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Cardiovascular and cerebrovascular mortality in patients with preceding asthma exacerbation

To the Editors:

Asthma is a common respiratory disease with an estimated prevalence of 1%–18%.[1] Cardiovascular and cerebrovascular diseases (CCVDs) are the leading cause of death worldwide with an increasing prevalence.[2] Greater incidences of coronary heart disease, heart failure, and stroke have been noted in patients with asthma than in those without,[3,4] with a higher mortality rate due to cardiovascular diseases in the former than in the latter.[5,6] However, the effect of acute exacerbation of asthma on CCVD mortality has not been analysed. Therefore, we assessed whether acute exacerbation increases mortality following CCVD in patients with asthma.

We used the National Health Insurance Service-National Sample Cohort database, a nationwide population-based sample cohort, that provides representative health insurance and health examination data to public health researchers in Korea.[7] We defined three study cohorts using data from 2004 to 2018: patients with asthma experiencing first-time acute myocardial infarction (AMI) ($n = 1900$), ischemic stroke ($n = 3864$), and heart failure ($n = 2529$). The cohorts comprised participants diagnosed with asthma at least 1 year before CCVD onset, beginning in 2002. In each cohort, 285 (15.0%), 451 (11.7%), and 456 (18.0%) patients experienced acute exacerbation within 1 year preceding the index AMI, ischemic stroke, and heart failure, respectively. Patients who did not experience acute exacerbation within 1 year constituted the control group.

Asthma patients in whom both the diagnostic and asthma medication codes could be identified more than twice within 1 year during the study period were included. To better identify the effect of asthma on CCVD events, we excluded patients who had been hospitalized more than once for the same CCVD event and those whose index CCVD event occurred during the first 2 years or the final year of the study period. Patients with other respiratory ailments, including chronic obstructive pulmonary disease (COPD), interstitial lung disease, and bronchiectasis, were excluded. Moreover, we excluded patients with cancer because of its interference with mortality analyses.

Acute exacerbation was defined as the presence of an asthma diagnostic code (J45, J46) together with any of the following events: high-dose systemic corticosteroid use (≥20 mg over three consecutive days), hospitalization, or an emergency department visit. Acute exacerbation for which the patient was treated with high-dose systemic corticosteroids on an outpatient basis was defined as mild, whereas one that required the patient to present to the emergency room or be hospitalized was defined as moderate to severe. The primary outcomes were 90-day, 1-year, and overall mortality rates. All patients were followed up from the admission date for index events until their death or the end of 2018, whichever came first.

We used Cox proportional hazards models to estimate the all-cause and cause-specific adjusted hazard ratio (HR) and 95% CI for the study groups, compared with the control group. Subsequently, we performed multivariate Cox regression analysis to evaluate the association between risk factors and mortality-related outcomes.

Table 1 summarizes the patient characteristics of the three cohorts. Compared to control subjects, patients who experienced moderate-to-severe exacerbations were older with more underlying comorbidities. Table 2 summarizes the HRs for the 90-day, 1-year, and overall mortality rates associated with acute exacerbation severity for each cohort in comparison with those of the control group. HRs were adjusted for sex, age, insurance level, medical comorbidities, hospital levels, and year. In all cohorts, a significantly higher proportion of deaths was observed in the moderate-to-severe group compared to that in the mild and control groups. In the asthma-AMI cohort, the HRs of the 90-day, 1-year, and overall mortality rates in patients with moderate-to-severe exacerbation were 3.12 (95% CI, 1.91–5.09; $p < 0.001$), 2.85 (95% CI, 1.88–4.33; $p < 0.001$), and 2.21 (95% CI, 1.59–3.06, $p < 0.001$), respectively, whereas the mortality rate was unaffected by mild exacerbation. We obtained similar results for ischemic stroke and heart failure. The HRs for the 90-day, 1-year, and overall mortality rates in the asthma-ischemic stroke cohort with moderate-to-severe antecedent exacerbation were 2.54 (95% CI, 1.63–3.96; $p < 0.001$), 2.00 (95% CI, 1.39–2.88; $p < 0.001$), and 1.65 (95% CI, 1.26–2.18; $p < 0.001$), respectively, compared with the control group; however, mild exacerbation had no association with mortality following ischemic stroke. Likewise, the moderate-to-severe exacerbation group in the asthma-heart failure cohort displayed increased 90-day, 1-year, and overall HRs of 1.90 (95% CI, 1.33–2.73; $p < 0.001$), 1.98 (95% CI, 1.49–2.64; $p < 0.001$), and 1.99 (95% CI, 1.60–2.47; $p < 0.001$), respectively; nonetheless, the mild exacerbation group did not demonstrate significant HRs.

Figure 1 represents the Kaplan–Meier estimates of 90-day, 1-year, and overall survival based on the severity of acute exacerbation within 1 year prior to AMI, ischemic stroke, and heart failure. The moderate-to-severe

TABLE 1 Demographics of patients with asthma, with and without acute exacerbation 1 year preceding a CCVD event in three asthma-CCVD cohorts

	Asthma–AMI cohort ($n = 1900$)			Asthma–ischemic stroke cohort ($n = 3864$)			Asthma–heart failure cohort ($n = 2529$)		
		Acute exacerbation within 1 year			Acute exacerbation within 1 year			Acute exacerbation within 1 year	
Variables	Control ($n = 1615$)	Mild ($n = 216$)	Moderate-to-severe ($n = 69$)	Control ($n = 3413$)	Mild ($n = 348$)	Moderate-to-severe ($n = 103$)	Control ($n = 2073$)	Mild ($n = 313$)	Moderate-to-severe ($n = 143$)
Male sex	716 (44.3)	84 (38.9)	26 (37.7)	1340 (39.3)	132 (37.9)	40 (38.8)	730 (35.2)	100 (32.0)	43 (30.1)
Age group, year									
20–49	212 (13.1)[a]	26 (12.0)	6 (8.7)	258 (7.6)[a]	20 (5.8)[b]	3 (2.9)	135 (6.5)	26 (8.3)[b]	2 (1.4)
50–59	283 (17.5)	227 (12.5)	5 (7.3)	383 (11.2)	44 (12.6)	12 (11.7)	192 (9.3)	30 (9.6)	17 (11.9)
60–69	359 (22.2)	46 (21.3)	10 (14.5)	723 (21.2)	81 (23.3)	14 (13.6)	362 (17.5)	59 (18.9)	18 (12.6)
70–79	458 (28.4)	66 (30.6)	18 (26.1)	1207 (35.4)	135 (38.8)	33 (32)	673 (32.5)	105 (33.6)	44 (30.8)
80–	303 (18.8)	51 (23.6)	30 (43.5)	842 (24.7)	68 (19.5)	41 (39.8)	711 (34.3)	93 (29.7)	62 (43.4)
Insurance level									
Medicaid	134 (8.3)[a]	19 (8.8)	12 (17.4)	339 (9.9)	44 (12.6)	17 (16.5)	242 (11.7)[a]	45 (14.4)	31 (21.7)
1–6	678 (41.9)	91 (41.9)	30 (43.5)	1385 (40.6)	139 (30.9)	44 (42.8)	795 (38.4)	112 (35.8)	44 (30.8)
7–10	803 (49.8)	106 (49.0)	27 (39.1)	1689 (49.5)	165 (47.4)	42 (40.7)	1036 (50.0)	156 (49.9)	68 (47.6)
Institution									
Tertiary hospital	424 (26.3)	51 (23.6)	14 (20.3)	942 (27.6)[a,c]	103 (29.6)[b]	17 (16.5)	501 (24.2)[a]	64 (20.5)	22 (15.4)
Secondary hospital	712 (44.1)	112 (51.9)	29 (42)	1683 (49.3)	190 (54.6)	44 (42.7)	1120 (54.0)	178 (26.9)	71 (49.7)
Other	479 (29.7)	53 (24.5)	26 (37.7)	788 (23.1)	55 (15.8)	42 (40.8)	452 (21.8)	71 (22.7)	50 (35.0)
Medical comorbidities									
Hypertension	956 (59.8)[a]	126 (58.3)[b]	57 (82.6)	2562 (66.3)[a]	236 (67.8)[b]	84 (81.6)	1535 (74.1)[a]	226 (72.2)[b]	121 (84.6)
Diabetes	548 (33.9)[a]	78 (36.1)	36 (52.2)	1467 (38.0)[a]	130 (37.4)[b]	64 (62.1)	863 (41.6)	113 (36.1)[b]	74 (51.8)
Hyperlipidemia	659 (40.8)	84 (38.9)	32 (46.4)	1581 (40.9)	154 (44.3)	51 (49.5)	975 (47.0)	141 (45.1)	71 (49.7)
Chronic kidney disease	42 (2.6)	4 (1.9)	2 (2.9)	99 (2.6)[a]	9 (2.6)[b]	14 (13.6)	101 (4.9)[a]	10 (3.2)[b]	18 (12.6)
Ischemic heart disease	437 (27.4)	60 (27.8)	28 (40.6)	751 (19.4)[a]	80 (23.0)[b]	41 (39.8)	678 (32.7)	93 (29.7)	51 (35.7)
Peripheral artery Disease	128 (7.9)	9 (4.2)	3 (4.4)	265 (6.9)	33 (9.5)	8 (7.8)	148 (7.1)	20 (6.4)	9 (6.3)
Atrial fibrillation	69 (4.3)[a]	5 (2.3)[b]	8 (11.6)	225 (5.8)[a]	23 (6.6)	14 (13.6)	245 (11.8)[a]	44 (14.1)	29 (20.3)
AMI	72 (4.5)	13 (6.0)	7 (10.1)	116 (3)[a]	10 (2.9)[b]	11 (10.7)	110 (5.3)[a]	13 (4.2)[b]	18 (12.6)
Stroke	170 (10.5)[a]	22 (10.2)[b]	19 (27.5)	728 (18.8)	68 (19.5)	17 (16.5)	291 (14.0)[a]	35 (11.2)[b]	43 (30.1)
Heart failure	117 (7.2)[a]	23 (10.7)[b]	21 (30.4)	304 (7.9)[a]	32 (9.2)[b]	23 (22.3)	477 (23.0)	73 (23.3)	27 (18.9)
Follow-up duration, year	3.3 ± 2.9[a,c]	4.4 ± 3.6[b]	2.1 ± 2.9	3.3 ± 2.9[a,c]	4 ± 3.3[b]	2.2 ± 2.5	2.4 ± 2.5[a,c]	3.5 ± 3.3[b]	1.8 ± 2.3

Note: Variables are expressed as means ± standard deviations or *n* (%); Control: no acute exacerbation within 1 year to CCVD; Mild: acute exacerbation treated at the outpatient department; Moderate to severe: acute exacerbation treated in the emergency room or were hospitalized.

Abbreviations: AMI, acute myocardial infarction; CCVD, cardiovascular and cerebrovascular disease.

[a] $p < 0.05$ for the comparison between the control group and moderate-to-severe group.

[b] $p < 0.05$ for the comparison between the mild group and moderate-to-severe group.

[c] $p < 0.05$ for the comparison between the control group and mild group.

exacerbation group displayed a lower survival rate than the mild exacerbation and control groups (all $p < 0.001$). Multivariate analysis based on the frequency of acute exacerbation (control vs. single acute exacerbation vs. multiple acute exacerbations) did not demonstrate a significant relationship.

Furthermore, we examined each patient's medication possession ratio (MPR) during the 1 year before and after the CCVD event. The MPR was calculated as the number of days for which asthma medication was supplied divided by the number of days between refills.[8] Patients with low medication adherence (MPR < 50%) before but high adherence (MPR ≥ 50%) after the CCVD event showed lower risks of 1-year mortality in the asthma-heart failure cohort (adjusted odds ratio [aOR] = 0.16; 95% CI, 0.03–0.83) than those with

TABLE 2 Hazard ratios of mortality rates following CCVD events and acute exacerbation within 1 year preceding the event in three asthma-CCVD cohorts

Outcome	Control	Acute exacerbation	
		Mild	Moderate-to-severe
Asthma-AMI cohort ($n = 1900$)			
90-day mortality			
N (%)[a,b]	141 (8.7)	15 (6.9)	23 (33.3)
Crude HR (95% CI)	1.00	0.79 (0.46–1.34)	4.50 (2.90–7.00)
Adjusted HR (95% CI)[c]	1.00	0.80 (0.47–1.37)	3.12 (1.91–5.09)
1-year mortality			
N (%)[a,b]	200 (12.3)	24 (11.1)	31 (44.9)
Crude HR (95% CI)	1.00	0.88 (0.58–1.34)	4.32 (2.96–6.31)
Adjusted HR (95% CI)[c]	1.00	0.89 (0.58–1.37)	2.85 (1.88–4.33)
Overall mortality			
N (%)[a,b]	402 (24.8)	68 (31.4)	48 (69.5)
Crude HR (95% CI)	1.00	1.03 (0.80–1.34)	3.80 (2.82–5.13)
Adjusted HR (95% CI)[c]	1.00	0.94 (0.72–1.23)	2.21 (1.59–3.06)
Asthma-ischemic stroke cohort ($n = 3864$)			
90-day mortality			
N (%)	214 (6.2)	22 (6.3)	25 (24.2)
Crude HR (95% CI)	1.00	1.01 (0.65–1.57)	4.28 (2.83–6.47)
Adjusted HR (95% CI)[c]	1.00	1.27 (0.82–1.97)	2.54 (1.63–3.96)
1-year mortality			
N (%)	395 (11.5)	41 (11.7)	36 (34.9)
Crude HR (95% CI)	1.00	1.02 (0.74–1.41)	3.50 (2.49–4.93)
Adjusted HR (95% CI)[c]	1.00	1.24 (0.90–1.71)	2.00 (1.39–2.88)
Overall mortality			
N (%)	1007 (29.5)	96 (27.5)	62 (60.1)
Crude HR (95% CI)	1.00	0.81 (0.66–1.00)	2.79 (2.16–3.61)
Adjusted HR (95% CI)[c]	1.00	0.86 (0.70–1.07)	1.65 (1.26–2.18)
Asthma-heart failure cohort ($n = 2529$)			
90-day mortality			
N (%)	239 (11.5)	26 (8.3)	37 (25.8)
Crude HR (95% CI)	1.00	0.69 (0.46–1.04)	2.37 (1.67–3.34)
Adjusted HR (95% CI)	1.00	0.81 (0.54–1.21)	1.90 (1.33–2.73)
1-year mortality			
N (%)	389 (18.7)	50 (15.9)	59 (41.2)
Crude HR (95% CI)	1.00	0.82 (0.61–1.10)	2.45 (1.86–3.22)
Adjusted HR (95% CI)	1.00	0.96 (0.71–1.29)	1.98 (1.49–2.64)
Overall mortality			
N (%)	762 (36.7)	118 (37.7)	99 (69.2)
Crude HR (95% CI)	1.00	0.81 (0.66–0.98)	2.37 (1.92–2.92)
Adjusted HR (95% CI)	1.00	0.87 (0.71–1.06)	1.99 (1.60–2.47)

Note: Mild exacerbation is characterized by outpatient-based treatment. Moderate-to-severe exacerbation is characterized by emergency room visits or hospitalization.
Abbreviations: AMI, acute myocardial infarction; CCVD, cardiovascular and cerebrovascular disease; HR, hazard ratio.
[a]$p < 0.05$ for the comparison between the control group and moderate-to-severe group.
[b]$p < 0.05$ for the comparison between the mild group and moderate-to-severe group.
[c]Adjusted for sex, age, insurance level, medical comorbidities, hospital levels, and year.

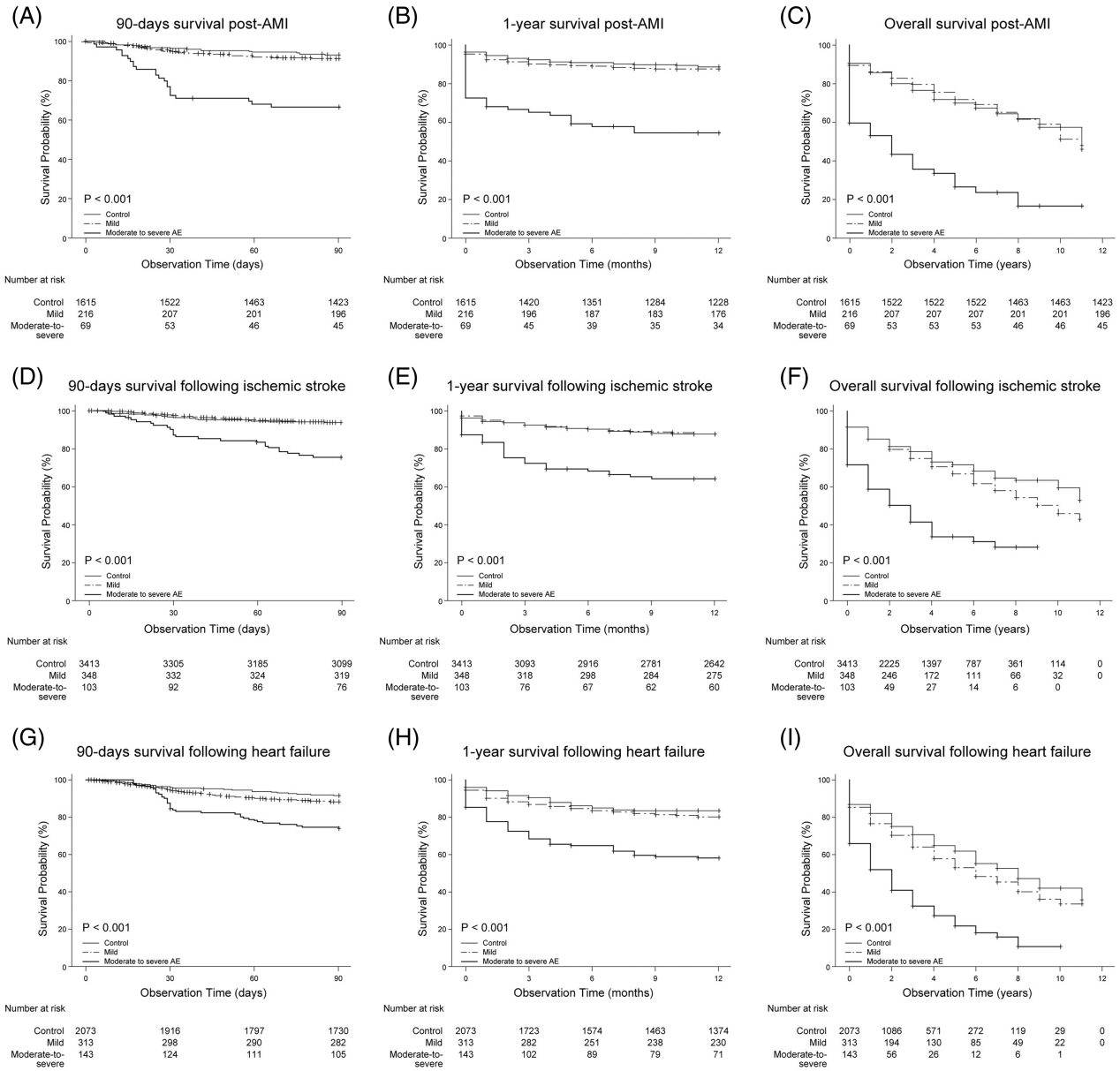

FIGURE 1 Kaplan–Meier survival curves of patients with asthma following a cardiovascular and cerebrovascular disease (CCVD) event, depending on recent experience of acute exacerbation. Kaplan–Meier survival curves of 90-day, 1-year, and overall survival following acute myocardial infarction (AMI), ischemic stroke, and heart failure events were compared between the control, mild exacerbation, and moderate-to-severe exacerbation groups. The moderate-to-severe exacerbation group displayed lower survival than the mild and control groups in all cohorts (all $p < 0.001$); (A) 90-day survival following AMI, (B) 1-year survival following AMI, (C) overall survival following AMI, (D) 90-day survival following ischemic stroke, (E) 1-year survival following ischemic stroke, (F) overall survival following ischemic stroke, (G) 90-day survival following heart failure, (H) 1-year survival following heart failure, and (I) overall survival following heart failure. The control group comprises patients with asthma who did not experience acute exacerbation within 1 year prior to CCVD. The mild exacerbation group was defined as patients with asthma who experienced acute exacerbation within 1 year prior to CCVD, and acute exacerbation was treated on an outpatient basis. The moderate-to-severe exacerbation group was defined as patients with asthma who experienced acute exacerbation within 1 year prior to CCVD, and required an emergency room visit or hospitalization.

low adherence both before and after the CCVD event. Contrarily, those with high adherence before and low adherence after the CCVD event displayed higher risks of 1-year mortality in all cohorts (asthma-AMI aOR = 3.31 [95% CI, 1.45–7.58], asthma-ischemic stroke aOR = 2.47 [95% CI, 1.00–6.11], asthma-heart failure aOR = 3.06 [95% CI, 1.46–6.40]).

Existing research suggests a strong association between asthma and CCVD incidence and associated mortality.[3,5] An analysis of the Framingham Offspring cohort data revealed asthma as an independent risk factor for CCVD, resulting in a 1.28-fold increased risk.[4] A self-controlled case series study demonstrated an increased incidence of AMI and ischemic stroke following acute exacerbation.[9] While

current medicine holds evidence for connecting acute exacerbation with CCVD incidence, no studies have yet examined the lineal effect of acute exacerbation on the aftermath of CCVD. This is the first study to evaluate the impact of acute exacerbation on mortality following CCVD in patients with asthma, as confirmed by its severity and frequency. An analysis of three cohorts—the asthma-AMI, asthma-ischemic stroke, and asthma-heart failure cohorts—showed increased mortality following CCVD events in patients with asthma who had experienced moderate-to-severe acute exacerbation within 1 year prior to the event.

The interrelation between asthma and CCVD is explained by a shared pathophysiological process. Persistent airway inflammation will lead to the recruitment of more inflammatory cells, causing inflammatory cytokines to spillover and spread into the systemic circulation, ultimately arriving at a vulnerable endothelium.[10] Inflammation is crucial for the maturation of fibrous plaque in the endothelium. Therefore, intensified acute exacerbation will lead to a greater inflammatory burden, which will eventually impact the disease course of CCVD.

Our results have been derived from a large population database with data obtained over a long period, reinforcing its validity. However, this study had several limitations. The administrative data might have included some inaccurate codes and cases of underdiagnosed COPD. Moreover, it did not contain information on relevant variables such as smoking status, environmental exposures, pulmonary function test results, and cause of death, and their possible confounding effects were not verified. Likewise, in the analysis of MPR and mortality, potential confounding factors affecting medical adherence, such as disability and psychological changes after CCVD, were not examined. Additionally, the strong associations identified in this study do not represent cause-and-effect relationships. Lastly, we did not investigate the mechanism behind the association between recent acute exacerbation and cardiovascular mortality. Asthma is a heterogeneous disease with numerous phenotypes, and the cause of acute exacerbation is also heterogeneous, thereby necessitating further exploration.

AUTHOR CONTRIBUTION

Soojoung Yu: Data curation (equal); formal analysis (equal); investigation (equal); project administration (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Sang Chul Lee:** Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Jung Hwa Hong:** Data curation (equal); formal analysis (equal); resources (equal); software (equal); writing – review and editing (equal). **Chang Hoon Han:** Conceptualization (equal); methodology (equal); project administration (equal); resources (equal); writing – review and editing (equal). **Ji Ye Jung:** Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); software (equal); supervision (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Seon Cheol Park:** Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); software (equal); supervision (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal).

KEYWORDS

acute myocardial infarction, asthma, asthma exacerbation, heart failure, ischemic stroke, mortality

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CONFLICT OF INTEREST

None declared.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

HUMAN ETHICS APPROVAL DECLARATION

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by Institutional Review Board of the National Health Insurance Service Ilsan Hospital—approval number: NHIMC 2020-03-042. Participant consent was not required because anonymous health claims data were used.

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