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THE IMPACT OF SARS-COV-2 ON VESSELS AND THE MUTUAL INFLUENCE OF THE MEDICINES

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Abstract. In March 2020 the World Health Organization (WHO) declared the Coronavirus disease 2019 (COVID-2019) outbreak a global pandemic. Almost two years later, there have been more than 600 million cases and more than 6.5 million deaths worldwide [1]. Despite the exact mechanisms underlying severe COVID-19 remaining unknown, it has been suggested that during the response to SARS-CoV-2 the immune dysregulation and the high levels of pro-inflammatory cytokines might represent pivotal causes of tissue damage. In this context, statins, which are usually used to treat dyslipidemia, gained attention due to their potential role in COVID-19 prognosis [2]. Several studies highlighted their anti-inflammatory, immunomodulatory, antithrombotic, and antiviral properties that may translate into improved short- and long-term outcomes in COVID-19 patients. Apparently, vascular lesions in COVID-19 are more significant than the cytotoxicity of the virus in cardiomyocytes. Of course, cardiovascular implications of COVID-19 are most dangerous for those who, on the basis of preexisting atherosclerosis, already have chronic lesions of the coronary/cerebral arteries and marginally reduced perfusion reserves of the myocardium and other vital organs.

Key words: COVID-19 ,dyslipidemia, inflammation, cytokines.

This study aimed to assess whether preadmission statin use in patients with CVDs who tested positive for SARS-CoV-2 and were hospitalized was associated with less severe COVID-19 prognosis.

The population under study included all inhabitants (≥18 years old) in the territory of Bergamo- and Brescia-HPA, Italy, with a CVD such as ischemic heart disease, peripheral vascular disease, cerebrovascular disease and heart failure, and who tested positive for SARS-CoV-2 and were hospitalized between 20 February 2020 and 31 December 2020. For each selected individual, demographic characteristics such as sex and age were extracted at ID, whereas clinical information (comorbidities and drug exposure) were investigated in the period prior to the ID. Data on comorbidities were retrieved by using the chronic disease registry updated on 1 January 2020. In the chronic disease registry, each disease is assessed by merging data from different data sources such as pharmacy claims and inpatient and outpatient care. Therefore, for each selected individual the presence of the following comorbidities was evaluated: Alzheimer or dementia, respiratory diseases, hypertension, diabetes, chronic liver diseases, rheumatic diseases, cancer, and infection with human immunodeficiency virus (HIV).

Among the statins users, atorvastatin was the most prescribed (60.4%) medication, followed by simvastatin (20%), rosuvastatin (16.3%), pravastatin (2.1%), fluvastatinn (1.1%), and lovastatin (0.2%); 71% of users showed high adherence (PDC ≥ 80%) to the treatment in the year prior to the ID. Statin users were more likely to be male compared with LLT non-users (69% vs. 57%), whereas no age difference was observed between groups. Statins users also

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reported significantly higher prevalence of diabetes (40% vs. 26%) compared with non-LLT users. Use of statins prior to hospitalization was not associated with significant changes in the risk of need of MV (OR: 1.00; 95% CI: 0.38–2.67) and ICU access (OR: 0.54; 95% CI: 0.22–1.32)

In this retrospective cohort analysis of patients with CVDs who tested positive for SARS-CoV-2 and were hospitalized, statins use before hospital admission was not associated with a decreased risk of ICU access and MV need compared with non-LLT users. Similar results were found in different ages, genders, and levels of statins exposure, regardless of whether the participants had comorbidities. On the other hand, results suggested a protective role of statins on mortality at 30 days. Additionally, sensitivity analyses performed by selecting only patients with specific CVD (i.e., ischemic heart diseases, cerebrovascular diseases, heart failure) were consistent with the main results. Our findings on ICU access and MV need are in line with those reported in most published studies, suggesting no association between statins use and variation in the risk of ICU access and/or need of MV in hospitalized COVID-19 patients with history of CVDs

Indeed, the 61% decreased risk of mortality at 30 days in statin users is also consistent with the range of 30–70% lower mortality risk reported in previous studies [2] but it does contrast with other two studies reporting no association between statins use and in-hospital mortality.

CVDs, prominent risk factors for developing severe COVID-19, are commonly treated with statins. Therefore, in COVID-19 patients, a complex interplay between the effects of these diseases and statins can be hypothesized. For example, statins might inhibit either the main protease of SARS-CoV-2 with consequent alteration of its infectivity properties, or the expression of receptors (i.e., Toll-like receptors) on immune cells with consequent down-regulation of the activity of mediators (i.e., NF-κB) which are typically involved in inflammatory processes, cytokine storms and respiratory distress [3]. Furthermore, statins might cause a decrease of cholesterol levels in the plasma membranes, which causes alteration in the ACE2 assemblage, with consequent failure in SARS-CoV-2 internalization and egression from the cells [5]. Additionally, cholesterol is an important component for viral membrane formation and for the repair of the host's membrane after the virus cycle is completed in order to prevent the loss of cell homeostasis. Therefore, a low level of cholesterol could be associated with a low ability of the virus to complete its vital cycle and to continue its replication in the host [4]. Finally, the antithrombotic effects of statins might reduce the risk of cardiovascular complications typically observed in COVID-19 patients, thus resulting in their improved survival. Statins have been shown to increase cellular expression of angiotensin-converting enzyme 2 (ACE2) [7], the primary receptor used by SARS-CoV 2 to gain entry into lung cells [9]. Of note, the patient populations most likely to be prescribed statins for their cardioprotective effects, i.e., males, the elderly, and those with hypertension, diabetes, dyslipidemia, and cardiovascular disease, are also the same populations at greatest risk for COVID-19-related mortality [3]. Although generally statins are well tolerated, their use may be associated with rhabdomyolysis and related kidney injury, as well as liver toxicity, which may compound COVID-19 systemic disease. Since most statins are substrates of the hepatic cytochrome P450 system, co-administration of statins with protease inhibitor-based antiretroviral agents or certain immunosuppressive drugs may markedly increase the risks of adverse effects in patients with COVID-19 due to drug interactions. Despite these considerations, continuation of statin therapy is

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recommended in patients with newly diagnosed COVID-19 infection due to their proven beneficial effects on cardiovascular outcomes in appropriate clinical settings. The heterogeneous nature of our study population and the large sample size, allowed us to assess the relationship between COVID-19 mortality/severity and statin use among a widely varied patient population, thus improving our study's generalizability to other hospitalized patients with COVID-19. The utilization of a backward stepwise regression approach made for a reproducible method for predictor selection in this study, helping to reduce the potential for bias in selecting predictor variables for inclusion in our regression models. Additionally, the use of propensity score matching when comparing statin and non-statin users reduced the potential for selection bias (confounding by indication) and provided a more statistically robust estimate of our primary and secondary outcomes. Furthermore, use of the Elixhauser Score to account for comorbidities in our statistical models provided a more comprehensive approach to account for comorbidities. In this large cohort from a single tertiary medical center, we found that statin use during hospitalization for COVID-19 was associated with improved short-term mortality. The survival benefit was seen in those who continued statin therapy, as well as those who newly initiated therapy while hospitalized. A sensitivity analysis found that statin use was associated with improved mortality for patients older than 65 years, but not for patients 65 years old or younger.[7]

Our study confirms and expands on prior work. A recent propensity score-matched analysis found that statin use prior to hospitalization reduces the risk of short-term in-hospital mortality from COVID-19. Our study probed further, into whether in-hospital statin use had a similar effect on mortality. To investigate the impact of statins administered during hospitalization, we used marginal structural models, which account for both survivorship bias (i.e., patients need to survive long enough to begin statins) and time-varying confounding bias (i.e., patient health status during hospitalization changes over time, affecting the propensity of initiating treatment). Our study accounted for a wide variety of time-varying confounders, which we believe accurately captures shifts in the propensity of initiating treatment. We further expanded on prior work by specifically evaluating the effect of statin initiation during hospitalization without prior use, because 26% of our cohort was newly initiated on statins during COVID-19 hospitalization. Overall, the novel findings presented here are that statin therapy during hospitalization, whether it be a new or continued prescription, was associated with improved mortality.[6]

The composition of our cohort was similar to other published patient databases of patients with COVID-19. The median age of patients was 60 years old (IQR 47-73 years). Obese patients with a BMI ≥30 represented almost half the population, consistent with evidence that obesity is a risk factor for hospitalization with COVID-19 . Racial and ethnic demographics vary immensely across the literature. In this study, White/Non-Hispanic (38.5%) and Hispanic patients (36.4%) were most common, followed by Black/Non-Hispanic patients (10.8%). This cohort's mortality rate (13.1%) was similar to the mean published United States hospital mortality rates for patients admitted with COVID-19 during the first 6 months of the pandemic (11.8%) among 955 hospitals

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