Arteriosclerosis, Thrombosis, and Vascular Biology

CLINICAL AND POPULATION STUDIES

Beneficial Effect of Statins in COVID-19–Related Outcomes—Brief Report

A National Population-Based Cohort Study

Hae-Young Lee,* Juhee Ahn,* Juhong Park, Chang Kyung Kang, Sung-Ho Won, Dong Wook Kim, Jong-Heon Park, Ki-Hyun Chung, Joon-Sung Joh, Ji Hwan Bang, Cheong Hee Kang, Wook Bum Pyun, Myoung-don Oh, the Korean Society of Hypertension, National Committee for Clinical Management of Emerging Infectious Diseases

OBJECTIVE: Although statins are widely prescribed lipid-lowering drugs, there are concerns about the safety of their use in the context of coronavirus disease 2019 (COVID-19), since statins increase the expression of ACE2 (angiotensin-converting enzyme 2). This study aimed to disclose the association between statins and 60-day COVID-19 mortality.

APPROACH AND RESULTS: All patients hospitalized with laboratory-confirmed COVID-19 were enrolled in this study from January 19 to April 16, 2020, in Korea. We evaluated the association between the use of statins and COVID-19–related mortality in the overall and the nested 1:2 propensity score–matched study. Furthermore, a comparison of the hazard ratio for death was performed between COVID-19 patients and a retrospective cohort of patients hospitalized with pneumonia between January and June 2019 in Korea. The median age of the 10 448 COVID-19 patients was 45 years. Statins were prescribed in 533 (5.1%) patients. After adjusting for age, sex, and comorbidities, Cox regression showed a significant decrease in hazard ratio associated with the use of statins (hazard ratio, 0.637 [95% CI, 0.425–0.953]; P=0.0283). Moreover, on comparing the hazard ratio between COVID-19 patients and the retrospective cohort of hospitalized pneumonia patients, the use of statins showed similar benefits.

CONCLUSIONS: The use of statins correlates significantly with lower mortality in patients with COVID-19, consistent with the findings in patients with pneumonia.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: cohort studies ■ COVID-19 ■ hydroxymethylglutaryl-CoA reductase inhibitors ■ mortality ■ propensity score

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, Hubei, China, in December 2019 and since then became a pandemic, as declared by the World Health Organization on March 11, 2020.[1] As of October 20, >40 118 333 confirmed cases and 1 114 749 deaths have been reported worldwide.[2] Although the fatality rate associated with SARS-CoV-2 is lower than that in the context of SARS-CoV or Middle East respiratory syndrome–related coronavirus, the elderly and people experiencing chronic conditions are prone to serious outcomes.[1]

The most common comorbidities among COVID-19 patients include hypertension, diabetes, and coronary artery disease[1]; therefore, frequently, such patients are treated with HMG-CoA (hydroxy-methyl-glutaryl-coenzyme A) reductase inhibitors, known as statins. Of note, statin treatment was reported to increase the expression of ACE2 (angiotensin-converting enzyme 2) in the heart of experimental models via epigenetic histone modifications.[3] Given that SARS-CoV-2 enters the target cell via ACE2 cell surface receptors,[4] the use of statins in the context of COVID-19 initially brought some concerns. In fact, the increased

Correspondence to: Myoung-don Oh, MD, Department of Internal Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul, Korea. Email mdohmd@snu.ac.kr

*These authors contributed equally to this article.

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Nonstandard Abbreviations and Acronyms

COPD	chronic obstructive pulmonary disorder
COVID-19	coronavirus disease 2019
HMG-CoA	hydroxy-methyl-glutaryl-coenzyme A
HR	hazard ratio
PSM	propensity score matching
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

expression of ACE2 was shown to facilitate infection with SARS-CoV[5]; therefore, statins might increase the risk of COVID-19. In contrast, besides their lipid-lowering activity, statins are well known for pleiotropic effects on inflammation, contributing to their beneficial impact in patients with conditions other than cardiovascular diseases, including autoimmune diseases,[6] community-acquired pneumonia, and sepsis.[7,8] The immunomodulatory effect of statins depends on the inhibition of the production of isoprenoids and the consequent downregulation of redox-sensitive proinflammatory transcription factors such as NF-κB (nuclear factor-κB).[6] Moreover, statins were suggested to potentially inhibit the SARS-CoV-2 main protease—a key coronavirus enzyme—thus exerting antiviral activity.[9] Of note, previously, statins were effective in targeting the host response and preventing endothelial barrier damage in patients infected with the Ebola virus during the recent Ebola outbreak in West Africa.[10] Therefore, some hospitals included stains in the COVID-19 treatment protocol.[11]

Korea has registered all SARS-CoV-2–infected patients and managed them either in hospitals or in community treatment centers; therefore, follow-up information is available for all patients.[12] Therefore, Korea offers the ideal scenario to comprehensively evaluate the association between the use of statins and the severity of COVID-19. Therefore, in the present study, we investigated the association between the use of statins and COVID-19–related deaths in all COVID-19 patients in Korea. Moreover, the hazard ratio (HR) was compared between COVID-19 patients and a retrospective cohort of patients hospitalized with pneumonia between January and June 2019 in Korea.

Highlights

- The use of statins was significantly associated with lower mortality in coronavirus disease 2019 (COVID-19) patients.
- The protective effect of statins was similar to pneumonia patients in Korea, in 2019.
- Statins can be considered as a part of the supportive regimen during the treatment of COVID-19.

METHODS

Study Design

We report a population-based cohort study supported by the Korea Disease Control and Prevention Agency, the National Health Insurance Service, and the Korean Society of Hypertension. The study was approved by the Institutional Review Board of Seoul National University Hospital (No. 2003-102-1109). Informed consent was waived by the institutional review board. All authors reviewed the manuscript for the accuracy and completeness of the data.

Data Collection

Data related to all of the 10 448 patients, with laboratory-confirmed infection with SARS-CoV-2 since the first case on January 19 up to April 16, 2020, in Korea, were retrieved from the compiled information available at the National Health Insurance Service. A case designated confirmed for COVID-19 was defined as one whose nasal and pharyngeal swab specimens tested positive in the context of high-throughput sequencing or real-time reverse transcriptase polymerase chain reaction assays.[13,14] Diagnoses, prescription records, and information related to medical utilization were extracted from the national health information database—a public database compiled by the National Health Insurance Service.[15] Furthermore, for the National Health Insurance Service claim data analysis, operational definitions using the *ICD-10-CM (International Classification of Diseases, Tenth Revision, Clinical Modification)* codes were applied (Table I in the Data Supplement).

The association between the use of statins and the severity of pneumonia in hospitalized Korean patients between January and June 2019 was investigated using the information retrieved from the national health information database.[15] Of note, the national health information database holds information related to health care utilization, health screening, sociodemographic variables, and mortality of the entire Korean population; overall, the information available refers to data gathered during the process of claiming health care services. It includes information related to the records of inpatient and outpatient usage (diagnosis, length of stay, treatment costs, and services received) and prescription records (drug code, days prescribed, and daily dosage). Importantly, in our analysis, all potential identifiers in the national health information database data were removed, and the information was linked with new unidentifiable codes representing individual patients.

Study Outcomes and Definitions

In the present study, the association between the use of statins and COVID-19–related mortality within 60 days was investigated. All commercially available statins (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin) in Korea were included in the analysis. Dichotomous variables were created to identify the use of statins defined as a filled prescription with >60% of the proportion of days covered during 3 months before the diagnosis of COVID-19.[16]

Statistical Analysis

The association of the clinical characteristics with mortality within 60 days was tested using bivariate statistics.

Continuous variables were analyzed using *t* test, and categorical variables were analyzed with the χ^2 test. The time to occurrence of the COVID-19–related death in patients prescribed with statins was analyzed using Kaplan-Meier survival curves displaying the failure functions. Statistical significance was assessed using the log-rank test. Moreover, a Cox proportional hazard model was used for the estimation of unadjusted HRs and 95% CIs for statins. The additional factors included in the model as covariates were age group, sex, comorbidities including hypertension, type 2 diabetes, coronary heart diseases, heart failure, stroke, chronic obstructive pulmonary disorder (COPD), cancer, and chronic kidney diseases. To control confounding biases, we performed propensity score matching (PSM) using sex, age at diagnosis, and history of comorbidities (hypertension, diabetes, coronary artery disease, and COPD) in both study populations. Each statin user was matched with 2 nonstatin users; the details are provided in Tables II and VII in the Data Supplement. We diagnosed the proportional hazard assumption using the goodness-of-fit test and the Schoenfeld residual plots. Furthermore, we similarly analyzed with pneumonia 2019 patients. We standardized the difference of the coefficient of prior statin use for risk of death between COVID-19 patients and pneumonia patients in 2019. If the absolute value of *Z* score is >1.96, we regarded that the comparative analyses show the significant difference. $P<0.05$ was considered statistically significant. All analyses were performed using SAS, version 7.15 (SAS Institute, Inc, Cary, NC), and R, version 4.0.0 (R Development Core Team, Vienna, Austria).

Role of the Funding Source

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RESULTS

The present study includes data related to a total of 10 448 COVID-19 patients who were hospitalized in Korea from January 19, 2020, through April 16, 2020. As of April 24, 2020, 228 of these patients (2.18%) died. Among them, 533 statin and 1066 nonstatin users were examined in the nested case-control study.

The demographic and clinical characteristics of the patients in the cohort and the nested 1:2 matched study are summarized in Table 1. Of the patients, 60% were women. The median age of all patients was 45 years; of note, 4.8% were aged ≤19 years, 20.3% were aged 60 to 79 years, and 5.1% were aged ≥80 years. Furthermore, 38.1% had at least one preexisting comorbidity; 20.6% had hypertension, 17.9% had diabetes, 14.2% had COPD, and 4.5% had cancer. Patients prescribed

Table 1. Clinical Characteristics of COVID-19 Patients

		Overall cohort			1:2 PSM		
	Total (n=10448)	Nonstatin (n=9915)	Statin (n=533)	*P* value	Nonstatin (n=1066)	Statin (n=533)	*P* value
Age, y; mean (SD)	44.87 (19.81)	43.75 (19.53)	65.53 (12.17)	<0.0001	64.81 (15.98)	65.53 (12.17)	0.359
0–19, n (%)	503 (4.81)	502 (5.06)	1 (0.19)	<0.0001	6 (0.56)	1 (0.19)	0.003
20–59, n (%)	7293 (69.80)	7139 (72.00)	154 (28.89)		338 (31.71)	154 (28.89)	
60–79, n (%)	2124 (20.33)	1814 (18.30)	310 (58.16)		526 (49.34)	310 (58.16)	
80+, n (%)	528 (5.05)	460 (4.64)	68 (12.76)		196 (18.39)	68 (12.76)	
Sex (female), %	6264 (59.95)	5912 (59.63)	352 (66.04)	0.0032	704 (66.04)	352 (66.04)	1.000
Region				<0.0001			0.004
Daegu	6409 (61.34)	6027 (60.79)	382 (71.67)		687 (64.45)	382 (71.67)	
Non-Daegu	4039 (38.66)	3888 (39.21)	151 (28.33)		379 (35.55)	151 (28.33)	
Comorbidity							
Any ≥1 comorbidity	3979 (38.08)	3489 (35.19)	490 (91.93)	<0.0001	925 (86.77)	490 (91.93)	0.002
Hypertension	2149 (20.57)	1767 (17.82)	382 (71.67)	<0.0001	750 (70.36)	382 (71.67)	0.586
Diabetes	1874 (17.94)	1554 (15.67)	320 (60.04)	<0.0001	590 (55.35)	320 (60.04)	0.074
Coronary artery disease	633 (6.06)	521 (5.25)	112 (21.01)	<0.0001	188 (17.64)	112 (21.01)	0.103
Heart failure	345 (3.30)	294 (2.97)	51 (9.57)	<0.0001	107 (10.04)	51 (9.57)	0.767
Stroke	393 (3.76)	328 (3.31)	65 (12.20)	<0.0001	136 (12.76)	65 (12.20)	0.749
COPD	1487 (14.23)	1331 (13.42)	156 (29.27)	<0.0001	272 (25.52)	156 (29.27)	0.110
Cancer (any)	470 (4.50)	425 (4.29)	45 (8.44)	<0.0001	93 (8.72)	45 (8.44)	0.850
Chronic kidney disease	112 (1.07)	96 (0.97)	16 (3.00)	<0.0001	29 (2.72)	16 (3.00)	0.748
Death within 60 d	228 (2.18)	200 (2.02)	28 (5.25)	<0.0001	88 (8.26)	28 (5.25)	0.029

COPD indicates chronic obstructive pulmonary disorder; COVID-19, coronavirus disease 2019; and PSM, propensity score matching.

Table 2. Results of Univariable and Multivariable Regression Analysis for the COVID-19 Mortality Within 60 d (Overall Cohort)

	No. of patients	No. of deaths	HR	95% CI	*P* value
Univariable analysis					
Age, y (0–64)	8636	28	1	24.590–54.249	<0.0001
Age, y (65+)	1812	200	36.524		<0.0001
Sex (male)	4184	121	1	0.446–0.750	<0.0001
Sex (female)	6264	107	0.578		<0.0001
Comorbidity (upper, no; lower, yes)					
Hypertension	8299	51	1	10.321–19.245	<0.0001
	2149	177	14.093		<0.0001
Diabetes	8574	95	1	5.093–8.625	<0.0001
	1874	133	6.628		<0.0001
Coronary artery disease	9815	173	1	3.787–6.948	<0.0001
	633	55	5.129		<0.0001
Stroke	10055	182	1	5.078–9.703	<0.0001
	393	46	7.020		<0.0001
COPD	8961	136	1	3.179–5.397	<0.0001
	1487	92	4.142		<0.0001
Cancer (any)	9978	196	1	2.465–5.204	<0.0001
	470	32	3.581		<0.0001
Chronic kidney disease	10336	210	1	5.220–13.671	<0.0001
	112	18	8.447		<0.0001
Heart failure	10103	175	1	7.186–13.290	<0.0001
	345	53	9.772		<0.0001
Medication					
Nonstatin	9915	200	1	1.689–3.725	<0.0001
Statin	533	28	2.508		<0.0001
Multivariable analysis					
Age, y (0–64)	8636	28	1	10.487–25.646	<0.0001
Age, y (≥ 65+)	1812	200	16.400		<0.0001
Sex (male)	4184	121	1	0.427–0.723	<0.0001
Sex (female)	6264	107	0.556		<0.0001
Comorbidity (upper, no; lower, yes)					
Hypertension	8299	51	1	1.621–3.623	<0.0001
	2149	177	2.423		<0.0001
Diabetes	8574	95	1	1.118–2.000	0.0128
	1874	133	1.495		0.0128
Coronary artery disease	9815	173	1	0.613–1.206	0.3815
	633	55	0.860		0.3815
Stroke	10055	182	1	0.887–1.739	0.2080
	393	46	1.242		0.2080
COPD	8961	136	1	1.141–1.996	0.0040
	1487	92	1.509		0.0040
Cancer (any)	9978	196	1	0.743–1.617	0.6438
	470	32	1.096		0.6438
Chronic kidney disease	10336	210	1	1.038–2.814	0.0352
	112	18	1.709		0.0352
Heart failure	10103	175	1	1.294–2.577	0.0006
	345	53	1.826		0.0006
Medication					
Nonstatin	9915	200	1	0.425–0.953	0.0283
Statins	533	28	0.637		0.0283

Multivariable analysis adjusted for age, sex, history of comorbidities (hypertension, diabetes, cancer, COPD, stroke, coronary artery disease, heart failure, and chronic kidney disease) before diagnosis of COVID-19. COPD indicates chronic obstructive pulmonary disorder; COVID-19, coronavirus disease 2019; and HR, hazard ratio.

with statins were >20 years older with a higher number of comorbidities than that of the nonusers and accounted for 5.1% of the overall cases. On the other hand, most of variables in the nested matched study are balanced, compared with the overall cohort (Table II in the Data Supplement).

The crude HRs of elderly (>65 years) and hypertension were 36.5 ([95% CI, 24.6–54.2] $P<0.0001$) and 14.1 ([95% CI, 10.3–19.2] $P<0.0001$) in the overall cohort, respectively (Table 2). Even in the context of multivariate regression analysis, old age (>65 years) was by far the most important predictor of COVID-19–related mortality in patients. After adjusting for age, sex, and the history of comorbidities (hypertension, diabetes, cancer, COPD, stroke, coronary artery disease, heart failure, and chronic renal disease) before the diagnosis of COVID-19, Cox regression showed a significant decrease in HR associated with the use of statins (HR, 0.637 [95% CI, 0.425–0.953]; $P=0.0283$; Figure 1A). Next, the association of statins was stratified by age, sex, and comorbidities. A decreased risk of death with statin use was consistent across all subgroups (Figure 2). After PSM, Cox regression showed a more significant decrease in HR by 45% associated with the use of statins (HR, 0.553 [95% CI, 0.360–0.852]; $P=0.0071$; Table III in the Data Supplement).

Then, the HR of COVID-19 patients and a retrospective cohort of patients hospitalized with pneumonia between January and June 2019 was compared. Importantly, in 2019, there was no viral pneumonia epidemic in Korea, for example, due to severe acute respiratory syndrome or Middle East respiratory syndrome infection. Therefore, the 2019 pneumonia cohort was composed of bacterial and viral pneumonia patients combined. This retrospective cohort included 179 265 patients with a mean age of 39 years, of whom 49.4% were women. The most common comorbidity in the cohort was hypertension (33.3%), followed by COPD (25.1%), diabetes (23.4%), and any cancer (6.9%; Table IV in the Data Supplement). The mortality rate at 60 days was 7.4% and sharply increased among elderly patients (≥60 years); of note, it was even higher than that in the context of COVID-19 (Figure 1B). Moreover, after considering secondary factors, the results of the present study indicated a significantly lower risk of 60-day mortality in the context of the use of statins (HR, 0.519 [95% CI, 0.495–0.544]; $P<0.0001$; Tables V and VI in the Data Supplement both in the overall cohort and the 1:2 PSM). Of note, the HR values were comparable between COVID-19 patients and the retrospective cohort of patients hospitalized with pneumonia (2019) in Korea, in the context of the use of statins ($P=0.3244$ in the overall cohort, $P=0.7162$ in the 2:1 PSM; Table VIII in the Data Supplement).

DISCUSSION

In the present study, we showed that statins are not associated with COVID-19–related fatal outcomes. In fact, the use of statins correlated with significantly lower mortality in COVID-19 patients (by 36%).

Higher event rates in elderly patients with comorbidities are a common finding reported previously.[17] Of note, in this study, patients with comorbidities were much older than those without comorbidities. For example, the mean age of hypertensive patients was >20 years older than that of nonhypertensive patients. In fact, after adjusting

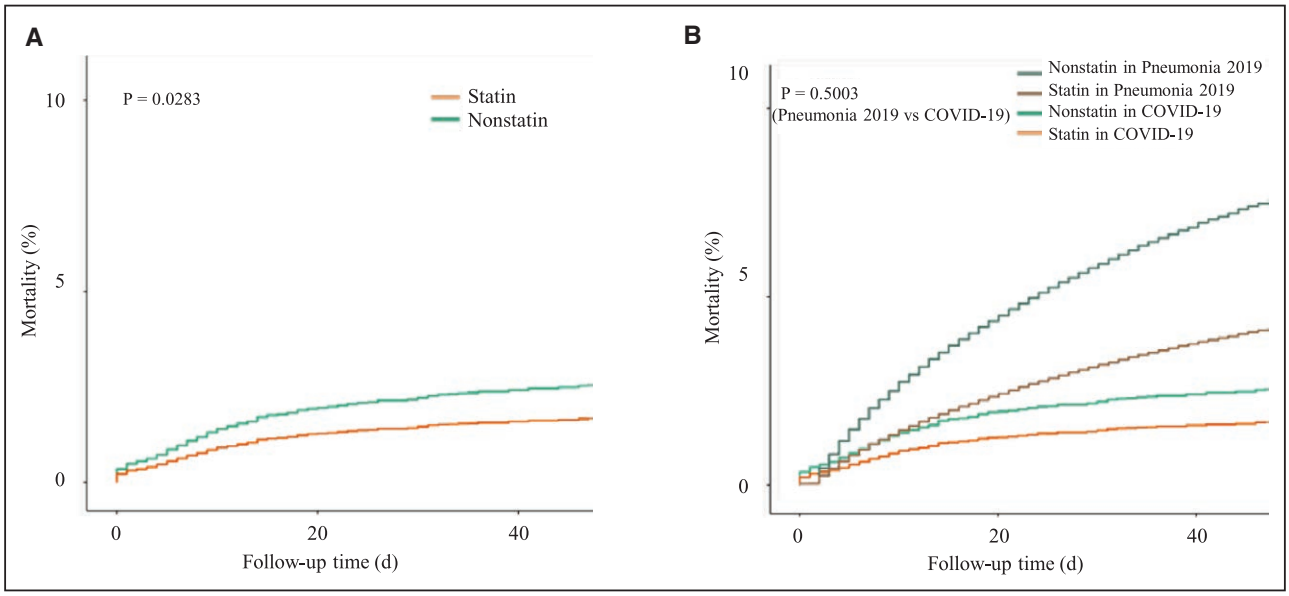

Figure 1. Survival within 60 d in severe acute respiratory syndrome coronavirus 2–infected patients and retrospective cohort of hospitalized pneumonia patients between January and June 2019 (overall cohort).
A, Comparison of statin-treated vs statin-nontreated coronavirus disease 2019 (COVID-19) patients (adjusted). **B**, Comparison of statin-treated vs statin-nontreated COVID-19 and hospitalized pneumonia patients between January and June 2019 (retrospective cohort; adjusted).

Subgroup	N	Event	Adjusted HR (95% CI)	P Value
Age				
0-64 YO	8636	28	1.832 (0.589-5.699)	0.2957
65+ YO	1812	200	0.578 (0.375-0.891)	0.013
Sex				
Male	4184	121	0.969 (0.582-1.613)	0.9034
Female	6264	107	0.361 (0.181-0.72)	0.0039
Hypertention				
No	8299	51	0.606 (0.142-2.586)	0.4984
YES	2149	177	0.635 (0.417-0.966)	0.0339
Diabetes mellitus				
No	8574	95	0.184 (0.045-0.753)	0.0186
YES	1874	133	0.809 (0.525-1.246)	0.3354
Coronary artery disease				
No	9815	173	0.66 (0.405-1.075)	0.0953
YES	633	55	0.648 (0.315-1.333)	0.2385
Stroke				
No	10055	182	0.702 (0.452-1.09)	0.1152
YES	393	46	0.427 (0.152-1.202)	0.107
COPD				
No	8961	136	0.383 (0.193-0.761)	0.0061
YES	1487	92	0.974 (0.58-1.638)	0.9223
Cancer (Any)				
No	9978	196	0.609 (0.394-0.942)	0.0259
YES	470	32	0.628 (0.212-1.867)	0.403
Chronic kidney disease				
No	10336	210	0.694 (0.46-1.048)	0.0821
YES	112	18	0.092 (0.01-0.837)	0.0342
Heart failure				
No	10103	175	0.538 (0.331-0.875)	0.0124
YES	345	53	1.024 (0.486-2.154)	0.9511

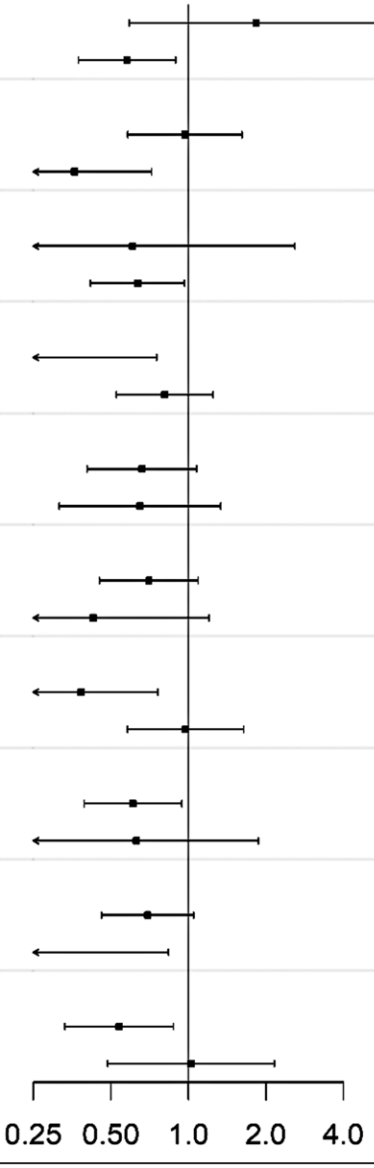

Figure 2. Hazard ratio (HR) for 60-d survival in the context of prior statin treatment: stratified subgroup analysis (overall cohort). COPD indicates chronic obstructive pulmonary disorder.

for secondary factors such as age and sex, our results revealed that the association between comorbidities and mortality was much reduced. However, still, patients with hypertension, diabetes, chronic kidney disease, or heart failure showed higher mortality compared with those without comorbidities.

The most important finding of our study was that prior use of statins was significantly associated with lower mortality in COVID-19 patients. There are a few recently published studies investigating the effect of the use of statins on COVID-19,[18,19] showing results consistent with those in our study. Moreover, this finding was consistent with previous meta-analyses in pneumonia patients[16,20] and also with pneumonia patients in Korea, in 2019, evaluated in this study. Lastly, this protective effect was supported by the potential inhibitory effect in the context of the SARS-CoV-2 main protease—a key coronavirus enzyme.[9] In spite of the controversy regarding the role ACE2, the detailed effect of statins has not been comprehensively evaluated.[21,22] As a result, the prescription of statins was reportedly reduced during the COVID-19 pandemic in the United States.[23] The concern is that the use of statins in COVID-19 patients may be further reduced due to possible drug interaction with antiviral/antibacterial agents and lower cholesterol levels in the acute stress condition.[24,25] However, our findings suggested that statins need not be discontinued during the COVID-19 treatment.

The current study has several limitations. First, data related to drug exposure were measured based on the claims data. Hence, detailed information about drug exposure, such as adherence to the medication or discontinuation during COVID-19 hospitalization, remains unknown. Second, the follow-up duration of the study was limited to a short period of time. However, most outcomes (86%) occurred within 2 weeks of the COVID-19 treatment. Third, although we evaluated a total of 10 448 COVID-19 patients who were hospitalized in Korea from January 19, 2020, through April 15, 2020, the interpretation of our findings is influenced by the limited sample size. To overcome this limitation, we compared the results with those obtained with a retrospective cohort of >170 000 pneumonia patients hospitalized from January to June 2019. The results indicated similar trends in COVID-19 and pneumonia cases. Lastly, although we performed PSM and multivariate analyses, there might be still a healthy user bias, for example, due to the healthy adherer effect or selective prescribing,[26] potentially influencing the association between the use of statins and lower mortality in COVID-19 patients. The healthy adherer effect might affect the observational study result, which reported that patients who showed complete compliance to antihypertensive medication regardless of either calcium channel blockers or angiotensin II receptor blockers had a lower risk of COVID-19.[27] Therefore, we cannot exclude the possibility that the healthy adherer effect confounded the report's finding.

CONCLUSIONS

Statins were associated with significantly lower mortality of COVID-19, consistent with usual pneumonia patients. Overall, the findings of this article suggest that statins might be considered as a part of the supportive regimen during the treatment of COVID-19. The prospective randomized studies might be warranted to confirm the benefit of statins in COVID-19.

ARTICLE INFORMATION

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Affiliations

Korean Society of Hypertension (H.-Y.L., W.B.P.). Department of Internal Medicine, Seoul National University College of Medicine, Korea (H.-Y.L., M.-d.O.). Department of Internal Medicine, Seoul National University Hospital, Korea (H.-Y.L., C.K.K., M.-d.O). Department of Public Health Sciences (J.A., J.P., S.-H.W.) and Institute of Health and Environment (S.-H.W.), Seoul National University, Korea. National Health Insurance Service, Wonju, Korea (D.W.K., J.-H.P., C.H.K.). Department of Benefits Strategy, National Health Insurance Service, Wonju, Korea (J.-H.P.). National Medical Center, Seoul, Korea (K.-H.C., J.-S.J.). Central Infectious Disease Hospital, Seoul, Korea (J.H.B.). National Committee for Clinical Management of Emerging Infectious Diseases, Korea (K.-H.C., J.H.B., M.-d.O.).

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Disclosures

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