiovascular disease burden was substantial with regard to increased health-care costs and leading causes of emergency room visits, hospitalizations, and mortalities.[4,8] Patients with bronchiectasis with severe coronary artery calcification (CAC) were five times more likely to die than

patients with no CAC.[15] UK primary care electronic records showed a higher risk of coronary heart disease (OR = 1.33) and stroke (OR = 1.92) among people with bronchiectasis than that of the general population.[5] Not only the prevalence of pre-existing comorbidities of coronary heart disease or stroke was higher in people with bronchiectasis but also the severity of diseases requiring intervention was higher.[5]

Mortality in patients with bronchiectasis has been reported ranging from 13% to 25%.[16,17] Patients with bronchiectasis have shown an increased risk of death than the control population.[18] The all-cause mortality (HR = 1.25) and respiratory-related mortality (HR = 3.49) risks were higher in the bronchiectasis group than in the control group in Korea.[19] Risk factors for mortality in bronchiectasis have not been thoroughly investigated. In a prospective cohort in Belgium, age and number of lobes affected in bronchiectasis were risk factors associated with higher mortality.[20] Hospitalization with bronchiectasis exacerbation was associated with significant hospital mortality (9%) and 1-year mortality (30%).[11] Patients with bronchiectasis exacerbation admitted to the ICU showed high cumulative mortality of 40% at 1 year and 60% at 4 years.[12,21] The relative risk of mortality in patients with bronchiectasis exacerbation, however, has not been investigated compared with that in those without exacerbations.

Exacerbation is an important endpoint in bronchiectasis because it is a major contributor to health-care costs, lung function decline, and poor prognosis.[9] Clinical significance of bronchiectasis exacerbation in association with cardiovascular disease has been reported. Navaratnam *et al.*[6] reported that a respiratory tract infection increased the risk of first-time ASCaVD or ASCeVD. They, however, did not further evaluate the effect of respiratory infection on mortality after a cardiovascular disease event.

In this study, among the patients with bronchiectasis hospitalized with ASCaVD, those with prior bronchiectasis exacerbations showed more proportion of older and underweight individuals, higher CCI, lower level of income represented by the level of Medicaid, and higher mortality than those without prior bronchiectasis exacerbation. Among the patients with bronchiectasis with ASCeVD, those with prior bronchiectasis exacerbations showed similar age distribution but a higher proportion of underweight individuals, higher CCI, and higher mortality. As the age increased, the prevalence of bronchiectasis and the proportion of exacerbators, especially in the ASCaVD cohort, increased. Moreover, the different proportion of male and female was observed in different age groups (Online Supplement Table S6). Therefore, age-related biological changes including hormonal changes could affect the severity of bronchiectasis with the incidence of ASCCVD and might have played major contributory roles in increased mortality. In both cohorts, airway diseases such as asthma and COPD were more frequent in those with prior exacerbation, suggesting that chronic airway inflammation and airflow limitation may contribute to more exacerbation. In Europe and Israel, COPD [incident rate ratios (IRRs) = 1.43] and asthma (IRR = 1.16) were significantly related to exacerbation frequency among the patients with bronchiectasis. Moreover, as the predicted percentage of forced expiratory volume in the first second increased by 10%, IRR of exacerbation decreased by 4%.[9]

In this study, BMI was a significant risk factor for 90-day, 1-year, and all-cause mortalities in the both ASCaVD and ASCeVD cohorts. Lee *et al.*[22] reported that being underweight was a risk factor for mortality, while obese patients showed a reduced risk of death compared with that of normal-weight patients. Although the mechanism of this association is unclear, low fat-free mass index and diaphragmatic muscle weakness may be attributable, similar to that in COPD.[23] BMI is included in BSI, which is a clinical predictive tool that identifies patients at risk of future mortality, hospitalization, and exacerbations.[10] Among the other comorbidities, bronchiectasis overlapped with COPD or rheumatoid arthritis was shown to be associated with higher mortality than that with other etiologies.[20,24]

The mechanisms of increased risk of mortality by bronchiectasis exacerbation preceding ASCaVD or ASCeVD events remain largely unexplored. UK electronic primary care data suggested that respiratory tract infections were strongly associated with a transiently increased risk of first-time myocardial infarction or stroke among people with bronchiectasis.[6] Shared risk factors included hypoxia and transient increase in systemic inflammation.[6] Respiratory tract infections contribute to the progression of atherosclerotic plaques, which coupled with elevated levels of inflammatory

cytokines, precipitate the cardiovascular event.[6] Elastin degradation is a common pathological feature of both bronchiectasis and cardiovascular disease.[25] Serum desmosine represents systemic elastic degradation and vascular aging.[26] In a study, desmosine level was correlated with sputum elastase level and was associated with the risk of severe exacerbations (HR = 2.7).[25] In COPD, elevated plasma desmosine levels are related to cardiovascular comorbidities, arterial stiffness, and mortality.[27] Huang *et al.* reported an association of serum desmosine with long-term all-cause and cardiovascular mortalities in bronchiectasis.

This study has certain strengths. This is the first study to evaluate the effects of bronchiectasis exacerbation preceding ASCaVD or ASCeVD on mortality using large population data over a long period. A significant risk of mortality was observed even after the BMI was adjusted in subgroups with known BMI.

The study, however, has several limitations. First, the data were obtained from administrative claims; therefore, diagnostic codes might not have identified all participants corresponding to bronchiectasis patients with ASCaVD or ASCeVD. Patients who were hospitalized under ASCaVD and ASCeVD were only included, however. Second, the cohort study included patients with bronchiectasis experiencing hospitalization for ASCaVD or ASCeVD once to evaluate the impact of moderate bronchiectasis exacerbation on mortality after ASCaVD or ASCeVD events and to exclude the effects of recurrent ASCCVD events. Therefore, the results of this study cannot be applied to those experiencing multiple hospitalizations for ASCCVD. Third, smoking is a well-known risk factor for ASCaVD and ASCeVD, but NHIS-NSC does not provide data on the smoking status of the study population. Williams *et al.*, however, reported that smoking was not associated with mortality in patients with bronchiectasis when they evaluated the association between CAC and bronchiectasis severity for long-term outcomes. Finally, the severity of bronchiectasis was not considered because BSI could not be evaluated owing to a lack of clinical data to estimate BSI.[15]

Conclusion

Preceding hospitalization or emergency room visit for bronchiectasis exacerbation increased the mortality risk of ASCaVD or ASCeVD events in patients with bronchiectasis. Increased awareness of bronchiectasis exacerbation preceding ASCCVD events is needed to improve the quality of care for these patients. Our findings are clinically important because exacerbation reduction is one of the key goals of bronchiectasis management.[28] This study also highlights the importance of preventing exacerbation in patients with bronchiectasis to reduce the subsequent ASCCVD-related mortalities. Future research works, however, are warranted to elucidate the effects of bronchiectasis exacerbation prior to hospitalization with ASCCVD events on mortalities using well-designed study.

Declarations

Ethical approval and consent to participate

The study was approved by the Institutional Review Board of National Health Insurance Service Ilsan Hospital and adhered to the tenets of the Declaration of Helsinki (NHIMC 2020-03-042). As this study was based on anonymous health claims data, the requirement for patient consent was waived.

Consent for publication

Not applicable.

Author contributions

Sang Chul Lee: Conceptualization; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

Kang Ju Son: Data curation; Formal analysis; Resources; Software; Writing – review & editing.

Chang Hoon Han: Conceptualization; Methodology; Project administration; Resources; Writing – review & editing.

Seon Cheol Park: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Visualization; Writing – original draft; Writing – review & editing.

Ji Ye Jung: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Visualization; Writing – original draft; Writing – review & editing.

Acknowledgements

The authors thank the Department of Research and Analysis, National Health Insurance Service

Ilsan Hospital for assistance with statistical analysis.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Korea Environment Industry & Technology Institute (KEITI) through the Digital Infrastructure Building Project for Monitoring, Surveying, and Evaluating the Environmental Health, funded by the Korean Ministry of Environment (MOE) (2021003340002).

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

Availability of data and materials
The data sets used and/or analyzed during this study are not publicly available due to patient data privacy regulations by HIRA.

ORCID iD
Ji Ye Jung https://orcid.org/0000-0003-1589-4142

Supplemental material
Supplemental material for this article is available online.

References

1. Roberts HJ and Hubbard R. Trends in bronchiectasis mortality in England and Wales. *Respir Med* 2010; 104: 981–985.
2. Ringshausen FC, de Roux A, Pletz MW, *et al.* Bronchiectasis-associated hospitalizations in Germany, 2005–2011: a population-based study of disease burden and trends. *PLoS ONE* 2013; 88: e71109.
3. Diel R, Chalmers JD, Rabe KF, *et al.* Economic burden of bronchiectasis in Germany. *Eur Respir J* 2019; 53: 1802033.
4. McDonnell MJ, Aliberti S, Goeminne PC, *et al.* Comorbidities and the risk of mortality in patients with bronchiectasis: an international multicentre cohort study. *Lancet Respir Med* 2016; 4: 969–979.
5. Navaratnam V, Millett ER, Hurst JR, *et al.* Bronchiectasis and the risk of cardiovascular disease: a population-based study. *Thorax* 2017; 72: 161–166.
6. Navaratnam V, Root AA, Douglas I, *et al.* Cardiovascular outcomes after a respiratory tract infection among adults with non-cystic fibrosis bronchiectasis: a general population-based study. *Ann Am Thorac Soc* 2018; 15: 315–321.
7. Onen ZP, Gulbay BE, Sen E, *et al.* Analysis of the factors related to mortality in patients with bronchiectasis. *Respir Med* 2007; 101: 1390–1397.
8. Choi H, Yang B, Nam H, *et al.* Population-based prevalence of bronchiectasis and associated comorbidities in South Korea. *Eur Respir J* 2019; 54: 1900194.
9. Chalmers JD, Aliberti S, Filonenko A, *et al.* Characterization of the 'Frequent Exacerbator Phenotype' in Bronchiectasis. *Am J Respir Crit Care Med* 2018; 197: 1410–1420.
10. Chalmers JD, Goeminne P, Aliberti S, *et al.* The bronchiectasis severity index. An international derivation and validation study. *Am J Respir Crit Care Med* 2014; 189: 576–585.
11. Finklea JD, Khan G, Thomas S, *et al.* Predictors of mortality in hospitalized patients with acute exacerbation of bronchiectasis. *Respir Med* 2010; 104: 816–821.
12. Dupont M, Gacouin A, Lena H, *et al.* Survival of patients with bronchiectasis after the first ICU stay for respiratory failure. *Chest* 2004; 125: 1815–1820.
13. Lee J, Lee JS, Park SH, *et al.* Cohort profile: The National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. *Int J Epidemiol* 2017; 46: e15.
14. Kim H, Kim S, Han S, *et al.* Prevalence and incidence of atherosclerotic cardiovascular disease and its risk factors in Korea: a nationwide population-based study. *BMC Pub Health* 2019; 19: 1112.
15. Williams MC, van Beek EJR, Hill AT, *et al.* Coronary artery calcification on thoracic computed tomography is an independent predictor of mortality in patients with bronchiectasis. *J Thorac Imaging* 2021; 36: 166–173.
16. Steinfort DP, Brady S, Weisinger HS, *et al.* Bronchiectasis in Central Australia: a young face to an old disease. *Respir Med* 2008; 102: 574–578.
17. Keistinen T, Säynäjäkangas O, Tuuponen T, *et al.* Bronchiectasis: an orphan disease with a

poorly-understood prognosis. *Eur Respir J* 1997; 10: 2784–2787.

18. Quint JK, Millett ER, Joshi M, *et al.* Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. *Eur Respir J* 2016; 47: 186–193.
19. Sin S, Yun SY, Kim JM, *et al.* Mortality risk and causes of death in patients with non-cystic fibrosis bronchiectasis. *Respir Res* 2019; 20: 271.
20. Goeminne PC, Nawrot TS, Ruttens D, *et al.* Mortality in non-cystic fibrosis bronchiectasis: a prospective cohort analysis. *Respir Med* 2014; 108: 287–296.
21. Alzeer AH, Masood M, Basha SJ, *et al.* Survival of bronchiectatic patients with respiratory failure in ICU. *BMC Pulm Med* 2007; 7: 17.
22. Lee JM, Lee SA, Han CH, *et al.* Body mass index as a predictor of mortality in bronchiectasis: a nationwide population-based study. *Respir Med* 2021; 180: 106370.
23. Vestbo J, Prescott E, Almdal T, *et al.* Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City Heart Study. *Am J Respir Crit Care Med* 2006; 173: 79–83.
24. De Soyza A, McDonnell MJ, Goeminne PC, *et al.* Bronchiectasis Rheumatoid overlap syndrome is an independent risk factor for mortality in patients with bronchiectasis: a multicenter cohort study. *Chest* 2017; 151: 1247–1254.
25. Chalmers JD, Moffitt KL, Suarez-Cuartin G, *et al.* Neutrophil elastase activity is associated with exacerbations and lung function decline in bronchiectasis. *Am J Respir Crit Care Med* 2017; 195: 1384–1393.
26. Huang JT-J, Kuzmanova E, Dicker AJ, *et al.* Serum desmosine is associated with long-term all-cause and cardiovascular mortality in bronchiectasis. *Am J Respir Crit Care Med* 2020; 202: 897–899.
27. Rabinovich RA, Miller BE, Wrobel K, *et al.* Circulating desmosine levels do not predict emphysema progression but are associated with cardiovascular risk and mortality in COPD. *Eur Respir J* 2016; 47: 1365–1373.
28. Polverino E, Goeminne PC, McDonnell MJ, *et al.* European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J* 2017; 50: 1700629.