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Atorvastatin Reduces the Severity of COVID-19: A Nationwide, Total Population-Based, Case-Control Study

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Abstract: Background: Statins have a pleiotropic effect in addition to a lipid-lowering effect. Several studies have demonstrated that statins may reduce the mortality and severity of infectious diseases, such as pneumonia or sepsis. We investigated the protective effects of various statins on the coronavirus disease 2019 (COVID-19) using a population-based cohort covering the entire Korean population. Methods: Consecutive patients diagnosed with COVID-19 between January 2020 and May 2020 were enrolled from the Korean National Health Insurance Service database. Current statin users were defined as patients who used statins within 30 days before the diagnosis of COVID-19. We compared the mortality and severity of COVID-19 between statin users and non-users to confirm the efficacy of statins. Results: Of the 7723 patients with COVID-19 who were enrolled, 255 died due to COVID-19 and 493 had severe COVID-19 (defined as mortality, admission to the intensive care unit, or mechanical ventilator use). Compared with non-users, atorvastatin users had a lower risk of COVID-19 mortality (odds ratio [OR], 0.54; 95% confidence interval [CI], 0.34–0.86) and severe COVID-19 (OR, 0.65; 95% CI, 0.45–0.93). However, other statins did not reduce the COVID-19 mortality and severity. Conclusions: Among the statins, only atorvastatin was effective in reducing the COVID-19 mortality and severity. Further randomized controlled trials are required to clarify the protective effects of atorvastatin.

Keywords: COVID-19; hydroxymethylglutaryl-CoA reductase inhibitors; atorvastatin; mortality; incidence

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1. Introduction

Statins, initially developed as antibiotic candidates because of their bacteriostatic effect, are currently the most widely used lipid-lowering medications. In addition to their effect on lipid metabolism, statins exert pleiotropic effects on oxidative stress and inflammation [1]. Moreover, statins exert antiplatelet and antithrombotic effects by reducing platelet activation and tissue factor activity [2,3]. Several studies have reported that statins may be beneficial in patients with bacterial sepsis or pneumonia [4–6]. Some studies have reported that statins have a protective effect on the prognosis of patients with viral infections, such as severe acute respiratory syndrome coronavirus (SARS-CoV) infection [7–10]. The pandemic coronavirus disease 2019 (COVID-19), currently ongoing worldwide, is an infectious disease caused by SARS-CoV-2. Some studies have demonstrated that the use of statins decreases COVID-19 severity or mortality [11–13]. However, no studies have confirmed whether the use of statins is related to the incidence and severity of COVID-19. This is an unanswered key question in the ongoing COVID-19 pandemic. There are various types of statins, and each type of statin has different characteristics. They may be hydrophilic or lipophilic. There are differences in enzymes that metabolize statins and potency that

lowers lipid levels. Pharmacokinetics and pharmacodynamics of statins differ according to the type of statin. In addition, the beneficial pleiotropic effects of statins in sepsis, cancer, and other diseases differ according to the type of statin [14–16]. Thus, this study aims to determine whether the incidence and severity of COVID-19 differ according to the type of statin used.

2. Methods

2.1. Study Design and Data Source

The Korean National Health Insurance Service COVID database contains health insurance claims data of approximately all patients with COVID-19 and test-negative control subjects confirmed up to 4 June 2020. The database includes information on demographics, use of medical services, medication prescriptions, and disease diagnosis from 1 January 2015 to 18 August 2020. This database was used to conduct the present nationwide, retrospective case-control study. Patients aged > 20 years with COVID-19 were considered case subjects and the date of COVID-19 diagnosis was considered the index date. Further, we randomly selected up to 10 control subjects who had tested negative for SARS-CoV-2 and were matched by sex, age, and residence with each case subject at the index date. The patient enrollment process is illustrated in Figure 1. We examined the underlying comorbidities and medication history before the index date for all subjects. In addition, we evaluated outcomes of case subjects after the diagnosis of COVID-19. This study was approved by the Institutional Review Board of the Korea University Anam Hospital (2020AN0292).

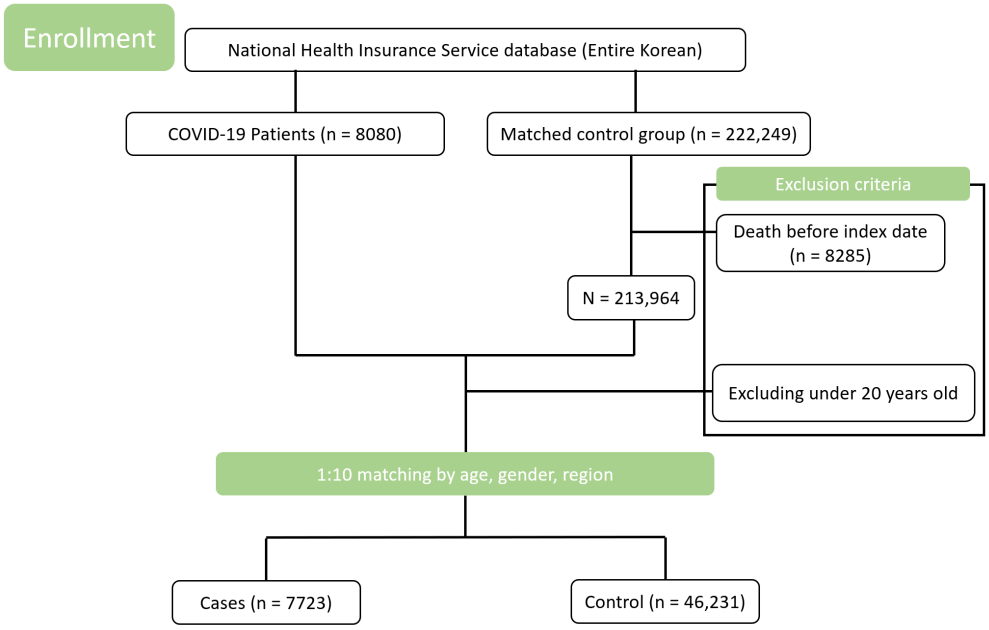

Figure 1. Disposition of subjects.

2.2. Exposure and Clinical Variables

The use of statins was defined as a record of statin prescriptions within 30 days before the index date. The use of other medications was defined as the same. A medical history of hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease (ischemic heart disease, peripheral arterial disease, or stroke), heart failure, chronic kidney disease, or cancer was defined based on claims data, which included the International Classification of Diseases, 10th revision (ICD-10) codes, and disease-related medication prescriptions before the index date. To determine the clinical outcomes of COVID-19, admission to the intensive care unit (ICU), mechanical ventilation use, and mortality were investigated. Severe COVID-19 was defined as a composite of admission to the ICU, mechanical ventilation use, and/or mortality.

2.3. Statistical Analysis

The clinical characteristics and use of statins were compared between the COVID-19 case group and the matched control group. The comparison data are presented as frequency and percentage. A conditional logistic regression analysis was performed using matched data to determine the difference in baseline and clinical characteristics between the two groups. Moreover, a conditional logistic regression analysis was performed to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for the association between the risk of COVID-19 and the use of statins after adjusting for socioeconomic status; presence of hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, chronic kidney disease, and cancer; and the use of anticoagulants and antiplatelet agents. Multiple logistic regression analysis was performed to compare COVID-19 mortality and severity between statin users and non-users among case subjects after adjusting for age; sex; residence; socioeconomic status; presence of hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, heart failure, chronic kidney disease, and cancer; and the use of anticoagulants and antiplatelet agents.

3. Results

3.1. Baseline Characteristics

This study enrolled 7723 patients with COVID-19 and 46,231 matched control subjects with negative test results for SARS-CoV-2 during the study period. The baseline characteristics of patients with COVID-19 and matched control subjects are listed in Table 1. Age, sex, and region of residence were not different between two groups. The prevalence of hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, heart failure, chronic kidney disease, and cancer was lower in the COVID-19 case group than in the matched control group.

Table 1. Demographic and clinical characteristics of patients with COVID-19 (case subjects) and subjects with negative test results (matched control subjects).

	Case Subjects		Matched Control Subjects		*p* *
N (%)	**(*n* = 7723)**		**(*n* = 46,231)**		
Age, mean (SD)	55.9 (14.4)		52.1 (16.2)		–
Male subjects	3056	(39.6)	21,366	(46.2)	–
City of residence					–
Seoul	515	(6.7)	5150	(11.1)	
Daegu	5036	(65.2)	20,108	(43.5)	
Gyung-gi	435	(5.6)	4350	(9.4)	
Gyung-buk	933	(12.1)	8583	(18.6)	
Other	804	(10.4)	8040	(17.4)	
Income					<0.001
Low	2767	(35.8)	12,163	(26.3)	
Middle	2180	(28.2)	14,736	(31.9)	
High	2776	(35.9)	19,332	(41.8)	
Medical history					
Hypertension	1914	(24.8)	13,991	(30.3)	<0.001
Diabetes mellitus	845	(10.9)	6152	(13.3)	<0.001
Dyslipidemia	1834	(23.7)	12,571	(27.2)	<0.001
Cardiovascular disease	1468	(19.0)	10,822	(23.4)	<0.001
Ischemic heart disease	74	(1.0)	1339	(2.9)	<0.001
Peripheral arterial disease	1253	(16.2)	8667	(18.7)	<0.001
Stroke	125	(1.6)	1353	(2.9)	<0.001
Heart failure	207	(2.7)	2213	(4.8)	<0.001
Chronic kidney disease	62	(0.8)	1505	(3.3)	<0.001
Cancer	660	(8.5)	9148	(19.8)	<0.001
Medications prescribed					
Statins	1162	(15.0)	8503	(18.4)	<0.001
Other lipid lowering agents	98	(1.3)	565	(1.2)	0.504
Antiplatelet agents	682	(8.8)	5562	(12.0)	<0.001
Anticoagulants	74	(1.0)	1135	(2.5)	<0.001

* *p* value by conditional logistic regression model.

3.2. Statin Use and COVID-19 Incidence

The percentage of statin users was lower in the COVID-19 case group than in the matched control group (15% vs. 18.4%, $p < 0.001$). Statin use was associated with a lower risk of COVID-19 in univariate analysis (OR, 0.72; 95% CI, 0.67–0.78, $p \leq 0.001$), but not in multivariate analysis (OR, 0.94; 95% CI, 0.85–1.04, $p = 0.209$). However, all types of statins, including atorvastatin and rosuvastatin, were not associated with a lower risk of COVID-19. Table 2 demonstrates the association between the use of statins and the risk of COVID-19.

Table 2. Association of the risk of coronavirus disease and use of statins in all study subjects.

	Case Subjects (*n* = 7723)	**Matched Control Subjects (*n* = 46,231)**	**Odds Ratio for COVID-19 (95% Confidence Interval)**			
	N (%)	**N (%)**	**Unadjusted**	***p***	**Adjusted ***	***p***
Use of any statins	1162 (15.0)	8503 (18.4)	0.72 (0.67–0.78)	<0.001	0.94 (0.85–1.04)	0.209
Type of statins						
Atorvastatin	550 (7.1)	4247 (9.2)	0.71 (0.64–0.78)	<0.001	0.92 (0.82–1.05)	0.210
Rosuvastatin	470 (6.1)	504 (1.1)	0.81 (0.73–0.89)	<0.001	0.92 (0.82–1.05)	0.215
Others	181 (2.3)	1198 (2.6)	0.89 (0.72–1.10)	0.294	1.07 (0.86–1.34)	0.558

p value by conditional logistic regression model. * Adjusted for socioeconomic status; presence of hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, heart failure, chronic kidney disease, and cancer; and use of anticoagulants and antiplatelet agents.

3.3. Statin Use and COVID-19 Mortality

A total of 255 (3.3%) of 7723 case subjects died during the study period. Table 3 presents the association between mortality risk and statin use in case subjects. After adjusting for confounding factors, statin use was not associated with COVID-19 mortality. The association between use of each statin and COVID-19 mortality was assessed. Atorvastatin was significantly associated with decreased COVID-19 mortality (OR, 0.53; 95% CI, 0.33–0.85, $p = 0.008$). However, rosuvastatin and other statins were not associated with COVID-19 mortality. Age; male sex; socioeconomic status; and history of diabetes mellitus, heart failure, chronic kidney disease, and cancer were correlated with COVID-19 mortality (Figure 2).

Table 3. Association of risk of mortality and use of statins in COVID-19 patients.

	Death (*n* = 255)	**Survival (*n* = 7468)**	**Odds Ratio for Death (95% Confidence Interval)**			
	N (%)	**N (%)**	**Unadjusted**	***p***	**Adjusted ***	***p***
Use of any statins	96 (37.7)	1066 (14.3)	3.63 (2.79–4.71)	<0.001	0.68 (0.45–1.03)	0.069
Type of statins						
Atorvastatin	51 (20.0)	499 (6.7)	3.49 (2.54–4.81)	<0.001	0.53 (0.33–0.85)	0.008
Rosuvastatin	30 (11.8)	440 (5.9)	2.13 (1.44–3.16)	<0.001	0.80 (0.48–1.33)	0.391
Others	18 (7.1)	163 (2.2)	4.31 (0.81–2.38)	<0.001	1.58 (0.75–3.30)	0.227

p value by multiple logistic regression model. * Adjusted for age; sex; residence; socioeconomic status, presence of hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, heart failure, chronic kidney disease, and cancer; and use of anticoagulants and antiplatelet agents.

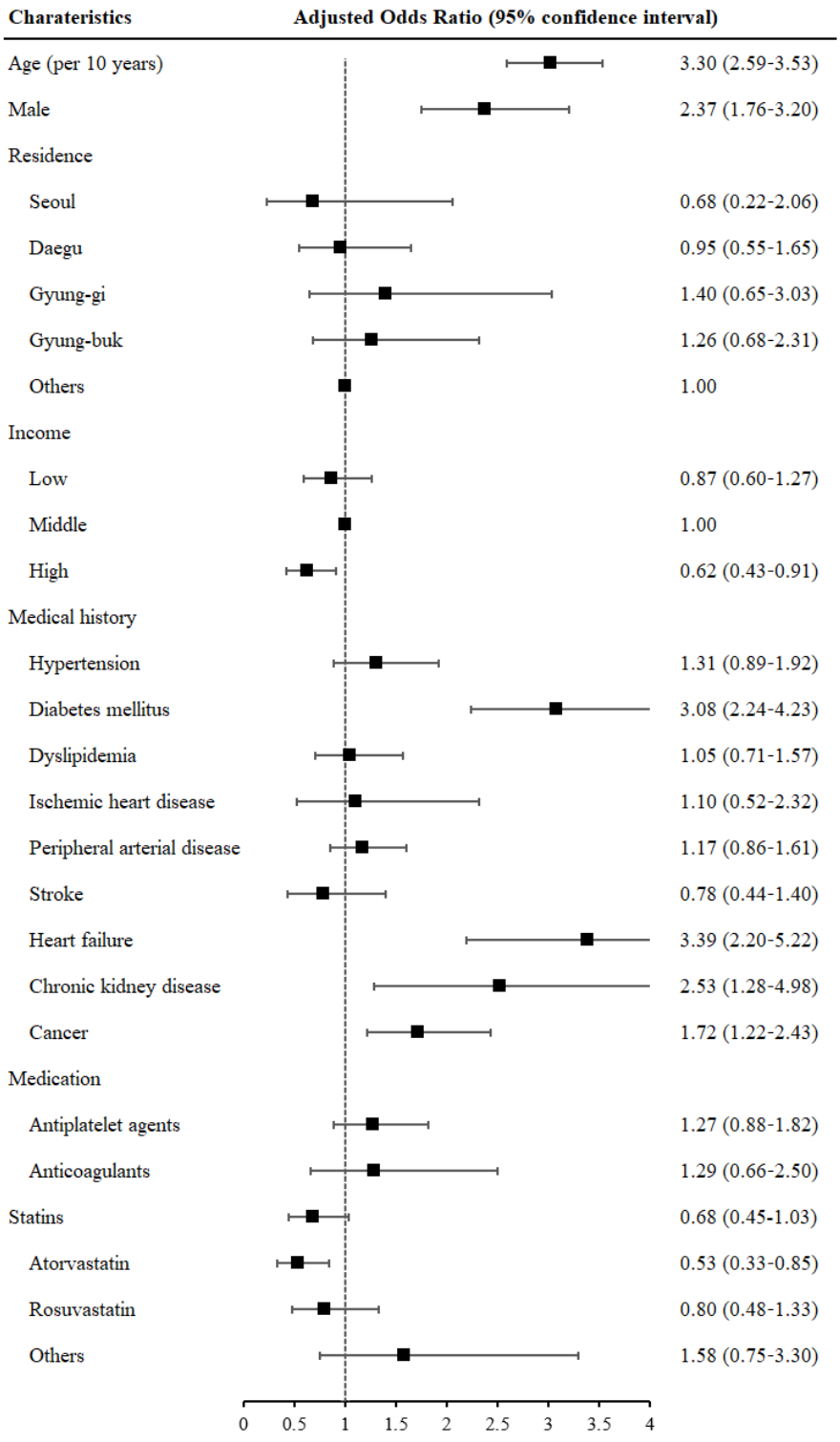

Figure 2. Forest plot based on odds ratios for COVID-19 mortality.

3.4. Statin Use and COVID-19 Severity

A total of 493 case subjects had severe COVID-19. Table 4 shows that statin use was associated with a lower risk of severe COVID-19 (OR, 0.72; 95% CI, 0.53–0.98, $p = 0.035$). Among statins, atorvastatin was associated with a lower risk of severe COVID-19 (OR, 0.65; 95% CI, 0.46–0.93, $p = 0.019$), but not rosuvastatin and other statins (OR, 0.74; 95% CI, 0.51–1.09, $p = 0.129$). The risk factors associated with the severity of COVID-19 were age;

male sex; socioeconomic status; and presence of diabetes mellitus, heart failure, chronic kidney disease, and cancer (Figure 3).

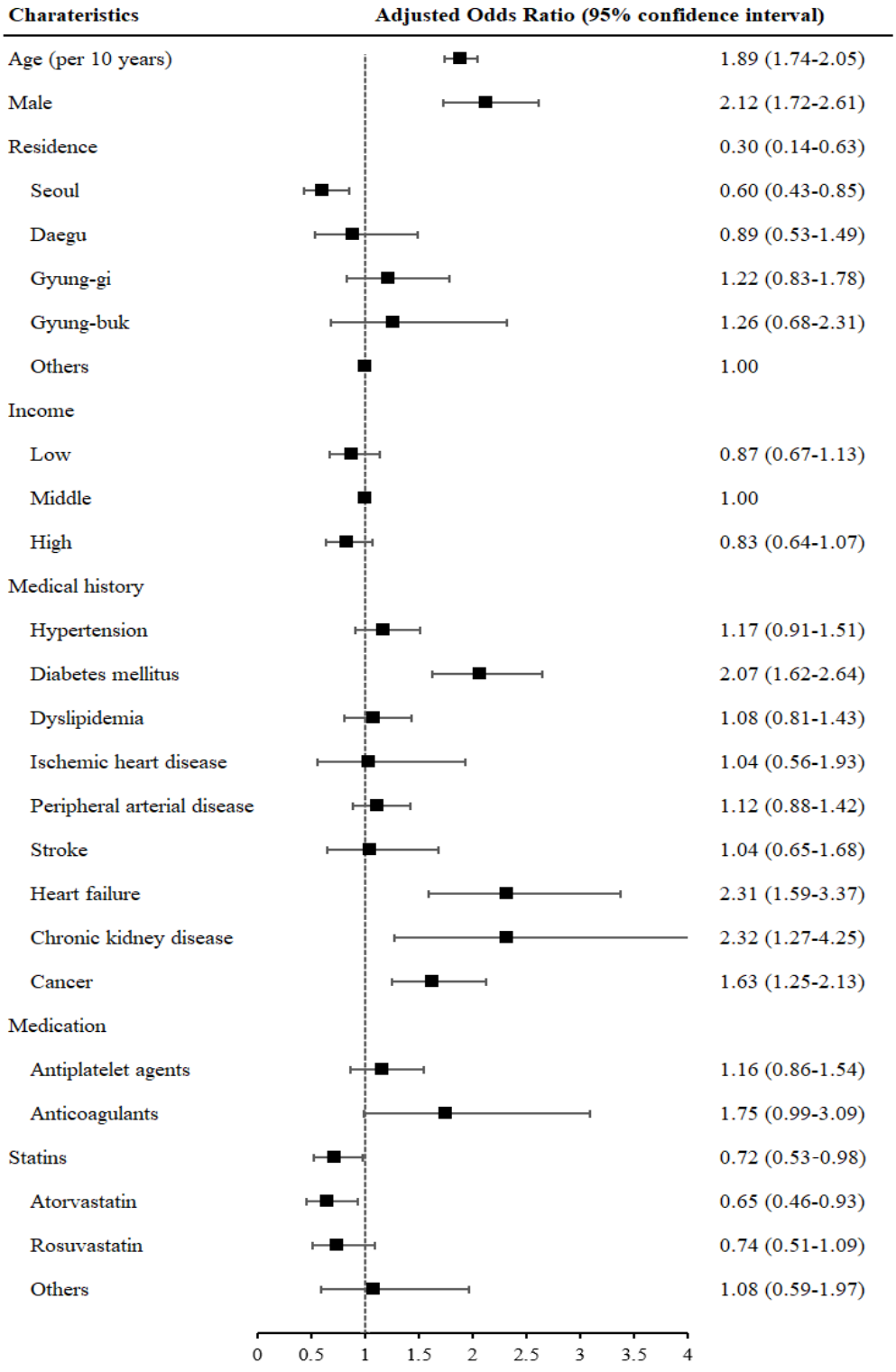

Figure 3. Forest plot based on odds ratio for COVID-19 severity.

Table 4. Association of the severity and use of statins in COVID-19 patients.

	Severe (*n* = 493)	**Mild (*n* = 7230)**	**Odds Ratio for Severity (95% Confidence Interval)**			
	N (%)	**N (%)**	**Unadjusted**	***p***	**Adjusted ***	***p***
Use of any statins	158 (32.0)	1004 (13.9)	2.93 (2.39–3.57)	<0.001	0.72 (0.53–0.98)	0.035
Type of statins						
Atorvastatin	84 (17.0)	466 (6.4)	2.98 (2.32–3.84)	<0.001	0.65 (0.46–0.93)	0.019
Rosuvastatin	52 (10.5)	418 (5.8)	1.92 (1.42–2.60)	<0.001	0.74 (0.51–1.09)	0.129
Others	28 (5.7)	153 (2.1)	2.90 (1.71–4.91)	<0.001	1.08 (0.59–1.97)	0.800

p value by multiple logistic regression model. * Adjusted for age; sex; residence; socioeconomic status; presence of hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, heart failure, chronic kidney disease, and cancer; and use of anticoagulants and antiplatelet agents.

4. Discussion

This was a Korean nationwide retrospective study. Antecedent use of statins was not associated with the risk of COVID-19; however, it was correlated with lower COVID-19 mortality and severity. However, the effect of reducing COVID-19 mortality and severity was only observed among patients using atorvastatin; this relationship was not statistically significant among patients using rosuvastatin. Atorvastatin and rosuvastatin have similar lipid-lowering potencies. The differences in outcomes related to COVID-19 may be due to different pleiotropic effects of each type of statin. The pleiotropic effect of each statin is different because of the difference in their pharmacokinetic and antiviral power [9,17–19].

In this study, only atorvastatin was associated with decreased COVID-19 severity and mortality. Several hypotheses can explain the fact that compared with other statins, atorvastatin has a greater effect on reducing the severity of COVID-19. First, atorvastatin has better antiviral effects than other statins—the direct mechanism. Atorvastatin can inhibit virus multiplication at an early stage and increase the viability of virus-infected cells [20]. A recent study has demonstrated that pretreatment with atorvastatin reduced the infection capacity and production of new viruses [8]. Second, compared with other statins, atorvastatin has a greater anti-inflammatory effect. Many studies consider the anti-inflammatory effect as mechanisms underlying the antiviral effect of statins [21–23]. In a meta-analysis by Alireali et al., atorvastatin had the highest effect of lowering interleukin 6, an inflammation marker, among several types of statins [24]. Beside interleukin 6 (IL-6), atorvastatin inhibits IL-8 and the adhesion molecule of the vascular cell-1 (VCAM-1) [25].

Third, compared with hydrophilic statins, lipophilic statins, such as atorvastatin, produce more membrane lipid raft clustering [26]. The process of endocytosis of coronaviruses requires angiotensin-converting enzyme 2, and a substantial portion of angiotensin-converting enzyme 2 is associated with membrane lipid raft clustering; thus, the use of lipophilic statins reduce viral entry and infectivity [27]. Fourth, lipophilic statins have a large distribution volume, permeate multiple organs, and reach all body tissues, including adipose tissue and tissues protected by functional barriers, such as the blood–brain barrier. Thus, compared with hydrophilic statins, lipophilic statins can effectively exert various antiviral effects, such as TLR4/MyD88/NF-kB and NLRP3 pathway modulation [28], antithrombotic effect [2], and prevention of endothelial dysfunction [29]. This is consistent with the findings that the lipophilic statins, simvastatin and atorvastatin, have more potent antibacterial activity than rosuvastatin [14,30]. A study to confirm that it affects the mortality and severity of COVID-19 will need to be conducted in the future, because the PCSK-9 (Proprotein convertase subtilisin/kexin type 9) inhibitor, a potent lipid-lowering agent, has a cardiovascular pleotropic effect, similarly to statins [31].

This study has several advantages, which differentiate this study from other retrospective studies that have investigated the relationship between statins and COVID-19. First, this is a nationwide population-based study. Other studies have reported a higher prevalence of comorbidities in the study population because they included only hospitalized severe patients [12,13]. A variety of underlying diseases may have affected the severity of

COVID-19 in those populations. However, in our study, the COVID-19 case group included healthy patients with fewer underlying diseases, considering the baseline characteristics compared with the matched control group. Our study analyzed real-world data of patients diagnosed with COVID-19. Second, patients in this study used drugs antecedently. Other studies have not confirmed whether the preemptive use of statins is related to the incidence of COVID-19; however, our study confirmed that the use of statins is associated with the incidence of COVID-19 [11–13].

This study has some limitations. First, no laboratory findings of case and matched control subjects were assessed. Hence, the lipid profile and degree of inflammation were not confirmed. In this study, only atorvastatin was related to the reduction in COVID-19 mortality and severity. One of the hypotheses for this finding is that atorvastatin is more effective in lowering inflammation than other types of statins. However, it was not possible to confirm the levels of interleukin 6 and C-reactive protein, the inflammation indicators, due to the lack of lipid profile data. Moreover, it was not possible to determine whether statins were used at appropriate doses. Second, the ICU admission criteria were not the same in all hospitals. This study used data of the entire Korean population. Thus, the case subjects in this study were treated in ICUs of several hospitals. However, because all hospitalized patients with COVID-19 were treated at national hospitals in Korea, the criteria for ICU admission were mostly controlled and the application criteria for mechanical ventilation did not significantly differ between hospitals. Third, differences in races were not studied. All the study subjects were Asian, and antiviral effects of statins may vary by race. Therefore, the results of this study may not be applicable to other races.

5. Conclusions

The use of statins was not associated with a lower risk of COVID-19. However, atorvastatin was associated with decreased COVID-19 mortality and severity. Appropriate use of atorvastatin may reduce COVID-19 mortality and severity. However, further randomized controlled trials are required to clarify the protective effects of atorvastatin.

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Conflicts of Interest: The authors declare no conflict of interest.

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