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

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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.

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 differ 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

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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...

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

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

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). This study consisted of two separate cohorts of patients, namely, those with bronchiectasis experiencing first-time ASCaVD and those with bronchiectasis experiencing first-time ASCeVD 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). 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.

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.
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 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* kg/m²                   | 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]            |         |
| Mildb           |                |                          |                      | 0.010   |
| 0               | 717 [67.3]     | 617 [67.3]               | 100 [67.1]           |         |
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 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]       |           |
| \( \geq 2 \)     | 119 [11.1]      | 93 [10.1]       | 26 [17.5]       |           |
| Moderate\(^b\)  | 0 [0]           | 0 [0]           | 0 [0]           | <0.001    |
| 0               | 133 [89.3]      | 0 [0]           | 133 [89.3]      |           |
| \( \geq 2 \)     | 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.
| 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]            |         |
| **BMIa, kg/m²**                 | 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)
| 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)            |         |
| Mildb                                |               |                          |                      |         |
| 0                                    | 592 (71.8)    | 517 (72.5)               | 75 (67.0)            | 0.368   |

(Continued)
SC Lee, KJ Son et al.

Table 2. (Continued)

| Characteristics | Total (n = 825) | Non-exacerbators (n = 713) | Exacerbators (n = 112) | p-value |
|-----------------|----------------|---------------------------|----------------------|---------|
| 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)            |         |

[^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    |

[^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 except 1-year survival in the bronchiectasis-ASCeVD 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
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. 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. Patients with bronchiectasis with severe coronary artery calcification (CAC) were five times more likely to die than...
Mortality in patients with bronchiectasis has been reported ranging from 13% to 25%.\textsuperscript{16,17} Patients with bronchiectasis have shown an increased risk of death than the control population.\textsuperscript{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.\textsuperscript{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.\textsuperscript{20} Hospitalization with bronchiectasis exacerbation was associated with significant hospital mortality (9%) and 1-year mortality (30%).\textsuperscript{11} Patients with bronchiectasis exacerbation admitted to the ICU showed high cumulative mortality of 40% at 1 year and 60% at 4 years.\textsuperscript{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.\textsuperscript{9} Clinical significance of bronchiectasis exacerbation in association with cardiovascular disease has been reported. Navaratnam et al.\textsuperscript{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 a higher 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%.\textsuperscript{9}

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.\textsuperscript{6} Shared risk factors included hypoxia and transient increase in systemic inflammation.\textsuperscript{6} Respiratory tract infections contribute to the progression of atherosclerotic plaques, which coupled with elevated levels of inflammatory
cytokines, precipitate the cardiovascular event.\textsuperscript{6} Elastin degradation is a common pathological feature of both bronchiectasis and cardiovascular disease.\textsuperscript{25} Serum desmosine represents systemic elastic degradation and vascular aging.\textsuperscript{26} In a study, desmosine level was correlated with sputum elastase level and was associated with the risk of severe exacerbations (HR = 2.7).\textsuperscript{25} In COPD, elevated plasma desmosine levels are related to cardiovascular comorbidities, arterial stiffness, and mortality.\textsuperscript{27} Huang \textit{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 \textit{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.\textsuperscript{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.\textsuperscript{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.

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Competing interests
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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.

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