EFFECT OF STATIN THERAPY ON SARS-CoV-2 INFECTION-RELATED MORTALITY IN HOSPITALIZED PATIENTS

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ABSTRACT:

Aim:

Assessing the effect of statin therapy at hospital admission for COVID-19 on in-hospital mortality.

Methods and Results:

Retrospective observational study. Patients taking statins were 11 years older and had significantly more comorbidities than patients who were not taking statins. A genetic matching (GM) procedure was performed prior to analysis of the mortality risk. A Cox proportional hazards model was used for the cause-specific hazard (CSH) function, and a competing-risks Fine and Gray (FG) model was also used to study the direct effects of statins on risk.

Data from reverse transcription-polymerase chain reaction-confirmed 2157 SARS-CoV-2-infected patients (1234 men, 923 women; age: 67 y/o (IQR 54-78)) admitted to the hospital were retrieved from the clinical records in anonymized manner. 353 deaths occurred. 581 patients were taking statins. Univariate test after GM showed a significantly lower mortality rate in patients on statin therapy than the matched non-statin group (19.8% vs. 25.4%, χ^2 with Yates continuity correction: p= 0.027). The mortality rate was even lower in patients (n=336) who maintained their statin treatments during hospitalization compared to the GM non-statin group (17.4%; p=0.045). The Cox model applied to the CSH function (HR=0.58(CI: 0.39-0.89); p=0.01) and the competing risks FG model (HR=0.60(CI: 0.39-0.92); p = 0.02) suggest that statins are associated with reduced COVID-19-related mortality.

Conclusions:

A lower SARS-CoV-2 infection-related mortality was observed in patients treated with statin therapy prior to hospitalization. Statin therapy should not be discontinued due to the global concern of the pandemic or in patients hospitalized for COVID-19.

Keywords: SARS-CoV-2, COVID-19, Statins, Cardiovascular risk, Mortality.

INTRODUCTION

The once-in-a-century pandemic caused by the SARS-CoV-2 virus has spread worldwide. More than 25 million people have been infected less than 1 year from the first reported case in Wuhan, and nearly one million people have died. Many questions about the pathophysiology of the SARS-CoV-2 infection are unanswered. The coronavirus virus enters the cells via binding to the angiotensin-converting enzyme 2 (ACE2) protein, which is located on the cell surface of different tissues. The virus triggers an overwhelming inflammatory and thrombotic response in severe cases after intracellular replication, which leads to severe lung injury (COVID-19) and multiorgan failure[1]. Approximately 15% of patients admitted to the hospital require invasive therapies in intensive care units, and approximately one in five of these patients die[2].

The reasons why some patients remain asymptomatic and others develop a deadly disease are not known. Several prognostic factors were identified, such as age (maximum lethality in the elderly), sex, race and comorbidities, including hypertension, cardiovascular diseases, obesity and diabetes, are the frequently reported in the more severely ill patients[3].

The effects of background therapies on prognosis was examined. The relevance of ACE2 in the pathogenesis of the disease highlights the role of drugs targeting the renin-angiotensin-aldosterone axis and increasing ACE2 expression, and the withdrawal of these therapies was recommended[4]. However, the clinical data show no effect or a protective effect of these therapies[5].

Statins are among the more frequently prescribed drugs in the general population. Statins block an early stage of cholesterol synthesis by inhibiting the enzyme hydroxy-methyl-glutaryl CoA reductase. Statins also modulate the production of some downstream intermediates in the

cholesterol synthesis cascade, which affects several intracellular pathways. Statins alter lipid oxidation, inflammation, immunomodulation and endothelial function, which are involved in COVID-19 pathophysiology[6]. *In silico* data suggest that statin molecules interfere with the main protease of SARS-CoV-2, which suggests a potential inhibitory effect on virus replication[7]. Therefore, statins were proposed as adjuvant therapy for COVID-19[8,9]. In contrast, statins upregulated ACE2 in animal models[10]. Statins may also increase the myopathy associated with COVID-19, and its drug-to-drug interaction profile should be considered, particularly when antiretroviral therapies are administered[11].

The effect of statins on viral infections was tested. Several studies reported a beneficial effect of statins on influenza outbreaks[12], but inconclusive results were also reported[13]. Statins are associated with a better prognosis of other viral infections[14,15,16]. The administration of statin therapy to Chinese patients with COVID-19 during hospitalization was associated with a better prognosis[17]. However, negative outcomes were reported in clinical trials of rosuvastatin and simvastatin in patients with acute respiratory distress syndrome (ARDS)[18], which contributes to the reluctance of clinicians to consider statin therapy in patients with COVID-19[19].

The present study clarified the potential benefits of pre-existing statin therapy on the clinical severity of patients admitted to the hospital for a SARS-CoV-2 infection.

PATIENTS AND METHODS

Study Design

This study used a retrospective observational design. Members of the Lipids and Arteriosclerosis Units Net (XULA) of Catalonia (Spain) were invited to retrieve clinical data of

consecutive patients who were admitted to their hospitals because of a SARS-CoV-2 infection. Nineteen hospitals participated in recruitment (Cohort registration code NCT04407273-STACOV).

Data acquisition and confidentiality

An ad hoc common database that included data on anthropometry, personal medical antecedents, the lipoprotein profile, statins and other lipid-lowering drugs and other therapies prior to admission and clinical data recorded during SARS-Cov-2 infection was designed. An instruction manual with clinical definitions was provided to each centre (supplementary material on-line).

All collected data were anonymized. All procedures were performed in accordance with legal provisions of the protection of personal data in Spain and European Union Regulations (EU) 2016/6799 on the physical protection of the treatment of personal data. The study was compliant with the Declaration of Helsinki. The Ethics Committee of the University Research Institute "Pere Virgili" (Reus) approved the study, including the exemption of the requirement for informed consent.

Eligibility criteria

Consecutive patients aged at least 18 years who were admitted to the hospital for at least 24 hours were eligible. Only data from patients with a definite SARS-CoV-2 diagnosis using reverse transcription-polymerase chain reaction (PCR) and whose infections were acquired in the community were included.

The exposure of interest was the patient's use of statin therapy in the previous year based on the clinical records. The statin therapy was categorized as high intensity (80 mg/day

atorvastatin and 20 mg/day rosuvastatin) or low-moderate intensity. The maintenance of therapy during hospitalizations (as included in the medical orders for at least 48 hours) was also recorded.

Main objective

The present study assessed the effect of background statin therapy on in-hospital SARS-CoV-2 infection-related mortality. The secondary objectives were the effects of statin therapy on surrogate markers of clinical severity.

Statistical analyses

Continuous variables were tested for normality using the Kolmogorov-Smirnov test. Data are presented as medians and 25th and 75th percentiles for continuous variables with a non-normal distribution or means and standard deviations (SD) for variables with a normal distribution. Differences between groups were analysed using the non-parametric Mann-Whitney test or Student's parametric t test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables.

Patients on statins were older and had more comorbidities than patients not on statins. To determine the association between statin treatment and mortality, we matched patients from our statin and no-statin groups to balance their baseline characteristics. We used a genetic matching (GM) (supplementary material reference [S1 S2]) procedure because the usual propensity score matching techniques failed to achieve acceptable balance. The GM uses a genetic search algorithm to iteratively determine the weight of each of the covariates to find an optimal balance between matched groups. The matching was 1:1 with replacement and ties (so that one treated unit could be matched to more than one untreated unit after weighting them appropriately) and

without callipers. We included all clinical variables prior to hospital admission in the matching procedure. A summary of matching results using standardized differences before and after is provided as supplementary material on-line (*Table S1*).

For the matched set, we constructed two types of survival models, a Cox proportional hazards model applied to a cause-specific hazard (CSH) function[S3] and a competing-risks Fine and Gray (FG) mode [S4 S5]. Models were constructed for a 6-week follow-up.

The CSH considered hospital discharge as a censoring event, i.e., incorporated the assumption that discharged individuals will not die from COVID-19 and are therefore different from simply censored individuals. Although this model under-estimates absolute survival probability, it allowed us to interpret aetiological relationships between covariates (specifically, statin use) and patient outcomes[S4].

The FG model computes the probability of any event (in our case, death or discharge) at time "t" based on the assumption that no other event has occurred. Therefore, it may be used to predict events[S6], and it complements the CSH interpretation. This procedure was performed using a sub-distribution hazard function[S5].

We checked the proportional hazards assumption model and the proportionality of the sub-distribution from the FG model. We stratified all models based on sex because it strongly violated these assumptions. Other smaller violations were ignored. The statins treatment hazard ratio was estimated using the (robust) Huber sandwich estimator.

For the CSH model, we provide survival estimate curves for participants stratified by sex to visualize the effects of statins on death and discharge. These curves were computed by predicting the survival curve for each individual in the dataset then averaging[S3]. The same

technique was used to plot the cumulative incidence functions of the two events, which illustrates the predictions of the FG model.

Two sub-analyses were also performed using the same techniques within the matched groups. The first approach considered that some patients stopped receiving statins during the 48 hours after hospital admission. These patients were previously included in the "treated" group and now formed a special "withdrawn" group. This analysis removed 26 patients who were censored for any reason prior to 48 h to avoid immortal time bias. The second approach differentiated statin intensity intake as none, moderate or high according to the aforementioned criteria.

Statistical analyses were performed using the R software package version 3.5, and all codes are found at https://github.com/ecorreig/STACOV.

A list of statistical key resources and references is provided in the supplementary material.

RESULTS

Data from 2157 (1234 men and 923 women) SARS-CoV-2-infected patients who were admitted to the hospital were analysed. The median age was 67 years (IQR 54-78 years). A total of 581 patients (38.7% women) were on statin therapy (ST) at admission, and 30% were on high intensity statin therapy. Statin therapy was withdrawn within the first 48 hours of admission in 245 patients (42,2%). The statins were maintained unchanged in 336 patients (57,8%). To assess the effect of withdrawing or maintaining statin therapy we exclude 22 patients censored within the first 48 hours for any reason, 9 in the GM-non-statin group (GM-NST) and 13 in the statin

group (ST). More males than females were on statins, and the median age of the statin group was 11 years older than the non-statin (NST) group. The NST group had significantly fewer comorbidities. Demographic and clinical data are shown in *Table 1*. Out of the total 353 patients, 16.3% died: 115 (19.8%) in the ST group and 238 (15%) in the NST group (p=0.04) (*Table 2*).

Table 1 also reports the demographics and clinical data of the GM groups. The percentage of deaths in the comparable GM-NST group was 25.7%, which was significantly higher than the ST group (19.8%) (p= 0.027) (*Figure 1A* and *Table 2*). Although no significant differences were observed in statin intensity, the percentage of deaths was even lower in patients who maintained their statin treatments during hospitalization compared to the GM-NST group (17.4%; p=0.045) (*Figure 1B*). *Table 2* also shows several biomarker values, COVID-19-specific therapies and main clinical outcomes sorted by statin therapy groups. Although statistically significant differences were observed in few items, observed rates of inflammation markers and severe clinical outcomes, such as ARDS, acute renal failure or the need for tracheal intubation, were lower in patients on statins, even if not statistically significant. (*Table 2*).

The effect of statin treatment on overall mortality was also shown using a CSH model stratified by sex (Supplementary material *Figure S1*). A significant difference in the mortality rate was observed between groups (HR = 0.58 with (0.39-0.89) 95% CI; p = 0.01).

The competing risk Fine and Gray analysis (*Figure 2*) showed that statins were associated with a significantly lower probability of mortality (sub-distribution HR = 0.60 with (0.39-0.92) 95% CI; p = 0.02) and showed a trend towards a higher probability of achieving hospital discharge. The CHS and FG methods suggest a stronger effect in females, but this result should be confirmed in a larger study.

We used the same methods within the GM groups to analyse differences between patients with and without statin treatment discontinuation (supplementary material *Table S2*). No significant differences were observed, in unadjusted comparisons, between the continuing and discontinuing groups, but the continued statin treatment was associated with lower risk of mortality compared to the NST group. (n=327, HR 0.60 with (0.39-0.92) 95% CI; p = 0.02). No differences were observed between high and moderate statin use.

DISCUSSION

The present study suggests that statin therapy prior to hospitalization with SARS-CoV-2 is associated with lower mortality compared to matched patients not on statin therapy. Prehospitalization statin therapy was significantly associated with a lower in-hospital mortality rate in patients with COVID-19. The mortality rate was significantly lower in patients in whom statin therapy was maintained compared to the NST group, but there were non-balanced confounding factors when compared to discontinued, because no further matching was applied to these analyses,. Patients on statins showed a less severe pulmonary effect on X ray examination and better oxygen parameters (PaFi). Although not statistically significant, the results showed lower severe clinical outcomes, such as ARDS, respiratory and renal failure and the need for tracheal intubation in the ST group.

Therefore, the first message is that background statin therapy should not be withdrawn based on COVID-19 concerns. Although the withdrawal of statins during hospitalization, primarily in severe cases requiring invasive treatments in the ICU, will not substantially alter its cardioprotective effects, the discontinuation of these treatments in the general population due to concerns related to the SARV-CoV-2 pandemic may lead to a prolonged suspension of statin therapy and a potential increased cardiovascular risk[20]. Our results are consistent with findings

from a recent study in a Chinese population that showed that in-hospital statin therapy was associated with a lower severity of COVID-19[17].

We used two types of survival models that revealed that statins were associated with a significantly lower mortality (*Figure 2* and *Figure S1*), suggesting a stronger beneficial effect in women. Although this point should be addressed in a focused study, a biological interaction between sex and statin effects must not be excluded[21].

Statins were discontinued in 42% of patients. In our study, 78% of statin withdrawal was coincident to antiretroviral prescription, primarily lopinavir/ritonavir, suggesting a concern about the drug-drug interactions, however, an even lower mortality rate was observed in patients who remained on statins, although a firm conclusion on the effects of statin continuation can not be drawn from our study because confounding factors as a significant different antiretroviral administration (supplementary material *Table S2*).

Despite the use of a robust matching method to balance the main demographic and comorbidity variables, some baseline characteristics were not totally balanced. Patients on statins more frequently received angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) and insulin therapy. The impact of these drugs on COVID-19 therapy remains controversial, and the low absolute differential number of patients receiving these treatments do not explain the overall differences observed.

Lipid concentrations are modified during COVID-19 infection. A more severe infection results in lower cholesterol concentrations[22]. Although our study was not focused on the association between lipids and COVID-19, lower total and LDL cholesterol concentrations were observed in the statin group (*Table 1*). The possible effect of statins on the COVID-19 prognosis

should be elucidated based on their non-lipid mechanisms, which are referred to as pleiotropic effects[23]. Statins exert effects on inflammation *in vitro* by interfering with several intracellular proinflammatory signalling cascades[1,6]. Although, its effect on inflammatory mechanisms at the clinical level remains controversial[24], our study observed a trend to lower concentrations of inflammatory biomarkers (e.g., white blood cells, ferritin, and C reactive protein). Statins exhibit antioxidant and antithrombotic activities and ameliorate endothelial dysfunction[25]. Dyslipidaemia was recently associated with the risk of pulmonary thromboembolism in patients with COVID-19, and statins were suggested as a preventive therapy[26].

In addition, statins may target other SARS-CoV-2-specific mechanisms. As mentioned above, statins upregulated ACE2 expression in rabbits[10], which could be a negative effect of statins[27]. In contrast, some studies suggest a protective effect of ACE2 expression in ARDS[28], and statin use was recommended during the previous SARS pandemic (Middle East Respiratory Syndrome)[29]. A direct interference with SARS-CoV-2 replication mechanisms was suggested recently[7]. Based on these findings, a role for statins in treating COVID-19 was proposed[8,30].

The present study has some limitations. It was a retrospective observational study, and causality could not be extrapolated from our data. The GM analysis reduced the clinical distance between the statin and non-statin groups, but it introduced some uncertainty. Because all hazard and risk analyses performed in the GM groups were designed to compare mortality between the statin and non-statin groups, the effects of other covariates on risk were not extrapolated from our results, and specific analyses are warranted.

In conclusion, background statin therapy exerted a beneficial effect on the in-hospital mortality of SARS-CoV-2-infected patients. The maintenance of statin therapy during admission correlated with an even better prognosis. The potential beneficial effect of statin therapy on

mortality rates in patients with COVID-19 should be considered hypothesis-generating evidence that requires confirmation in a prospective randomized controlled trial. The evidence does not support the discontinuation of statin therapy during the COVID-19 pandemic.

Financial support

The work was supported by unrestricted grants from the Institut de Investigació Sanitària Pere Virgili (IISPV) and Xarxa de Unitat de Lipids i Ateriosclerosis (XULA) de Catalunya.

Authors' conflicts of interest disclosures

LM: Personal fees for lectures and/or advisory work from Amgen, Sanofi, Mylan, Servier, MSD, Novartis, and Daiichi-Sankyo.

NP: Personal fees for lectures from Amgen, Mylan, and Sanofi.

JP-B: Personal fees for lectures and/or advisory work from Amgen, Astra-Zeneca, Esteve, Ferrer, MSD, Mylan, Sanofi, Servier, and Rovi.

CS: Personal fees for lectures from Almirall, MSD, VISO farmacèutica, Mylan, and Esteve.

MM: Personal fees for lectures and/or advisory work from Sanofi, Novartis, Novonordisk, Astra-Zeneca, Esteve, Lilly, MSD, Ferrer, and Janssen,

CJ: Personal fees for lectures and/or advisory work from Sanofi, Amgen, MSD, Ferrer, Astra-Zeneca, Boehringer-Ingelheim, Lilly, Esteve, Novo-Nordisk, and Rovi.

EA, EC, CR-B, AP, APe, SN, JAA, MU-P, VP, RP, RR-M, MR, and AZ: Declare no conflicts of interest.

Appendix.

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Figure Legends

Figure 1: Percentage of deaths according to statin use

1A. Statin use before admission. P=0.027 between non-statin and statins at admission groups.

1B. No statin, statin withdrawn, and statin continued groups. P=0.045 between non-statin and statins maintained during admission.

Figure 2: Cumulative mortality risk in patients stratified by sex, females (A) and males (B), as determined using a competing-risks Fine and Gray analysis. (global sub-distribution HR=0.60 with (0.39-0.92) 95% CI; p = 0.02)

Figure S1: Survival probability predicted using a cause-specific hazard model in patients stratified by sex: females (A) and males (B). (global HR = 0.58 with (0.39-0.89) 95% CI; p = 0.01)

Table 1: Demography, anthropometry and clinical characteristics of the studied population before admission.

Variable	All N(%)	No Statins N(%)	Statins N(%)	GM No Statins N(%)	P value *
Number	2157	1576	581	581	
Age [IQ]	67 [54-78]	62 [51-77]	73 [65 80]	74 [64-84]	0.43
Sex (Females)	923 (42.79)	698 (44.29)	225 (38.73)	245 (42.10)	0.27
Smokers	107 (4.96)	75 (4.76)	32 (5.51)	46 (7.90)	0.16
High Blood Pressure	1081 (50.12)	638 (40.48)	443 (76.25)	459 (79.04)	0.28
Hyperlipidaemia	818 (37.92)	284 (18.02)	534 (91.91)	531 (91.41)	0.84
Diabetes	501 (23.23)	244 (15.48)	257 (44.23)	259 (44.50)	0.97
Obesity	579 (26.82)	361 (22.89)	217(37.35)	203(34.88)	0.90
PERSONAL HISTORY OF CARDIOVASCULAR DISEASE					
Coronary Heart Disease	204 (9.46)	55 (3.49)	149 (25.65)	141 (24.23)	0.62
Stroke	135 (6.26)	61 (3.87)	74 (12.74)	66 (11.34)	0.52

Peripheral artery Disease	99 (4.59)	35 (2.22)	64 (11.04)	59 (10.14)	0.70
Heart Failure	182 (8.44)	98 (6.22)	84 (14.46)	61 (10.48)	0.05
NO CARDIOVASCULAR COMORBIDITIES					
COPD/Asma	366 (16.97)	229 (14.53)	137 (23.58)	110 (18.90)	0.06
Chronic Liver disease	58 (2.69)	44 (2.79)	14 (2.41)	19 (3.26)	0.48
Chronic Kidney disease	215 (9.97)	112 (7.11)	103 (17.73)	93 (15.98)	0.47
Rheumatologic disease	105 (4.87)	68 (4.31)	37 (6.37)	48 (8.25)	0.26
Cancer	240 (11.13)	163 (10.34)	77 (13.25)	68 (11.86)	0.47
DRUG THERAPY					
Ezetimibe	44 (2.04)	11 (0.70)	33 (5.68)	28 (3.36)	0.59
Fibrates	54 (2.50)	32 (2.03)	22 (3.79)	57 (9.84)	<0.01
ACE inhibitors	457 (21.19)	263 (16.69)	194 (33.39)	197 (33.85)	0.92
ARB	266 (12.33)	130 (8.25)	136 (23.41)	86 (14.87)	<0.01
Insulin	151 (7.00)	53 (3.36)	98 (16.87)	52 (9.01)	<0.01

SGLT2 inhibitors	34 (1.58)	11 (0.70)	23 (3.96)	5 (0.87)	<0.01
GLP1R agonists	33 (1.53)	9 (0.57)	24 (4.13)	14 (2.33)	0.12
Other therapies for diabetes	365 (16.93)	177 (11.23)	188 (32.36)	162 (27.81)	0.10
Antiplatelet	344 (15.95)	134 (8.50)	210 (36.14)	138 (23.75)	<0.01
NOACs.	101 (4.68)	50 (3.17)	51 (8.78)	35 (5.99)	<0.01
Acenocoumarin	112 (5.19)	66 (4.19)	46 (7.92)	58 (10.06)	<0.01
LIPID PROFILE BEFORE ADMISSION MMOL/L (MEDIAN [IQR])					
Total Cholesterol	4.79 [4.33-5.36]	4.87 [4.48-5.41]	4.48 [3.96-5.08]	5.01 [4.37-5.79]	<0.01
HDL-Cholesterol	1.29 [1.17-1.45]	1.31 [1.19-1.45]	1.25 [1.09-1.42]	1.28 [1.15-1.39]	0.69
LDL-Cholesterol	2.81 [2.47-3.28]	2.91 [2.60-3.37]	2.53 [2.07-2.98]	3.03 [2.61-3.70]	<0.01
Triglycerides	3.29 [2.63-3.94]	3.24 [2.63-3.84]	3.36 [2.43-4.08]	3.53 [2.82-4.6]	0.15

GM: Genetic [search algorithm based] Matched; COPD: Chronic Obstructive Pulmonary Disease; ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blockers; SGLT2: Sodium Glucose Co-Transporter 2; GLP-1R: Glucagon-Like Peptide-1 Receptor; NOACs: Novel Oral Anticoagulants; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein.
* P value between statin and non-statin matched groups.

Table 2. Main clinical biomarkers, specific therapies and clinical out-comes in groups sorted by statin use.

Variable	All N(%)	No Statins N(%)	Statins N(%)	GM No-Statin N(%)	P value *
	2157	1576	581	581	
CLINICAL INFLAMMATION AND RESPIRATORY FUNCTION BIOMARKERS					
White blood cells (cells*10^9L)	6.508 (3.850-8.788)	6.436 (3.800-8.605)	6.665 (3.460-8.950)	6.890 (4.250-8.850)	0.36
Lymphocytes (cells*10^9L)	0.690 (0.300-0.911)	0.700 (0.300-0.945)	0.643 (0.325 – 0.823)	0.694 (0.360-0.850)	0.27
Ferritin (μg/L)	837(417-1388)	811 (405-1351)	920 (500-1502)	1025 (526-1333)	0.84
C reactive protein (nmol/L)	228.6(85.7-952.4)	214.3(82.8-883.9)	247.6(101.9-1076.2)	294.3(112.4-847.6)	0.88
Dimer (μg/L)	1160 (537-2570)	964 (507-2318)	1467 (666 3699)	1077 (543-3283)	0.06
PaO_2(kPa)	9.3(7.9-10.5)	9.3(7.9-10.5)	9.1(7.7-10.5)	8.9(7.4-10.1)	0.08
PaO_2/FiO_2	38.6(28.5-46.1)	39.7(29.6-46.4)	36.8(25.7-44.4)	32.9(23.2-42.5)	0.03
SPECIFIC THERAPY FOR COVID-19					

hloroquine	1862 (86.32)	1368 (86.75)	494 (85.03)	475 (81.81)	0.15
Antibiotics	1926 (89.29)	1398 (88.65)	528 (90.88)	540 (93.02)	0.20
Antiretroviral therapy	1179 (55.66%)	862 (54.7%)	319 (54.91%)	292 (50.32%)	0.12
Corticoids	632 (29.3)	440 (27.9)	193 (33.22)	209 (36)	0.34
Immunomodulators	378(17.52)	277 (17.56)	101 (17.38)	121 (20.89)	0.14
Immunoglobulins	32 (1.48)	24 (1.52)	8 (1.38%)	6 (1.03%)	0.77
Anticoagulants	42(1.95)	29 (1.84%)	13 (2.24%)	31 (5.35%)	<0.01
Heparin (Full anticoagulant dose)	207(9.6)	131 (8.31)	76 (13.08%)	68 (11.79%)	<0.01
CLINICAL OUTCOMES					
Bilateral alteration Thorax X ray	1602(74.27)	1174 (74.45)	428(73.67)	443(76.27)	0.03
Respiratory Failure	541 (25.08)	374 (23.73)	166 (28.74)	191 (32.93)	0.12

Intensive Care Unit Hospitalization	336 (15.5)	233 (14.8)	103 (17.7)	111(19%)	0.59
Shock	144 (6.68)	94 (5.96)	50(8.61)	37(6.42)	0.19
Acute Respiratory Distress Syndrome	630 (29.21)	432 (27.41)	198 (34.08)	216 (34.08)	0.29
Disseminated Intravascular Coagulation	38 (1.76)	27 (1.71)	11 (1.89)	7 (1.29)	0.55
Acute Renal Failure	354 (16.41)	237 (15.04)	117 (20.14)	145 (24.95)	0.06
Liver alterations	68 (3.15)	45 (2.86)	23 (3.96)	12 (2.06)	0.09
High-Flow Mechanical Ventilation	390 (18.08)	260 (16.50)	130 (22.38)	130 (22.31)	1.00
Invasive Mechanical Ventilation. Tracheal Intubation	275 (12.75)	191 (12.12)	84 (14.46)	96 (16.59)	0.36
Death	353 (16.37)	238 (15.10)	115 (19.79)	148 (25.40)	0.03

GM: Genetic [search algorithm based] Matched.

* P value between statin and GM non-statin groups.

PaO_2: Partial pressure of oxygen. FiO_2: Fractional inspired oxygen. kPa: Kilopascal

FIGURE 1A

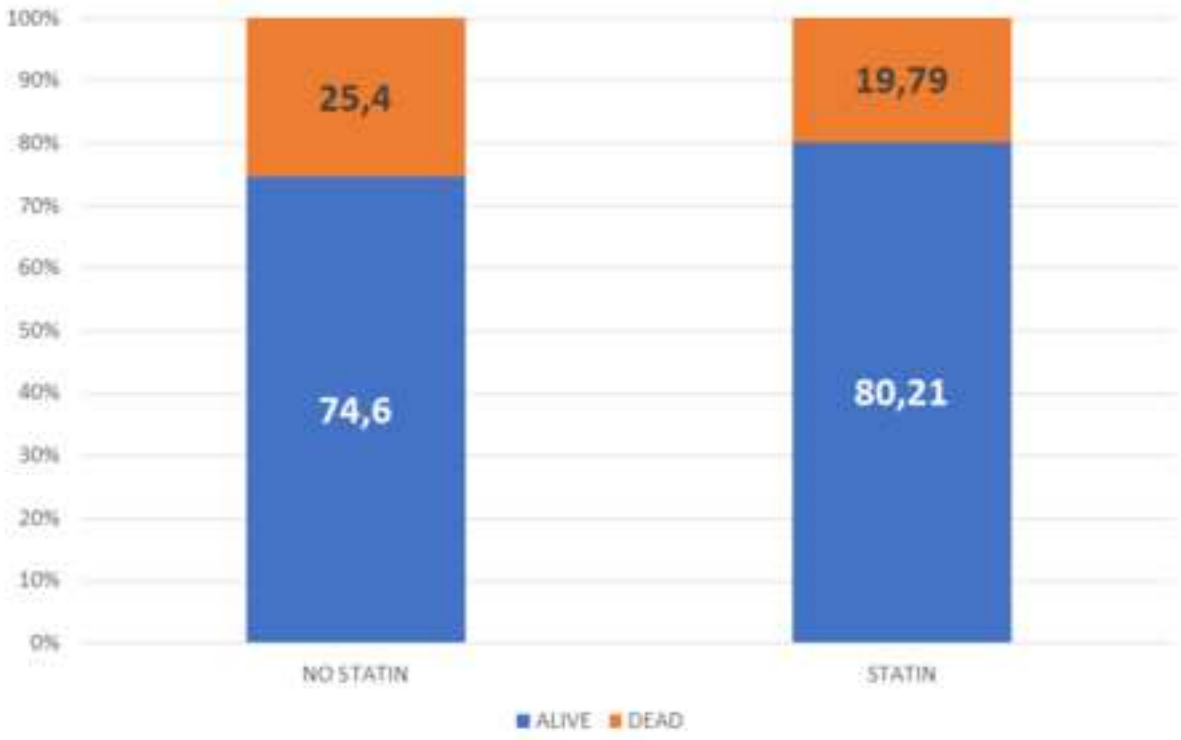


FIGURE 1B

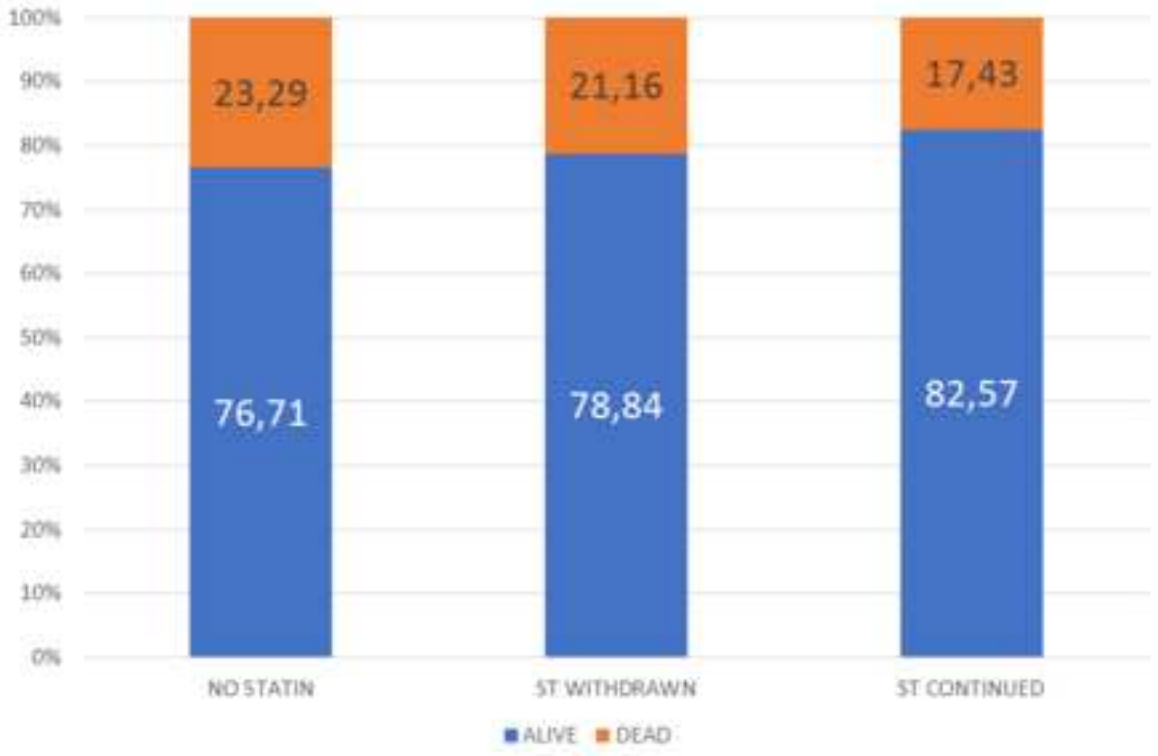
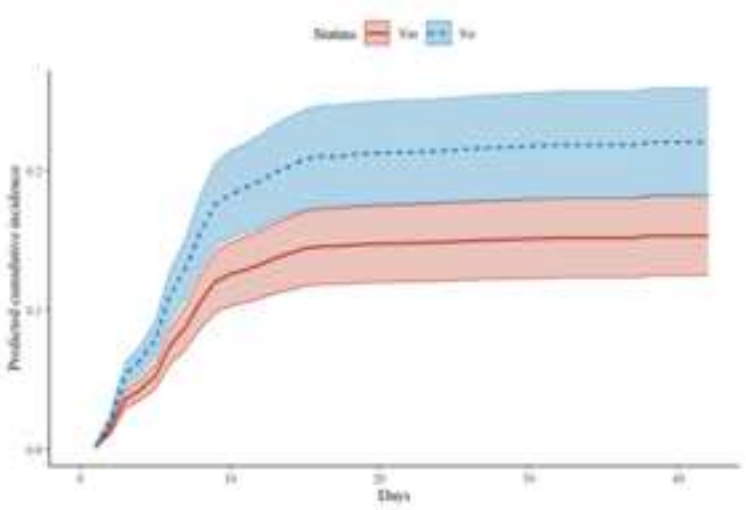


FIGURE 2

FEMALES



MALES