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RESEARCH ARTICLE

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Outpatient atorvastatin use and severe COVID-19 outcomes: A population-based study

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Abstract

Evidence of the effect of statins on patients with coronavirus disease (2019) COVID-19 is inconsistent. The aim of this study was to evaluate the association between chronic use of statins—both overall and by active ingredient—and severe outcomes of COVID-19 (risk of hospitalization and mortality), progression to severe outcomes, and susceptibility to the virus. We conducted a population-based case–control study with data from electronic records to assess the risk of (1) hospitalization: cases were patients admitted due to COVID-19 and controls were subjects without COVID-19; (2) mortality: cases were hospitalized patients who died due to COVID-19 and controls were subjects without COVID-19; (3) progression: cases were hospitalized COVID-19 subjects and controls were nonhospitalized COVID-19 patients; and (4) susceptibility: cases were patients with COVID-19 (both hospitalized and nonhospitalized) and controls were subjects without COVID-19. We collected data on 2821 hospitalized cases, 26 996 nonhospitalized cases, and 52 318 controls. Chronic use of atorvastatin was associated with a decreased risk of hospitalization (adjusted odds ratios [aOR] = 0.83; 95% confidence interval [CI]: 0.74–0.92) and mortality (aOR = 0.70; 95% CI: 0.53–0.93), attributable in part to a lower risk of susceptibility to the virus (aOR = 0.91; 95% CI: 0.86–0.96). Simvastatin was associated with a reduced risk of mortality (aOR = 0.59; 95% CI: 0.40–0.87). The wide degree of heterogeneity observed in the estimated odds ratios (ORs) of the different statins suggests that there is no class effect. The results of this real-world study suggest that chronic use of atorvastatin (and to a lesser degree, of simvastatin) is associated with a decrease in risk of severe COVID-19 outcomes.

KEYWORDS
atorvastatin, COVID-19, hospitalization, mortality, outpatient, statins

1 | INTRODUCTION

In recent decades, increased imbalances in the human–animal–ecosystem interaction,[1] driven by climate change, loss of biodiversity, the demographic explosion, globalization, and/or increased contact with wildlife, have given rise to a significant increase in emerging infectious diseases, including the 2019 coronavirus disease (COVID-19).[2]

The consequences of the lack of resources to tackle COVID-19 have highlighted the importance of having adequate means to prepare for new public health threats. In this respect, the World Health Organization (WHO) considers three action strategies to combat present and future pandemics effectively, that is, rapid diagnostic methods, vaccination, and therapeutic treatment.[3] In the case of COVID-19, challenges in the distribution and acceptance of vaccines,[4,5] as well as the vulnerability of elderly populations and/or populations with the presence of comorbidities,[6] make it necessary to have effective treatments that complement the vaccination plan, or alternatively, to provide treatment coverage in populations without access to vaccination.

Over the course of the pandemic, a number of medications indicated for chronic conditions have attracted attention as regards their possible effect on the susceptibility and severity of COVID-19.[7,8] In this same direction, a number of studies have reported that statins, which rank among the maintenance drugs most used by the elderly population and/or populations with comorbidities,[8] might improve prognosis of COVID-19.[9,10] The explanation for this possible protective activity of statins could lie in their many pleiotropic (or noncholesterol-dependent) effects, which include anti-inflammatory,[11] immunomodulator,[12] antithrombotic,[13] and antiviral properties.[14] Indeed, these medications have shown antiviral capacity in previous outbreaks, such as the H1N1/09 influenza[15] and Ebola virus pandemics.[16,17] It has also been suggested, on theoretical grounds, that they could be of use in severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) infections.[18]

To date, published studies (both observational and experimental) on the utility of statins in patients with COVID-19 report inconsistent results.[10,19–22] One of the possible causes of these discrepancies may be due to the structural diversity of statins, which endows them with significantly different properties.[23,24] Most of the studies, however, examine the effects of the pharmacological group of statins in general, without analyzing the effect of the active ingredients separately.[19] In the few studies of this type available, the results obtained also display inconsistencies.[25–27] Accordingly, the aim of our study was to evaluate the association between chronic use of statins—both overall and by active ingredient—and (1) severe COVID-19 outcomes (risk of hospitalization and mortality); (2) progression to severe COVID-19 outcomes; and (3) susceptibility to the virus.

2 | METHODS

2.1 | Study setting and population

The study population comprised all citizens of Galicia over 18 years of age who were beneficiaries of the Galician Health Service (GHS). This region, situated in the northwest of Spain, has a population of almost 3 million inhabitants, practically all of whom (98%) are covered by the GHS.

2.2 | Design

We used a population-based, case–control design. Cases (subjects with COVID-19, hospitalized and nonhospitalized) were selected by exhaustive sampling, and controls were drawn from the same population as cases, which enabled us to obtain a valid estimate of the prevalence of exposure and covariates in the source population. The study period was from March to December 2020.

2.3 | Cases and controls

We conducted a total of four substudies, which differed in their definitions of cases and controls (Figure 1 and Supporting Information: Table S1) to respond to each study's designated objectives, that is, the association between chronic use of statins and (1) risk of hospitalization; (2) risk of mortality; (3) progression to severe outcomes of COVID-19; and (4) susceptibility to the virus.

2.3.1 | Case–control 1: Severe COVID-19 outcomes—hospitalization

To analyze the risk of hospitalization due to COVID-19, cases were defined as all subjects with a confirmed diagnosis of COVID-19 (polymerase chain reaction [PCR+]) with a maximum gap of 10 days between PCR date and hospital admission and (1) with the reason for admission COVID-19 or (2) symptomatology compatible with COVID-19 (respiratory tract infection, viral pneumonia, shortness of breath, cough, fever, etc.), because in the first months of the pandemic, no specific coding was available.

Controls were randomly selected from among the general population that had no diagnosis of COVID-19 (no PCR+ test) in 2020 and were matched (up to 20 controls per case) by age, sex, primary-care service of reference, pandemic wave, and status of the health professional to ensure the same risk of exposure to SARS-CoV-2.

2.3.2 | Case–control 2: Severe COVID-19 outcomes—mortality

To assess the risk of mortality due to COVID-19, cases were defined as all subjects hospitalized for COVID-19

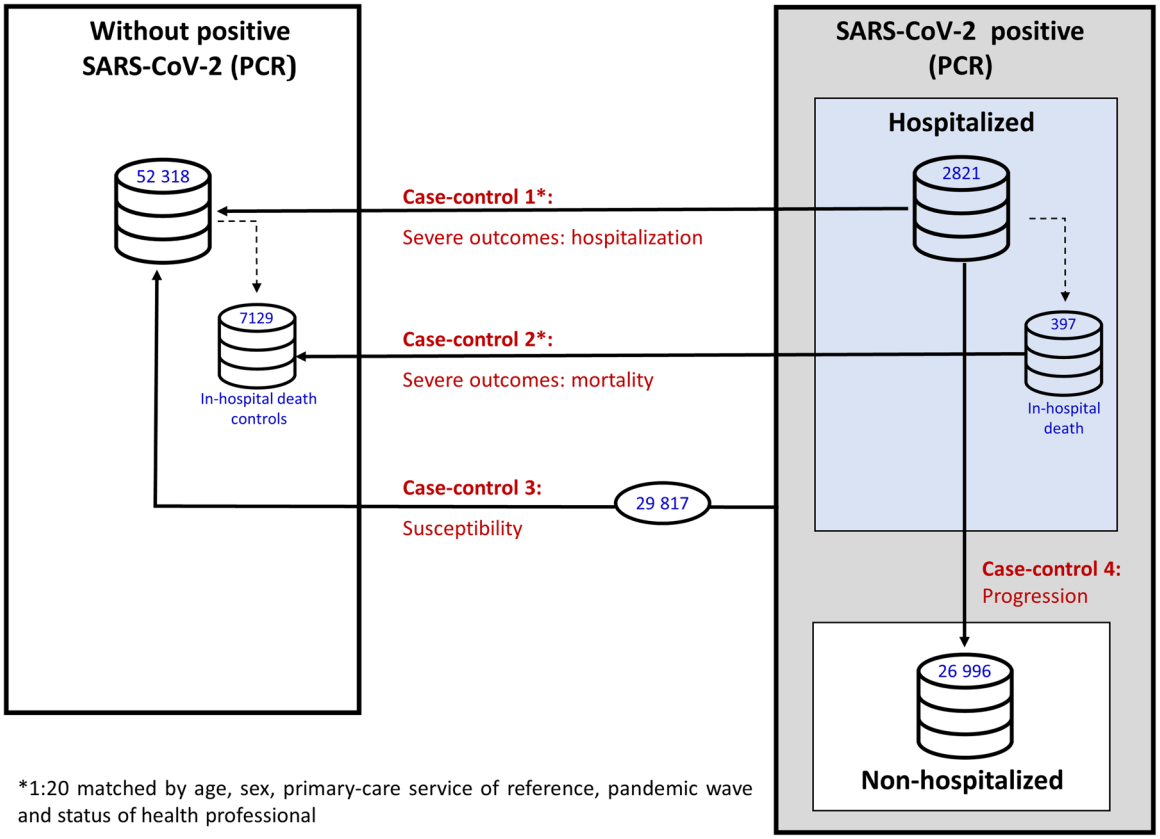

FIGURE 1 Population-based multiple case–control design.

(Case–control 1) who died during admission to any of the GHS hospitals in 2020.

The controls were the subgroup of controls from the case–control 1 substudy who were then matched with cases from this substudy.

2.3.3 | Case–control 3: Progression to severe COVID-19 outcomes

To study the risk of progression to severe COVID-19 outcomes, defined as infected patients' need for hospitalization due to COVID-19, cases were defined as all patients with COVID-19 (PCR+) hospitalized due to COVID in 2020 (Case–control 1).

Controls were all patients with COVID-19 (PCR+) who did not require hospital admission due to COVID-19 in 2020. In this model, the controls are not matched, so while a decrease in the study's effectiveness is to be expected, its validity is not affected.[28,29]

2.3.4 | Case–control 4: Susceptibility to the virus

To estimate the risk of infection, cases were all subjects that had a diagnosis of COVID-19 (PCR+) in 2020, both hospitalized and nonhospitalized.

As controls, we used the sample of subjects who had no diagnosis of COVID-19 (no PCR+) in 2020 (Case-control 1). As in the progression model, controls were also not matched.[28,29]

2.4 | Data sources and data collection

Real-world data were extracted from the Galician integrated healthcare database, which combines GHS system health records with other health databases (prescription and dispensing of medications, laboratory data, and National Health System hospital-discharge register [Minimum Basic Data Set (MBDS)/*Conjunto Mínimo Básico de Datos*]). We collected information on the clinical course of the disease, exposure to the drug under study, and other covariates. All data were extracted by an independent information technology company.

2.5 | Exposure

The variable of exposure was chronic use of statins (ATC C10AA code). We recorded data on statins prescribed and dispensed during each subject's follow-up period, which covered the 3 months immediately preceding the index date. The index date was defined as 10 days before diagnosis of COVID-19 (PCR+ test date), to prevent the presence of symptoms of the disease from altering exposure to the medication. For

controls, the index date was assumed to be the same as that of the cases with which they were matched.

Separate analyses were performed by pharmacological subgroup (C10AA) and by active ingredient, that is, simvastatin (C10AA01), lovastatin (C10AA02), pravastatin (C10AA03), fluvastatin (C10AA04), atorvastatin (C10AA05), rosuvastatin (C10AA07), and pitavastatin (C10AA08).

Study covariates included demographic and socioeconomic variables, hospitalization data and clinical variables of COVID-19 (where applicable), comorbidities (hypertension, diabetes mellitus, chronic obstructive pulmonary disease, obesity, ischaemic heart disease, cerebrovascular accident, heart failure, atrial fibrillation, chronic renal failure, cancer, asthma, and current smoker), and exposure to medications other than those specifically addressed by this study. To estimate patients' degree of chronicity, the number of different drugs prescribed and dispensed was used as a proxy.[30] All covariates were recorded across the 3 months preceding the index date.

2.6 | Statistical analysis

Owing to the structure of the data collected, we analyzed the outcome variables (severe COVID-19 outcomes, progression to severe outcomes, and susceptibility to the virus) using multilevel logistic regression.[31] These models have a number of advantages over conditional regression,[31–33] since they allow for (1) analysis of matched and unmatched models; (2) the introduction of random terms to control for heterogeneity of initial clusters and time periods; and (3) strata in which cases coincide in exposures with controls continue to count as events for the purpose of calculation and estimates.

To construct the models, the following four levels were considered: patient; case and control strata (for the severe COVID-19 outcomes models); health center; and pandemic wave. We used random effects to evaluate the effect of the pandemic wave and nested random effects for patients, case and control strata, and health area. Results were expressed as adjusted odds ratios (aORs) with their 95% confidence intervals (95% CIs), with adjustments being made for the above-mentioned covariates. We obtained adjusted estimates of the effect of treatment with statins (i.e., actually dispensed) in comparison with no lipid-lowering drug treatment. Statistical significance was set at 0.05, and all statistical analyses were performed using the free R statistical software programme (version 4.1.2).

3 | RESULTS

The breakdown of the 82 135 study patients was as follows: 2821 were hospitalized cases (PCR+), 397 of whom died during admission; 26 996 were nonhospitalized cases (PCR+); and 52 318 were subjects who did not test PCR+ during 2020.

The cohort's characteristics are defined in Tables 1 and 2.

TABLE 1 Demographic and clinical characteristics of COVID-19 cases and matched controls (severe outcomes: hospitalization and mortality).

	Severe COVID-19 outcomes			
	Hospitalization		Mortality	
Characteristic	Cases (*N* = 2821)	Controls (*N* = 52 318)	Cases (*N* = 397)	Controls (*N* = 7129)
Sex; *n* (%)				
Male	1457 (51.6)	26 998 (51.6)	236 (59.4)	4274 (60.0)
Female	1364 (48.4)	25 320 (48.4)	161 (40.6)	2855 (40.0)
Age, median (IQR)	74 (60–85)	73 (60–84)	84 (77–89)	84 (75–88)
Health professional; *n* (%)	78 (2.8)	1203 (2.3)	0 (0.0)	0 (0.0)
Comorbidities; *n* (%)				
Hypertension	1639 (58.2)	26 292 (50.3)	295 (74.3)	4687 (65.7)
Diabetes	782 (27.8)	10 233 (19.6)	157 (39.5)	1760 (24.7)
COPD	369 (13.1)	4305 (8.2)	87 (21.9)	875 (12.3)
Obesity	830 (29.5)	10 104 (19.3)	114 (28.7)	1536 (21.5)
Ischemic heart disease	326 (11.6)	4479 (8.6)	86 (21.7)	914 (12.8)
Cerebrovascular accident	277 (9.8)	3631 (6.9)	72 (18.1)	725 (10.2)
Heart failure	430 (15.3)	3780 (7.2)	106 (26.7)	796 (11.2)
Atrial fibrillation	425 (15.1)	5405 (10.3)	84 (21.2)	1137 (15.9)
Chronic renal failure	403 (14.3)	4059 (7.8)	99 (24.9)	882 (12.4)
Cancer	475 (16.9)	7277 (13.9)	98 (24.7)	1340 (18.8)
Asthma	267 (9.5)	3070 (5.9)	25 (6.3)	368 (5.2)
Current smoker	737 (26.1)	7842 (15.0)	83 (20.9)	866 (12.1)

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

TABLE 2 Demographic and clinical characteristics of COVID-19 cases and matched controls (progression to severe COVID-19 outcomes and susceptibility to the virus).

Characteristic	Progression to severe COVID-19 outcomes		Susceptibility to the virus	
	Cases (*N* = 2821)	Controls (*N* = 26 996)	Cases (*N* = 29 817)	Controls (*N* = 52 318)
Sex; *n* (%)				
Male	1457 (51.6)	11 217 (41.6)	12 674 (42.5)	26 998 (51.6)
Female	1364 (48.4)	15 779 (58.4)	17 143 (57.5)	25320 (48.4)
Age, median (IQR)	74 (60–85)	47 (33–63)	49 (34–67)	73 (60–84)
Health professional; *n* (%)	78 (2.8)	1238 (4.6)	1316 (4.4)	1203 (2.3)
Comorbidities; *n* (%)				
Hypertension	1639 (58.2)	6208 (23.0)	7847 (26.3)	26 292 (50.3)
Diabetes	782 (27.8)	2519 (9.3)	3301 (11.1)	10 233 (19.6)
COPD	369 (13.1)	759 (2.8)	1128 (3.8)	4305 (8.2)
Obesity	830 (29.5)	3960 (14.7)	4790 (16.1)	10 104 (19.3)
Ischemic heart disease	326 (11.6)	865 (3.2)	1191 (4.0)	4479 (8.6)
Cerebrovascular accident	277 (9.8)	867 (3.2)	1144 (3.8)	3631 (6.9)
Heart failure	430 (15.3)	678 (2.5)	1108 (3.7)	3780 (7.2)
Atrial fibrillation	425 (15.1)	1076 (4.0)	1501 (5.9)	5405 (10.3)
Chronic renal failure	403 (14.3)	712 (2.6)	1115 (3.7)	4059 (7.8)
Cancer	475 (16.9)	1755 (6.5)	2230 (7.5)	7277 (13.9)
Asthma	267 (9.5)	2170 (8.0)	2437 (8.2)	3070 (5.9)
Current smoker	737 (26.1)	4108 (15.2)	4845 (16.2)	7842 (15.0)

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

Among statin users, atorvastatin was the most popular, followed by simvastatin (Tables 3 and 4). In both cases, the doses most frequently dispensed were those of moderate intensity (68.0% and 62.1%, respectively).

3.1 | Severe COVID-19 outcomes—hospitalization

Evaluation of the risk of hospitalization was based on 2821 cases and 52 318 controls (Table 3). Statins as a whole displayed statistically significant differences (aOR = 0.87; 95% CI: 0.79–0.96, $p = 0.004$). In the analysis by active ingredient, atorvastatin (aOR = 0.83; 95% CI: 0.74–0.92, $p < 0.001$) showed a statistically significant reduction in the risk of hospitalization.

3.2 | Severe COVID-19 outcomes—mortality

Assessment of the risk of mortality was based on 397 cases and 7129 controls (Table 3). Statistically significant differences were observed for statins as a whole (aOR = 0.71; 95% CI: 0.56–0.90, $p = 0.005$). In the analysis by active ingredient, both atorvastatin (aOR = 0.70; 95% CI: 0.53 0.93, $p = 0.014$) and simvastatin (aOR = 0.59; 95% CI: 0.40–0.87, $p = 0.008$) showed a statistically significant reduction in risk of mortality.

3.3 | Progression to severe COVID-19 outcomes

A total of 2821 cases and 26 996 controls (nonhospitalized cases) were used to ascertain the risk of progressing to severe outcomes of COVID-19 (Table 1). No statistically significant differences were found for SSRIs overall or for any of the active ingredients individually.

3.4 | Susceptibility to the virus

In the analysis of the risk of SARS-CoV-2 infection, 82 315 patients were included: of these, 29 817 were COVID-19 cases (hospitalized and nonhospitalized) and 52 318 were controls (Table 4). A small significant reduction in risk was observed for statins as a whole (aOR = 0.94; 95% CI: 0.90–0.99, $p = 0.013$), and a reduction in risk of a slightly higher magnitude was observed for atorvastatin (aOR = 0.91; 95% CI: 0.86–0.96, $p < 0.001$).

TABLE 3 Severe COVID-19 outcomes: risk of hospitalization and mortality.

	Severe COVID-19 outcomes							
	Risk of hospitalization				Risk of mortality			
	CASES: PCR+ hospitalized (*N* = 2821)	CONTROLS: no PCR+(*N* = 52 318)	Adjusted OR[a] (95%CI)	*p* Value	CASES: PCR+ deceased (N = 397)	CONTROLS: no PCR+ (N = 7129)	Adjusted OR[a] (95%CI)	*p* Value
Statins (C10AA)	1009 (35.8)[b]	18 207 (34.8)[b]	0.87 (0.79–0.96)	0.004	164 (41.3)[b]	2896 (40.6)[b]	0.71 (0.56–0.90)	0.005
Simvastatin (C10AA01)	276 (9.8)	5272 (10.1)	0.91 (0.79–1.04)	0.168	33 (8.3)	824 (11.6)	0.59 (0.40–0.87)	0.008
Lovastatin (C10AA02)	4 (0.1)	54 (0.1)	1.21 (0.43–3.39)	0.721	2 (0.5)	8 (0.1)	3.65 (0.75–17.80)	0.109
Pravastatin (C10AA03)	73 (2.6)	1220 (2.3)	0.95 (0.74–1.22)	0.692	13 (3.3)	199 (2.8)	0.82 (0.44–1.51)	0.524
Fluvastatin (C10AA04)	17 (0.6)	205 (0.4)	1.40 (0.85–2.33)	0.190	5 (1.3)	34 (0.5)	2.14 (0.78–5.88)	0.141
Atorvastatin (C10AA05)	538 (19.1)	9732 (18.6)	0.83 (0.74–0.92)	<0.001	95 (23.9)	1603 (22.5)	0.70 (0.53–0.93)	0.014
Rosuvastatin (C10AA07)	83 (2.9)	1469 (2.8)	0.84 (0.66–1.06)	0.149	16 (4.0)	193 (2.7)	0.95 (0.54–1.69)	0.868
Pitavastatin (C10AA08)	29 (1.0)	420 (0.8)	1.10 (0.75–1.63)	0.615	4 (1.0)	67 (0.9)	0.84 (0.30–2.39)	0.750

Abbreviation: OR, odds ratio.

[a]Adjusted for: sex, age, status of health professional, comorbidities (hypertension, diabetes, COPD, obesity, ischemic heart disease, cerebrovascular accident, heart failure, atrial fibrillation, chronic renal failure, cancer, asthma, current smoker), current use of other pharmacological treatment, and number of treatments for chronic diseases. Additionally, the primary-care service of reference and the pandemic wave were included as random effects.

[b]The overall number of subjects exposed to statins (C10AA) is lower than the sum of those exposed to the active ingredients of individual statins (C10AA01, C10AA02, C10AA03, C10AA04, C10AA05, C10AA07, C10AA08), due to the fact that some subjects were exposed to more than one statin across the study period.

TABLE 4 Progression to severe COVID-19 outcomes and susceptibility to the virus.

	Progression to severe COVID-19 outcomes				Susceptibility to the virus			
	CASES: PCR+ cases hospitalized (*N* = 2821)	CONTROLS: PCR+ nonhospitalized (*N* = 26 996)	Adjusted OR[a] (95% CI)	*p* Value	CASES: PCR+ hospitalized & nonhospitalized (*N* = 29 817)	CONTROLS: no PCR+ (N = 52 318)	Adjusted OR[a] (95%CI)	*p* Value
Statins (C10AA)	1009 (35.8)[b]	4181 (15.5)[b]	0.95 (0.84–1.05)	0.332	5190 (17.4)[b]	18 207 (34.8)[b]	0.94 (0.90–0.99)	0.013
Simvastatin (C10AA01)	276 (9.8)	1202 (4.5)	0.94 (0.80–1.10)	0.422	1478 (5.0)	5272 (10.1)	0.98 (0.92–1.05)	0.623
Lovastatin (C10AA02)	4 (0.1)	6 (0.0)	1.22 (0.29–5.18)	0.784	10 (0.0)	54 (0.1)	0.94 (0.46–1.92)	0.862
Pravastatin (C10AA03)	73 (2.6)	240 (0.9)	1.15 (0.84–1.56)	0.386	313 (1.0)	1220 (2.3)	0.88 (0.77–1.01)	0.073
Fluvastatin (C10AA04)	17 (0.6)	27 (0.1)	1.93 (0.95–3.88)	0.067	44 (0.1)	205 (0.4)	0.95 (0.67–1.35)	0.774
Atorvastatin (C10AA05)	538 (19.1)	2204 (8.2)	0.95 (0.83–1.08)	0.411	2742 (9.2)	9732 (18.6)	0.91 (0.86–0.96)	<0.001
Rosuvastatin (C10AA07)	83 (2.9)	420 (1.6)	0.85 (0.65–1.12)	0.241	503 (1.7)	1469 (2.8)	0.97 (0.87–1.09)	0.635
Pitavastatin (C10AA08)	29 (1.0)	105 (0.4)	1.17 (0.74–1.86)	0.508	134 (0.4)	420 (0.8)	1.08 (0.88–1.34)	0.456

Abbreviation: OR, odds ratio.

[a]Adjusted for: sex, age, status of health professional, comorbidities (hypertension, diabetes, COPD, obesity, ischemic heart disease, cerebrovascular accident, heart failure, atrial fibrillation, chronic renal failure, cancer, asthma, current smoker), current use of other pharmacological treatment, and number of treatments for chronic diseases. Additionally, the primary-care service of reference and the pandemic wave were included as random effects.

[b]The overall number of subjects exposed to statins (C10AA) is lower than the sum of those exposed to the active ingredients of individual statins (C10AA01, C10AA02, C10AA03, C10AA04, C10AA05, C10AA07, C10AA08), due to the fact that some subjects were exposed to more than one statin across the study period.

4 | DISCUSSION

In this large population-based case–control study, chronic use of atorvastatin was associated with a lower risk of hospitalization (aOR = 0.83; 95% CI: 0.74–0.92, $p < 0.001$) and mortality (aOR = 0.70; 95% CI: 0.53–0.93, $p = 0.014$), attributable in part to a lower risk of susceptibility to SARS-CoV-2 (aOR = 0.91; 95% CI: 0.86–0.96, $p < 0.001$). Our results also indicate that simvastatin appears to be associated with an important decrease in risk of mortality (aOR = 0.59; 95% CI: 0.40–0.87, $p = 0.008$). The wide degree of heterogeneity observed in the estimated ORs of the different statins suggests that there is no class effect and that the effect of each statin must therefore be considered individually.

This study's large sample size enabled us to analyze the effect of statins by active ingredient, on the following outcome variables: (1) severe COVID-19 outcomes (defined as risk of hospitalization and mortality); (2) progression to severe outcomes; and (3) susceptibility to the virus. We were thus able to ascertain the role played by each in the clinical course of the disease. Specifically, we found relevant results for atorvastatin and simvastatin, the statins with the greatest prevalence of use in the study population and overall.[34,35]

Another important finding of our study is that the clinical benefits of statins in COVID-19 would not seem to be due to a class effect, in view of the variability observed in the estimated ORs of the respective active ingredients. Indeed, there is strong evidence to show that statins display independent pleiotropic effects of the common lipid-lowering mechanism of action and that these differ among the active ingredients.[36] Furthermore, pharmacokinetic characteristics might also have an influence on the protective capacity against COVID-19, since lipophilic statins, such as atorvastatin and simvastatin, show a wider tissue distribution and are thus able to exert protective effects on a greater number of tissues.[37] Hence, we feel that the results obtained by our study for statins as a whole could be due to the reduction in risk observed in the two most used active ingredients (atorvastatin and simvastatin).

The important reduction in risk of mortality associated with chronic use of atorvastatin (30%; 95% CI: 7%–47%) is in line with previous observational studies.[37–41] Comparison with experimental studies is more complicated because, in these types of studies, treatment commences when the disease has already been contracted, thereby rendering it impossible (i) to assess the possible effect on susceptibility to the virus (something which, in the case of our study, is taken into account by design) and (ii) to evaluate chronic use, which is precisely what is thought to have a protective effect against COVID-19.[19,42,43] We found only one study that examined the association between atorvastatin and risk of hospitalization due to COVID-19,[38] and reported a very similar effect magnitude (0.89; 95% CI: 0.84–0.95) versus (0.83; 95% CI: 0.74–0.92). Although hospitalization is more dependent on clinical criteria and the availability of hospital beds, it may be of great interest in public health.[44,45] Thus, our findings regarding the marked reduction in risk of hospitalization and mortality associated with atorvastatin, taken together with its benefit-risk-cost ratio,[40] could imply that consideration should be given to atorvastatin being recommended as a first-line drug for patients with indication of lipid-lowering treatment, in situations of high COVID-19 incidence.

Insofar as simvastatin is concerned, our mortality results are also consistent with the scant literature available.[34,37,38] Due to this drug's potential as adjuvant treatment for COVID-19 described in preclinical models,[46,47] we feel that the mortality-related results obtained by us should be the subject of further epidemiological research.

The main strengths of this study are its large sample size (encompassing more than 82 000 subjects) and adjustment for many confounding variables, which enabled us to accurately estimate the possible association between chronic use of different statins and prognosis of COVID-19 (susceptibility, progression to severe COVID-19 outcomes, hospitalization, and mortality). Furthermore, exposure to drugs was based on dispensing data (i.e., medications really acquired by patients), unlike other studies which use prescription-based data sources (prescriptions issued).

The study also has several limitations. First, the fact of it being an observational study with secondary databases means that one cannot rule out the existence of residual confounding of unmeasured or misclassified covariates, such as the absence of data on the degree of severity of the main comorbidities associated with greater COVID-19 severity. Second, the lack of matching in the substudies on susceptibility and progression to severe COVID-19 outcomes could be considered a further limitation. Even so, this circumstance has no impact on the validity of the study, since the absence of matching would only result in lower effectiveness rather than a higher risk of biases.[28,29] Finally, the data available for study purposes pertain to 2020, when the predominant SARS-CoV-2 variants in this country were those of the 19B clade.[48] That said, however, we have no reason to believe that the effect of atorvastatin (and simvastatin) against COVID-19 might be influenced by the presence of dominant variants.

5 | CONCLUSIONS

Despite notable scientific and medical advances, COVID-19 continues to be a public health threat. In present and future pandemics alike, rapid identification of known effective therapies is fundamental,[49] and to this end, it is necessary to distinguish between drug-class targets and molecule-specific mechanisms. Our results show that chronic use of atorvastatin (and possibly, of simvastatin) is associated with a reduction in severe COVID-19 outcomes. Given that the prevalence of statin use is very high in developed countries,[50] a great number of people could be doubly benefited (i.e., COVID-19 and cardiovascular prevention) by treatment with atorvastatin.

AUTHOR CONTRIBUTIONS

Irene Visos-Varela: Writing original draft preparation. **Maruxa Zapata-Cachafeiro**: Conceptualization; methodology; writing—review and editing. **Samuel Pintos-Rodríguez**: Writing—review and

editing. **Rosendo Bugarín-González**: Methodology; writing—review and editing. **Francisco Javier González-Barcala**: Methodology; writing—review and editing. **Maria T. Herdeiro**: Methodology; writing—review and editing. **María Piñeiro-Lamas**: Formal analysis. **Adolfo Figueiras**: Conceptualization; methodology; funding acquisition; writing—review and editing. **Ángel Salgado-Barreira**: Conceptualization; methodology; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data sets generated and analyzed during the current study are not publicly available due to Galician Public Health System restrictions.

ETHICS STATEMENT

The study was approved by the Galician Clinical Research Ethics Committee (reference 2020-349), certified by the Spanish Agency of Medicines and Medical Devices, and conducted in accordance with the Helsinki Declaration and Spanish legislation governing biomedical studies and respect for human rights. The study protocol was registered at the European Union Electronic Register of Post-Authorisation Studies (EU PAS, reg. no. EUPAS44587) and is available online at https://www.encepp.eu/encepp/viewResource.htm?id=44588. Data extraction was automated and anonymous to ensure subjects' confidentiality and privacy.

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