



University of Dundee

Systematic Review and Meta-Analysis of Statin Use and Mortality, Intensive Care Unit Admission and Requirement for Mechanical Ventilation in COVID-19 Patients Lao, Ut Sam; Law, Chak Fun; Baptista-Hon, Daniel T.; Tomlinson, Brian

Published in: Journal of Clinical Medicine

DOI: 10.3390/jcm11185454

Publication date: 2022

Licence: CC BY

Document Version Publisher's PDF, also known as Version of record

Link to publication in Discovery Research Portal

Citation for published version (APA): Lao, U. S., Law, C. F., Baptista-Hon, D. T., & Tomlinson, B. (2022). Systematic Review and Meta-Analysis of Statin Use and Mortality, Intensive Care Unit Admission and Requirement for Mechanical Ventilation in COVID-19 Patients. Journal of Clinical Medicine, 11(18), [5454]. https://doi.org/10.3390/jcm11185454

General rights

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.

You may not further distribute the material or use it for any profit-making activity or commercial gain.
You may freely distribute the URL identifying the publication in the public portal.

Take down policy If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.





Systematic Review and Meta-Analysis of Statin Use and Mortality, Intensive Care Unit Admission and Requirement for **Mechanical Ventilation in COVID-19 Patients**

Ut-Sam Lao^{1,†}, Chak-Fun Law^{1,†}, Daniel T. Baptista-Hon^{1,2,*} and Brian Tomlinson^{1,*}

- 1 Center for Biomedicine and Innovations, Faculty of Medicine, Macau University Science and Technology, Taipa, Macau SAR 999078, China
- 2 Division of Systems Medicine, School of Medicine, University of Dundee, Dundee DD1 4HN, UK

Correspondence: dbaptistahon@must.edu.mo (D.T.B.-H.); btomlinson@must.edu.mo (B.T.)

These authors contributed equally to this work. t

Abstract: There is mounting evidence that statin use is beneficial for COVID-19 outcomes. We performed a systematic review and meta-analysis to evaluate the association between statin use and mortality, intensive care unit (ICU) admission and mechanical ventilation in COVID-19 patients, on studies which provided covariate adjusted effect estimates, or performed propensity score matching. We searched PubMed, Embase, Web of Science and Scopus for studies and extracted odds or hazard ratios for specified outcome measures. Data synthesis was performed using a random-effects inverse variance method. Risk of bias, heterogeneity and publication bias were analyzed using standard methods. Our results show that statin use was associated with significant reductions in mortality (OR = 0.72, 95% CI: 0.67–0.77; HR = 0.74, 95% CI: 0.69, 0.79), ICU admission (OR = 0.94, 95% CI: 0.89-0.99; HR = 0.76, 95% CI: 0.60-0.96) and mechanical ventilation (OR = 0.84, 95% CI: 0.78-0.92; HR = 0.67, 95% CI: 0.47–0.97). Nevertheless, current retrospective studies are based on the antecedent use of statins prior to infection and/or continued use of statin after hospital admission. The results may not apply to the de novo commencement of statin treatment after developing COVID-19 infection. Prospective studies are lacking and necessary.

Keywords: COVID-19; intensive care unit; mechanical ventilation; meta-analysis; mortality; statin; systematic review

1. Introduction

Coronavirus infectious disease 2019 (COVID-19) continues to place an incredible burden on morbidity and mortality worldwide. Since the declaration of COVID-19 as a global pandemic, over 560 million confirmed cases and over 6.3 million deaths were reported (data from COVID-19 Data Repository by the Center for Systems Science and Engineering at Johns Hopkins University https://github.com/CSSEGISandData/COVID-19, accessed 25 July 2022) [1]. The development of severe COVID-19 is associated with a number of risk factors, such as older age, male sex and the presence of underlying medical conditions such as cardiovascular diseases [2] and diabetes. Severe COVID-19 cases may involve inflammatory cytokine storm (cytokine release syndrome) resulting in multi-organ failure and mortality [3]. Elevated interleukin-6 (IL-6), a mediator of cytokine release syndrome, has been demonstrated in severe COVID-19 patients [4]. Indeed, diabetic patients have significantly higher serum inflammatory biomarkers including IL-6, C-reactive protein (CRP), D-dimer, serum ferritin and coagulation indices, resulting in a higher chance of an inflammatory storm and eventually worsening the outcome of COVID-19 [5]. Statins are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors used in patients with cardiovascular disease or diabetes to reduce low-density lipoprotein cholesterol. Statins also have other effects, such as antitumor, antioxidative and anti-inflammatory effects [6].



Citation: Lao, U.-S.; Law, C.-F.; Baptista-Hon, D.T.; Tomlinson, B. Systematic Review and Meta-Analysis of Statin Use and Mortality, Intensive Care Unit Admission and Requirement for Mechanical Ventilation in COVID-19 Patients. J. Clin. Med. 2022, 11, 5454. https://doi.org/10.3390/jcm11185454

Academic Editors: Kevin Roedl, Dominic Wichmann and Valentin Fuhrmann

Received: 4 August 2022 Accepted: 14 September 2022 Published: 16 September 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/).

In particular, clinical trials have shown that statins can reduce the levels of CRP [7,8], which may mitigate the severity of the cytokine storm seen in COVID-19 patients.

Since the beginning of the COVID-19 pandemic, a remarkable number of studies, most of them retrospective, have examined the association between statin use and various clinical outcomes in COVID-19. A number of meta-analyses of these retrospective studies have been performed, and the findings are mixed [9-22]. The majority of these focused on mortality as the outcome. Interestingly, meta-analyses that used covariate-adjusted effect estimates found a significant benefit of statins [10,13–15,17,21–23]. Similarly, one meta-analysis that included propensity score-matched subjects also found a significant benefit of statins on COVID-19 outcomes [22]. This is hardly surprising since the development of severe COVID-19 and mortality are strongly associated with a number of risk factors. Therefore, retrospective studies that report effect estimates of statins that take into account these covariates are less likely to be confounded. Some meta-analyses have evaluated outcomes involving severe COVID-19 (e.g., ICU admission and mechanical ventilation) [12,14,17,19,23–25]. The findings are also mixed, since many of these metaanalyses used a mixture of unadjusted and adjusted effect estimates. However, those which focused on studies that adjusted for covariates have found a significant effect of statins on ICU admission or the development of severe COVID-19 [14,17,23]. Indeed, one study specifically evaluated the influence of covariate adjustment and found a significant improvement in the effect estimate of statins on mortality, ICU admission and mechanical ventilation [17].

In light of all the information available, and the availability of additional studies, we performed a systematic review and meta-analysis of the literature to evaluate the association between statin use and COVID-19 mortality, ICU admission and mechanical ventilation. We only analyzed studies reporting covariate-adjusted point estimates, or those which performed propensity score matching on the study population.

2. Materials and Methods

This systematic review and meta-analysis were performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines [26].

Search Strategy—The information sources used included the PubMed, Embase, Web of Science and Scopus databases. Published articles up to 22 April 2022 were included. The detailed search strategy is outlined in Supplementary Table S1. Reference lists of included articles were also hand searched to identify additional studies. The language of the article screened was limited to English only.

Eligibility Criteria—We included retrospective observational studies (e.g., cohort, casecontrol and case-series studies) in this systematic review. Letters with sufficient detail to evaluate quality and bias were included. The language of the included articles was restricted to English. Case reports, reviews, conference abstracts and editorials were excluded.

The study population must include patients with confirmed COVID-19, with or without statin use. Studies with no clearly defined control group (i.e., COVID-19 patients not on statins) were excluded. Studies were included irrespective of statin type and dosage. We did not limit our inclusion of studies on the basis of the length of study period. Studies with any of the following outcomes were included: mortality, ICU admission and requirement of assisted ventilation during hospitalization. Studies of statins administered specifically for the treatment of COVID-19 were excluded.

Articles identified from the electronic search were accumulated in EndNote 20 (Clarivate, Philadelphia, PA, USA). Any duplicated studies were removed. Two review authors (L.C.F. and L.U.S.) screened the titles and abstracts to identify eligible studies independently. Full-text screen was then performed and reasons for study exclusion were recorded. Any disagreement on study eligibility was resolved by two other review authors (D.T.B-H. and B.T.). For multiple studies published by the same group of authors, we included only the

latest study with the largest number of participants. All authors agreed on the studies included in the analysis.

Data extraction—The data from all included studies were extracted by two review authors (L.C.F. and L.U.S.) independently using a modified data extraction form from the Cochrane Foundation [27]. We extracted the following information from each article: name of first author, publication year, study country, sample size, population, propensity score matching, age range, sex, comorbidities, before or after hospital admission use of statins, statin type and dosage, mortality, intensive care admission and assisted ventilation. The unadjusted and adjusted effect estimates were also extracted where possible. Disagreements on data extractions were resolved by two other review authors (D.T.B-H. and B.T.).

Quality Assessment—All cohort studies were evaluated using the Newcastle-Ottawa scale (NOS) independently by two review authors (L.C.F. and L.U.S.). Each study was evaluated on a scale of 0–9, where articles with a high risk of bias scored 0–4, moderate risk of bias scored 5–7 and low risk of bias scored 8–9.

Statistical Analysis—Meta-analyses were performed using Review Manager 5.4 (RevMan version 5.4) [28] on extracted data using a random-effects model with an inverse-variance method. Odds ratios (ORs) for mortality, ICU admission and mechanical ventilation from propensity score-matched studies were pooled with studies with adjusted odds ratios (aORs) with their 95% confidence intervals. Similar pooling was performed with hazard ratios (HRs). Unadjusted data without propensity score matching were not included in the meta-analysis. Heterogeneity among studies was evaluated using the Chi-square test, with a threshold set at p < 0.10. The extent of heterogeneity was evaluated using the I² statistic, and classified as low (I² < 30%), moderate (I² = 30–60%) and high (I² > 60%). For analyses with more than 10 studies, funnel plots were constructed for the evaluation of publication bias. Asymmetry in funnel plots was analyzed using Egger's regression. Sensitivity analyses were performed by observing the effect of removing single, or groups of studies on the overall pooled estimate and heterogeneity.

3. Results

3.1. Literature Search and Study Characteristics

Using the search strategy outlined in the Methods Section and in the Supplemental Information, we identified a total of 5431 articles (PubMed—420, Embase—1549, Web of Science—338 and Scopus—3124; flowchart is shown in Figure 1). Furthermore, 14 additional articles were identified from other journals and hand searching. Following the removal of duplicates, we performed a title and abstract screen on 3937 studies. We applied the eligibility criteria outlined in the Methods Sections and found 2731 studies were not of the correct type, 708 studies did not observe statin use for hospitalized COVID-19 patients, 328 studies did not focus on our interested outcomes, 15 studies contained combined outcome data, 15 studies did not focus on COVID-19 patients and 67 studies contained neither adjusted results nor propensity score matched data. A total of 84 studies with aOR, aHR and/or propensity score-matched results were eligible for data extraction and meta-analysis. A summary of the baseline characteristics of the included studies are shown in Supplementary Table S2.



Figure 1. PRISMA flowchart for study selection.

3.2. Effect of Statins on Mortality

Studies reporting odds ratios-We included 58 studies with odds ratios corrected by covariate adjustments or propensity score matching between statin users and non-users [25,29–85]. Our quality assessment of these studies using the NOS revealed that all studies were of good quality, with a minimum score of 6 (range 6–9; Supplementary Table S3). The pooled estimate of odds ratio was 0.72 (95% CI: 0.67–0.77), and the Z-test revealed a statistically significant pooled odds ratio (Z = 9.36; p < 0.00001; Figure 2A). Our meta-analysis therefore showed that the risk of mortality for statin users was lower than non-users. We evaluated the possibility of publication bias in our meta-analysis using funnel plots of the standard error of the logarithmic odds ratio plotted against the odds ratio, followed by an Egger's regression (Supplementary Figure S1A). We found no significant asymmetry, suggesting there was no publication bias. Heterogeneity existed between the studies ($I^2 = 76\%$). Visual inspection of individual point estimates and their 95% CI suggest that some studies show statins use increase mortality. We performed a sensitivity analysis to see if individual studies contributed to the overall pooled effect or heterogeneity. We found no effect of sequentially removing individual studies on either the pooled estimate (Supplementary Figure S2), or extent of heterogeneity (data not shown). Our meta-analysis contained odds ratios that are either covariate adjusted or propensity score matched or both. We performed a sensitivity analysis of studies with or without propensity score matching (Supplementary Figure S3). We found no qualitative changes in the pooled estimate or heterogeneity.

\				Odda Datia	Odda Datia
- Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% C	IV, Random, 95% CI
Ageno 2021	0.392	0.6262	0.3%	1.48 (0.43, 5.05	
Alsulaiman 2021	-0.2488	0.1794	1.9%	0.78 [0.55, 1.11	-
Andrews 2022 Apparici 2021	-0.3285	0.0343	3.4%	0.72 [0.67, 0.77	
Basu 2021	-0.1508	0.1867	1.8%	0.86 [0.60, 1.24	
Bejan 2021	-0.1508	0.4457	0.5%	0.86 [0.36, 2.06	
Bejan 2021	-0.0619	0.4908	0.5%	0.94 [0.36, 2.46	
Bejan 2021 Bibliog 2021	-0.0202	0.3074	1.0%	0.98 [0.54, 1.79	
Bui 2021	-2.4079	1.061	0.4%	0.09 [0.01, 0.72	
Byttebier 2021	-0.5798	0.2588	1.2%	0.56 [0.34, 0.93	
Cabezon 2021	-0.596	0.2621	1.2%	0.55 (0.33, 0.92	
Chacko 2021	-1.9661	0.7509	0.2%	0.14 [0.03, 0.61	
Cho 2022	-0.3857	0.2119	1.6%	0.68 [0.45, 1.03	-
Chow 2021	-0.2831	0.0844	3.0%	0.75 [0.64, 0.89	
Daniels 2021	-0.6162	0.1251	2.5%	0.54 [0.42, 0.69	
De Spiegeleer 2021	-0.8675	0.4001	0.7%	0.42 [0.19, 0.92	
El-Solh 2021	-0.0619	0.0661	3.2%	0.94 [0.83, 1.07	
Espana 2021	-0.462	0.1468	2.2%	0.63 [0.47, 0.84	
Greco 2020	-1.2391	0.00009	0.3%	0.29 [0.08, 1.07	
Gupta 2021	-0.734	0.1547	2.1%	0.48 [0.35, 0.65	
Ikari 2021	0.1997	0.3503	0.8%	1.22 [0.61, 2.43	
Ikari 2021	-0.4557	0.3298	0.9%	0.63 [0.33, 1.21	
Kabootari 2022	-0.9943	0.406	0.6%	0.37 [0.17, 0.82	
Lee 2021	-0.0985	0.073	3.170	0.91 [0.79, 1.05	
Li 2022	-0.3425	0.0609	3.2%	0.71 [0.63, 0.80	-
Lohia 2021	-0.5866	0.2032	1.7%	0.56 [0.37, 0.83	
Luo 2020	1.0919	0.7805	0.2%	2.98 [0.65, 13.76	
Ma 2021 Mallow 2020	-0.0726	0.057	3.3%	0.93 [0.83, 1.04	+]
Maric 2020 Maric 2021	-0.0162	0.0538	3.3%	0.54 (0.49, 0.60	+
Masana 2022	-0.3257	0.1411	2.3%	0.72 10.55, 0.95	
McAlister 2021	-1.2379	2.7062	0.0%	0.29 [0.00, 58.33	• · · · · · · · · · · · · · · · · · · ·
McAlister 2021	0.0677	0.1655	2.0%	1.07 [0.77, 1.48	
McAlister 2021	-0.2744	0.0631	3.2%	0.76 [0.67, 0.86	
Mehra 2020 Mointrun 2021	-1.0498	0.202	1.7%	0.35 [0.24, 0.52	
Memurup 2021 Merzon 2021	-0.0102	1 558	0.1%	0.54 [0.34, 0.87	· · · · · · · · · · · · · · · · · · ·
Mitacchione 2021	-0.1044	0.2639	1.2%	0.90 [0.54, 1.51	
Monserrat Villatoro 2022	0.4187	0.1426	2.3%	1.52 [1.15, 2.01	
Nateghi 2021	-0.3425	0.2762	1.1%	0.71 [0.41, 1.22	
Nicholson 2021	-0.7614	0.3459	0.8%	0.47 [0.24, 0.92	
On 2021 Pazoki 2021	-0.3011	0.1785	1.9%	0.74 [0.52, 1.05	
Philipose 2020	0.0296	0.1745	1.9%	1.03 [0.73, 1.45	
Ramachandran 2020	0.4637	0.3273	0.9%	1.59 [0.84, 3.02	
Ramos-Rincon 2021	-0.0866	0.3922	0.7%	0.92 [0.43, 1.98	
Rosenthal 2020	-0.5108	0.0408	3.4%	0.60 [0.55, 0.65	-
Song 2020	-0.3711	0.1893	1.0%	0.69 [0.48, 1.00	
Terlecki 2021	-0.6244	0.2304	1.4%	0.54 [0.34, 0.84	
Tignanelli 2021	-0.2107	0.0972	2.8%	0.81 [0.67, 0.98	-
Torres-Pena 2021	-0.4005	0.1154	2.6%	0.67 [0.53, 0.84	
Umakanthan 2021	-0.6349	0.1196	2.5%	0.53 [0.42, 0.67	
Varieulari-Azimi 2021 Mander 2022	-1.7148	0.511	3.5%	0.18 [0.07, 0.49	•
Wargny 2021	0.3507	0.1798	1.9%	1.42 [1.00, 2.02	
Yetmar 2021	0.131	0.2944	1.0%	1.14 [0.64, 2.03	
Zhang 2020	-0.6363	0.1638	2.0%	0.53 [0.38, 0.73	
Zhong 2020	0.0583	1.1481	0.1%	1.06 [0.11, 10.06	
Total (95% CI)			100.0%	0.72 [0.67, 0.77	•
Heterogeneity: Tau ² = 0.0	4; Chi ² = 259.86, df =	= 62 (P <	0.00001); I ² = 76%	
Test for overall effect: Z =	9.36 (P < 0.00001)				U.U1 U.1 1 10 Favours Statin Users Favours Non-Statin Users
3				Hazard Ratio	Hazard Ratio
Study or Subgroup Io	g[Hazard Ratio]	SE V	Veight N	V, Random, 95% Cl	IV, Random, 95% Cl
Alsulaiman 2021	-0.3711 0	1299	3.8%	0.69 [0.53, 0.89]	-
An 2020	0.207 0	5247	0.4%	1.23 [0.44, 3.44]	
Ayeh 2021 Rerarvist 2021	-0.0834 0	2791	1.3%	0.92 [0.53, 1.59]	-
Buenen 2020	-0.1278 0	1932	2 3%	0.88 [0.79, 0.98]	
Butt 2020	-0.0408 0	1053	4.7%	0.96 [0.78, 1.18]	+
Castagna 2022	-0.5499 0	0717	6.1%	0.58 [0.50, 0.66]	-
Choi 2021	-0.3285 0	0725	6.0%	0.72 [0.62, 0.83]	+
El-Solh 2021	-0.1508	0.082	5.6%	0.86 [0.73, 1.01]	
Fan 2020	-1.3823 0	6644	0.3%	0.25 [0.07, 0.92]	
Grasselli 2020	-0.0202 0	1033	4.7%	0.81 [0.79, 0.83]	+
Haji 2021	-0.3871 0	1381	3.5%	0.68 [0.52, 0.89]	
Holman 2020	-0.1985 0	1163	4.2%	0.82 [0.65, 1.03]	
Holman 2020	-0.3285 0	0208	7.9%	0.72 [0.69, 0.75]	-
Kouhpeikar 2022	-0.6733 0	4237	0.6%	0.51 [0.22, 1.17]	
Lala 2020	-0.5621 0	2205	5.0%	0.57 [0.47, 0.69]	
Memel 2022	-0.5692 0	2146	2.0%	0.57 [0.37 0.86]	
Oddy 2021	-0.3147 0	2319	1.7%	0.73 [0.46, 1.15]	
Pazoki 2021	-0.1508 0	2486	1.6%	0.86 [0.53, 1.40]	-+
Peymani 2021	-0.2744 0	8103	0.2%	0.76 [0.16, 3.72]	
Rey 2021	-0.0513	0.14	3.5%	0.95 [0.72, 1.25]	+ T
Santosa 2022	-0.6733 0	0365	7.5%	0.51 [0.43, 0.61]	
Shen 2021	-2.0402 0	5197	0.4%	0.13 [0.05. 0.36]	
Vila-Corcoles 2021	-0.3147	0.118	4.2%	0.73 [0.58, 0.92]	-
Volff 2021	1.2782 0	4649	0.5%	3.59 [1.44, 8.93]	
Zhang 2020	-0.5447 0.	1641		Not estimable	
Total (95% CI)		-	00.0%	0.74 [0.69. 0.79]	•
Heterogeneity: Tau ² = 0.0	01; Chi ^a = 129.22 df	= 27 (P	< 0.0000	1); I ² = 79%	
Test for overall effect: Z =	8.60 (P < 0.00001)				U.UT U.1 1 10 10 Eavours Statin Users Eavours Non-Statin Leave
					. aroura oraun vasta ratours norrotaul USEIS

Figure 2. Forest plots of adjusted odds ratio (**A**) and hazard ratio (**B**) for mortality in statin users versus non-users among COVID-19 patients.

Studies reporting hazard ratios-We included 28 studies with hazard ratios corrected by covariate adjustments or propensity score matching between statin users and nonusers [30,41,45,47,53,70,84,86–106]. The NOS scores of these studies were in the good category (Supplementary Table S3). The pooled hazard ratio estimate for mortality was 0.74 (95% CI: 0.69-0.79) and was statistically significant (Z = 8.89; p < 0.00001; Figure 2B). Our funnel plot and Egger's regression analysis found no evidence of publication bias (Supplementary Figure S1B). We also found heterogeneity in this meta-analysis ($I^2 = 79\%$). Using the same approach as for the mortality OR above, we performed sensitivity analyses of individual studies and found no outliers (Supplementary Figure S4). Sensitivity analyses of studies with or without propensity score matching also revealed no qualitative effect on the pooled estimate or heterogeneity (Supplementary Figure S5). Taken together, our data therefore show that the statin users are less likely to die from COVID-19 but substantial unexplained heterogeneity exists in the data, suggesting that other factors may contribute to determine the effect of statins on COVID-19 patients. The one study showing a significant increase in mortality with statin treatment was in patients already receiving invasive mechanical ventilation [106].

3.3. Effect of Statins on ICU Admission

Studies reporting odds ratios—We included 15 studies [25,34,42,47,50,52,54,55,60,61,65, 67,76,81,107] with corrected odds ratios for ICU admission by covariate adjustments or propensity score matching between statin users and non-users. NOS risk of bias analysis show that these studies were in the good category (Supplementary Table S3). The pooled estimate of the odds ratio was 0.94 (95% CI: 0.89–0.99; Figure 3A). The Z-test revealed that statin users are significantly less likely to be admitted to the ICU (Z = 2.37; p = 0.02). We found no asymmetry in the funnel plots, suggesting no publication bias (Supplementary Figure S6A). We also found little heterogeneity in the meta-analysis ($I^2 = 7\%$).



Figure 3. Forest plots of adjusted odds ratio (**A**) and hazard ratio (**B**) for ICU admission in statin users versus non-users among COVID-19 patients.

Studies reporting hazard ratios—We included five covariate-adjusted or propensity score-matched studies reporting hazard ratios for ICU admission between statin users and non-users [45,47,84,99,103]. NOS risk of bias analysis show that these studies were in the good category (Supplementary Table S3). There was a statistically significant benefit of statin use on ICU admission (pooled estimate = 0.76; 95% CI: 0.60–0.96; Z = 2.29; *p* = 0.02). There was no evidence of publication bias (Supplementary Figure S6B). Some heterogeneity

exists in the data (I² = 57%), but the χ^2 test revealed this was not statistically significant (Figure 3B). Our meta-analysis therefore revealed that statin users with COVID-19 were less likely to be admitted to the ICU.

3.4. Effect of Statins on Requirement of Mechanical Ventilaion

Studies reporting odds ratios—We included 19 studies reporting covariate-adjusted or propensity score-matched odds ratios for requiring mechanical ventilation in statin users versus non-users [31,34,41,42,47,49,50,52,54,55,60,65,76,79,80,100,104,108,109]. NOS risk of bias analysis show that these studies were in the good category (Supplementary Table S3). Our meta-analysis revealed that the use of statins conferred a statistically significant benefit in terms of requiring mechanical ventilation in COVID-19 patients (pooled estimate = 0.84; 95% CI: 0.78–0.92; Z = 4.00; p < 0.00001; Figure 4A). There was no evidence of publication bias (Supplementary Figure S7). Some heterogeneity exists in the data (I² = 34%) but is not statistically significant (Figure 4A).

Study or Subgroup long Odds Ratio SE Weint IN, Random, 95% CI M. Random, 95% CI Andrews 2022 -0.2744 0.2897 2.0% 0.99 [0.56, 1.74] Bejan 2021 -0.0101 0.2897 2.0% 0.99 [0.56, 1.74] Bejan 2021 -0.1010 0.2897 2.0% 0.99 [0.56, 1.74] Bejan 2021 -0.1054 0.4675 0.8% 0.99 [0.56, 1.74] Cariou 2021 -0.0101 10044 4.4% 0.99 [0.70, 1.41] Chow 2022 0.0296 0.2567 2.4% 1.03 [0.62, 1.70] Fan 2020 -0.2846 0.391 1.5% 0.75 [0.39, 1.46] Gupta 2021 -0.1185 0.1525 5.6% 0.89 [0.66, 1.20] Kuar 2021 -0.0810 1.468 0.89 [0.71, 0.90] - Kuar 2021 -0.0813 0.0945 10.2% 1.08 [0.61, 1.84] Ikari 2021 -0.437 0.3117 1.7% 0.65 [0.32, 1.17] Masana 2022 -0.158 0.580 [0.21, 1.65] - - Shen 2021	Α				Oddo Datia	Odda Patia
Andrews 2022 -0.2744 0.026 10.000 0.76 (r.27, 0.60) Bejan 2021 -0.0101 0.287 7 2.0% 0.99 (0.56, 1.74) Bejan 2021 -0.2231 0.4222 1.0% 0.80 (0.35, 1.83) Bejan 2021 -0.0231 0.4222 1.0% 0.80 (0.36, 2.25) Cariou 2021 -0.0164 0.44% 0.99 (0.68, 1.45) - Choir 2021 -0.0184 4.1% 1.00 (0.69, 1.45) - Choir 2021 -0.0188 0.1% 1.06 (0.68, 1.45) - Choir 2021 -0.0188 0.1% 1.00 (0.68, 1.45) - Gupta 2021 -0.0188 0.1% 1.00 (0.68, 1.45) - Kari 2021 -0.437 0.311 1.0% 0.65 (0.35, 1.19) - Ikari 2021 -0.437 0.311 1.0% 0.80 (0.71, 0.90) - Li 2022 -0.0231 0.090 0.314 2.9% 0.86 (0.62, 1.17) - Masana 2021 -0.165 0.1625 5.1% 0.85 (0.62, 1.17) -	Study or Subgroup	log[Odde Patio]	ee.	Mojaht	V Bandom 05% Cl	Odds Rallo
Autorews 2022 0.214* 0.02877 2.0% 0.90 (0.74, 0.00) Bejan 2021 -0.0101 0.02877 2.0% 0.99 (0.56, 1.74) Bejan 2021 -0.0101 0.1804 4.4% 0.99 (0.70, 1.41) Chair 2021 -0.0101 0.1804 4.4% 0.99 (0.70, 1.41) Chair 2021 -0.0101 0.1804 4.4% 0.99 (0.70, 1.41) Chair 2021 -0.0101 0.1804 4.4% 0.99 (0.70, 1.41) Chow 2022 0.0296 0.2557 2.4% 1.03 (0.62, 1.70) Fan 2020 -0.2446 0.3391 1.5% 0.75 (0.38, 1.46) Gupta 2021 -0.1165 0.1525 5.6% 0.89 (0.66, 1.20) Ikari 2021 -0.437 0.3117 1.7% 0.05 (0.35, 1.19) Ikari 2021 -0.437 0.317 1.7% 0.05 (0.26, 1.17) Ikari 2021 -0.437 0.317 1.7% 0.05 (0.26, 1.17) Ikari 2021 -0.540 0.5303 0.6% 0.58 (0.27, 1.17) Miaschai 2021 -0.744 0.2962 1.9% 0.19 (0.67, 1.13) Shen 2021	Androwo 2022	0.2744	0.0262	10.0%	0.76 (0.72, 0.90)	
Depan 2021 -0.010 0.203 0.422 1.043 0.038 0.038 1.033 1.043 Bejan 2021 -0.1016 0.4222 1.0422 1.044 0.09 0.035 1.83 Cariou 2021 -0.01016 0.1804 4.44% 0.09 0.035 1.83 Choi 2021 -0.01016 0.1804 4.44% 0.09 0.036 1.451 Choi 2021 -0.0116 0.1804 4.44% 0.09 0.038 1.451 Choi 2021 -0.0246 0.0331 1.5% 0.75 0.39 1.03 0.62 1.070 Kari 2021 -0.1165 0.1525 5.6% 0.89 0.661, 1.841 1.01 1.06 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.03 1.01	Paian 2021	-0.2744	0.0202	2.0%	0.70 [0.72, 0.80]	
Depart 2021 -0.1054 0.4223 10.30 0.000 [0.35, 1.05] Cariou 2021 -0.0101 0.16475 0.867 0.89 0.36, 1.25] Cariou 2021 -0.0101 0.184 4.4% 0.99 [0.70, 1.41] 100 0.068, 1.45] Choi 2021 0 0.188 4.1% 1.00 [0.68, 1.45] 1.00 0.66, 1.20] Fan 2020 -0.2846 0.3331 1.5% 0.75 [0.39, 1.46] 1.00 1.00 0.066, 1.20] Kari 2021 -0.01616 0.1625 5.6% 0.89 [0.66, 1.20] 1.06 1.04 1.00 1.06 1.04 1.00 1.05 1.01 1.00 1.06 1.04 1.02 1.04 1.02 1.04 1.01 1.01 1.00 1.01	Dejan 2021	-0.0101	0.2077	1.0%	0.00 [0.00, 1.74]	
Depart 2021 -0.0104 0.01804 4.4% 0.030 [0.30, 2.29] Chow 2021 -0.0101 0.1804 4.1% 1.00 [0.60, 1.45] Chow 2022 0.0296 0.2557 2.4% 1.03 [0.62, 1.70] Fan 2020 -0.2846 0.3391 1.5% 0.75 [0.39, 1.46] Gupta 2021 -0.1165 0.1525 5.6% 0.89 [0.66, 1.20] Kari 2021 -0.0611 1.02744 2.1% 1.06 [0.61, 1.84] Kari 2021 -0.0611 1.02744 2.1% 1.06 [0.61, 1.84] Kari 2021 -0.0611 1.02744 2.1% 1.06 [0.62, 1.19] Kuno 2022 0.0803 0.945 1.028 [0.62, 1.17] - Masana 2022 -0.1580 0.1625 5.1% 0.85 [0.62, 1.17] Mtacchione 2021 -0.540 0.5303 0.6% 0.58 [0.21, 1.65] Permani 2021 -0.1650 0.1625 5.6% 0.89 [0.66, 1.20] Song 2020 -0.7985 0.4023 1.19 [0.67, 2.13] - Song 2020 -0.7985 0.4023 1.19 [0.67, 2.13] - Tortes-Pena 2021	Bejan 2021	-0.2231	0.4222	1.070	0.00 [0.30, 1.03]	
Control 2021 0.1080 4.439 0.0380 0.761 1.01 Choir 2021 0.0188 4.143 1.00 1.03 0.621, 1.11 Choir 2021 0.0296 0.2557 2.4% 1.03 0.621, 1.20 Gupta 2021 0.0186 0.1555 5.6% 0.89 0.661, 1.20 Ikari 2021 0.0611 0.2744 2.1% 1.06 0.635, 1.19 Kuno 2022 0.0803 0.945 10.2% 1.08 0.90, 1.30 Kuno 2021 -0.2311 1.7% 0.65 0.58, 1.19 4.43 Kuno 2022 0.0803 0.945 1.02 0.80 0.71, 0.90 Li 2022 -0.2231 0.0601 1.46% 0.80 0.71, 0.90 Mtacchione 2021 -0.54 0.530 0.68 0.58 0.21, 1.65 Shen 2021 -0.166 0.1622 1.9% 0.48 0.090 0.44 Shen 2021 -0.16584 0.1822 4.3% 0.52 0.68 0.74 Umakanthan 2021 -0.16584 0.1822 4.3% 0.52 0.56	Cariou 2021	-0.0101	0.4075	4 4 96	0.00 [0.30, 2.25]	<u> </u>
Chow 2021 0.0296 0.0557 2.4% 1.03 0.052, 1.79 Fan 2020 -0.2246 0.3391 1.5% 0.75 0.39, 1.46 Gupta 2021 -0.16165 0.1525 5.6% 0.89 10.66, 1.20 Ikari 2021 -0.4165 0.1525 5.6% 0.89 10.66, 1.20 Ikari 2021 -0.417 1.7% 0.056 0.39, 1.46 Kuno 2022 -0.02923 0.0945 10.2% 1.08 1.09, 10.90 Lohia 2021 -0.437 0.211 1.46, 80 0.80 1.01 1.01 Masana 2022 -0.2231 0.0601 1.46, 8% 0.80 1.01 1.01 Masana 2021 -0.54 0.530 0.68 0.68 1.02 1.03 1.05 Permani 2021 -0.744 0.2342 2.9% 0.68 1.02 1.03 1.03 1.03 Song 2020 -0.7985 0.4023 1.1% 0.45 1.02 0.99 1.1% 1.19 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.0	Choi 2021	-0.0101	0.1004	4.4 %	1 00 [0 60 1 46]	
Chow 2022 0.0290 0.2390 0.2391 1.5% 0.750 0.391, 1.69 Gupta 2021 -0.1264 0.3391 1.5% 0.75 0.39, 1.461 0.4 Kari 2021 -0.0264 0.3391 1.5% 0.75 0.39, 1.461 0.4 Kari 2021 -0.0165 0.1625 5.6% 0.89 [0.66, 1.20] 0.4 0.4 Kari 2021 -0.0437 0.3117 1.7% 0.65 [0.35, 1.19] 0.6 0.4 Kun 2022 0.0803 0.0945 10.2% 1.08 [0.90, 1.30] 0.4 0.4 Lohia 2021 -0.2349 0.6611 1.4% 0.86 [0.62, 1.17] 0.4 0.4 Masana 2022 -0.1680 0.1625 5.1% 0.05 [0.62, 1.13] 0.4 0.4 0.4 0.4 0.5 0.58 [0.21, 1.65] 0.590 <td>Chow 2022</td> <td>0 0 2 0 6</td> <td>0.100</td> <td>9.1%</td> <td>1.00 [0.03, 1.45]</td> <td></td>	Chow 2022	0 0 2 0 6	0.100	9.1%	1.00 [0.03, 1.45]	
Pair 2020 -0.2040 0.526 5.6% 0.89 0.59 0.58 1.79 Ikari 2021 0.0611 0.2794 2.1% 1.06 0.66 1.20 Ikari 2021 -0.637 0.0611 0.2794 2.1% 1.06 0.66 1.20 Ikari 2021 -0.437 0.7% 0.65 0.59 1.08 0.90 1.01 Ikari 2021 -0.2231 0.0601 14.6% 0.80 0.71 0.90 1.02 ILi 2022 -0.2231 0.0601 14.6% 0.80 0.61 1.01 1.01 Masana 2022 -0.158 0.1625 5.1% 0.85 0.68 0.11 1.01 Peymani 2021 -0.0408 0.2314 2.9% 0.86 0.68 1.151 1.19 1.19 0.66 1.20 1.19 0.66 1.19 1.19 0.66 1.11 1.19 1.19 0.20 0.99 1.15 5.7% 0.64 0.62 1.13 1.19 1.19 0.66 1.20 1.19 0.52 0.66 0.62 1.13	Ean 2020	-0.2230	0.2007	1.5%	0.75 [0.02, 1.70]	
Output 2021 -0.1103 61.033 50.39 50.50 50.39	Gunto 2020	-0.2840	0.3331	5.6%	0.75 [0.35, 1.40]	
Ikari 2021 0.0011 0.1371 1.7% 0.05 [0.3, 1.09] Kuno 2022 0.0803 0.0944 10.2% 1.08 [0.90, 1.30] L 2022 0.20231 0.0601 1.0.2% 1.08 [0.90, 1.30] Lohia 2021 -0.231 0.0601 1.0.2% 1.08 [0.90, 1.30] Masana 2022 -0.2321 0.0601 1.6% 0.80 [0.71, 0.90] Masana 2022 -0.158 0.1625 5.1% 0.85 [0.62, 1.17] Mitacchione 2021 -0.0408 0.2334 2.9% 0.86 [0.61, 1.51] Shen 2021 -0.1744 0.1596 1.19 [0.62, 0.73] 1.165 Song 2020 -0.7985 0.4023 1.1% 0.45 [0.20, 0.99] Svensson 2021 -0.1744 0.1513 5.7% 0.89 [0.66, 1.20] Umakanthan 2021 -0.165 5.6% 0.89 [0.66, 1.20] 1.01 1.01 Total (95% CI) 100.0% 0.84 [0.78, 0.92] 1.1% 1.02 1.01 1.01 1.00 Favours Statin Users Favours Non-Statin Users Favours Non-Statin Users Favours Non-Statin Users 1.01 1.01 1.01	Ikari 2021	-0.1105	0.1323	2.1%	1.06 [0.60, 1.20]	
Main 2021 -0.0437 0.0417 1.7.8 0.030 0.030 1.19 Li 2022 -0.2231 0.0465 1.0.8 0.090 1.39 1.019 Li 2022 -0.2231 0.0465 1.0.8 0.08 0.71 0.901 Li 2022 -0.2231 0.0465 1.0.8 0.80 0.71 0.901 Masana 2022 -0.158 0.1625 5.1% 0.85 0.62 1.1.71 Mitachione 2021 -0.54 0.530 0.6% 0.58 0.51 1.151 Shen 2021 -0.140 0.2314 2.9% 0.96 0.66 1.119 1.19 Song 2020 -0.7985 0.4023 1.1% 0.45 0.20 0.99 9.99 Svensson 2021 -0.1744 0.1513 5.7% 0.84 0.62 1.1% <t< td=""><td>Ikari 2021</td><td>-0.427</td><td>0.2754</td><td>2.1%</td><td>0.6510.25.1.101</td><td></td></t<>	Ikari 2021	-0.427	0.2754	2.1%	0.6510.25.1.101	
Name 2022 0.0030 0.0230 102.83 103.023 103.030 Labla 2021 0.0231 0.0601 14.65% 0.80 (0.71, 0.90) 104.030 Masana 2022 -0.158 0.1625 5.1% 0.86 (0.62, 1.17) 104.030 Masana 2022 -0.168 0.1625 5.1% 0.056 (0.62, 1.17) 104.053 Mitacchione 2021 -0.54 0.5303 0.6% 0.58 (0.21, 1.65) 105.05 Perymani 2021 -0.0408 0.2314 2.9% 0.36 (0.61, 1.51) 105.7, 2.13 Song 2020 -0.7985 0.4023 1.1% 0.45 (0.20, 0.99) 1.9 1.9 Svensson 2021 -0.1165 0.1525 5.6% 0.89 (0.66, 1.20) 100.0% 0.84 (0.78, 0.92) Heterogeneity: Tau* = 0.01; Chi* = 31.94, df = 21 (P = 0.06); F = 34% 0.52 (0.36, 0.74) 10 100 Test for overail effect: Z = 4.00 (P < 0.0001)	Kan 2021	0.437	0.0046	10.2%	1 00 00 00 1 201	+
L 1022 -0.2231 0.00197 (4.0.39) Masana 2021 -0.2559 0.0029 3.4% 0.72 (48, 1.09) Masana 2022 -0.158 0.1625 5.1% 0.85 [0.62, 1.17] Mitacchione 2021 -0.0408 0.2314 2.9% 0.86 [0.61, 1.51] Shen 2021 -0.1748 0.2962 1.9% 1.19 [0.67, 2.13] Song 2020 -0.7865 0.0231 1.1% 0.45 [0.62, 1.13] Torres-Pena 2021 -0.1165 0.1525 5.6% 0.89 [0.66, 1.13] Tortal (95% CI) 100.0% 0.84 [0.67, 2.13] -0.116 100 Test for overall effect: Z = 4.00 (P < 0.0001)	Li 2022	-0.2221	0.0545	14.6%	0.00 [0.30, 1.30]	•
Loins 2021 -0.539 0.639 0.48 0.72 (0.46, 1.09) Missana 2022 -0.158 0.1625 5.1% 0.05 (0.22, 1.17) Mitachione 2021 -0.64 0.5303 0.6% 0.68 (0.21, 1.15) Permani 2021 -0.0408 0.2314 2.29% 0.05 (0.61, 1.51) Song 2020 -0.7985 0.4023 2.1% 0.45 (0.20, 0.99) Svensson 2021 -0.1164 0.1513 5.7% 0.84 (0.62, 1.13) Torres-Pena 2021 -0.6684 0.1622 4.3% 0.52 (0.36, 0.74) Umakanthan 2021 -0.1165 0.1525 5.6% 0.89 (0.66, 1.20) Heterogeneity, Tau*=0.01; Ch*= 31.94, df = 21 (P = 0.06); P = 34% 0.1 0.1 10 Test for overall effect: Z = 4.00 (P < 0.0001)	Li 2022	-0.2251	0.0001	2.4%	0.00 [0.71, 0.00]	
Basin 2022 10,136 0.136 0.136 0.036 <td>Macana 2021</td> <td>-0.3255</td> <td>0.2092</td> <td>5.1%</td> <td>0.72 [0.46, 1.05]</td> <td></td>	Macana 2021	-0.3255	0.2092	5.1%	0.72 [0.46, 1.05]	
Bit Michael Solution 0.04 (0.534 (0.29%) 0.05 (0.61, 1.51) Shen 2021 0.0148 0.2962 1.9% 1.19 (0.67, 2.13) Song 2020 -0.7985 0.0023 1.1% 0.45 (0.20, 0.99) Svensson 2021 -0.1744 0.1513 5.7% 0.84 (0.62, 1.13) Torres-Pena 2021 -0.16584 0.1822 4.3% 0.52 (0.36, 0.74) Umakanthan 2021 -0.1165 0.1525 5.6% 0.89 (0.66, 1.20) Total (95% CI) 100.0% 0.84 (0.78, 0.92) Heterogeneity: Tau ² = 0.01; Ch ² = 31.94, df = 21 (P = 0.06); P = 34% 0.01 0.1 Test for overall effect: Z = 4.00 (P < 0.0001)	Mitacchione 2022	-0.158	0.1025	0.1%	0.53 [0.02, 1.17]	
Permain 2021 -0.0406 0.238 2.38 0.360 [0.67, 2.13] Song 2020 -0.7985 0.4023 1.19 [0.62, 1.13] Song 2020 -0.7985 0.4023 1.13 Torres-Pena 2021 -0.6584 0.1525 5.6% 0.89 [0.62, 1.13] Torres-Pena 2021 -0.6584 0.1525 5.6% 0.89 [0.66, 1.20] Umakanthan 2021 -0.1165 0.1525 5.6% 0.89 [0.66, 1.20] Heterogeneity: Tau*= 0.01; Chi*= 31.94, df = 21 (P = 0.06); P = 34% 0.01 0.1 1.1 10 Test for overall effect Z = 4.00 (P < 0.0001)	Reymoni 2021	-0.04	0.0303	2.0%	0.06 [0.21, 1.00]	
Bit Minu 201 0.1140 0.0140 1.150 0.116 [0.01, 1.03] Svensson 2021 -0.1785 0.023 1.15% 0.04 [0.62, 1.13] Torres-Pena 2021 -0.6584 0.1822 4.3% 0.52 [0.36, 0.74] Umakanthan 2021 -0.1165 0.1525 5.6% 0.89 [0.66, 1.20] Total (95% Cl) 100.0% 0.84 [0.78, 0.92] 101 10 Heterogeneity. Tau* = 0.01; Chi* = 31.94, df = 21 (P = 0.06); P = 34% 0.01 0.1 1 100 Test for overall effect. Z = 4.00 (P < 0.0001)	Shen 2021	0.1749	0.2014	1 9%	1 10 [0.67, 2 13]	
Bit Hazard Ratio Hazard Ratio Study or Subgroup logHazard Ratiol SE Weight V. Random, 95% CI Bit Hazard Ratio Hazard Ratio Hazard Ratio Hazard Ratio Study or Subgroup logHazard Ratiol SE Weight V. Random, 95% CI Bit Hazard Ratio Hazard Ratio Hazard Ratio Hazard Ratio Study or Subgroup logHazard Ratiol SE Weight V. Random, 95% CI Bit Hazard Ratio Hazard Ratio Hazard Ratio Hazard Ratio Study or Subgroup logHazard Ratiol SE Weight V. Random, 95% CI Haji 2021 0.0198 0.2185 23.1% 0.58 (0.38, 0.89) Haji 2021 Haji 2020 -0.6733 0.2168 23.3% 0.51 (0.33, 0.78) Haji 2020 Haji 2021 0.6733 0.2168 23.3% 0.51 (0.33, 0.78)	Song 2020	-0.7985	0.2902	1.5%	0.45 (0.07, 2.13)	
Bits Hazard Ratio Hazard Ratio Study or Subgroup logHazard Ratiol SE Weight N. Random, 95% CI Bits Hazard Ratio Hazard Ratio Hazard Ratio Study or Subgroup logHazard Ratiol SE Weight N. Random, 95% CI El-Solh 2021 0.0198 0.198 29.7% 1.02 (0.4), 0.90 Hazard Ratio Hazard Ratio Hazard Ratio Hazard Ratio Study or Subgroup logHazard Ratiol SE Weight N. Random, 95% CI Haj 0.0198 0.118 29.7% 1.02 (0.4), 0.90 Haji 2021 Haji 2021 0.0198 0.2185 23.1% 0.60 (0.40, 0.90) Haji 2021 Haji 2021 0.6733 0.2168 2.3.3% 0.61 (0.3), 0.78] Haji 2021	Svensson 2021	-0.7585	0.4023	5.7%	0.45 [0.20, 0.55]	
B Hazard Ratio Study or Subgroup log(Hazard Ratio) Study or Subgroup log(Ratio) Study or Subgroup log(Ratio) Study or Subgroup log(Ratio)	Torres-Pena 2021	-0.6594	0.1913	4 3%	0.52 [0.36 0.74]	- -
B Hazard Ratio Study or Subgroup log[Hazard Ratio] Haji 2021 -0.5447 -0.567 0.269 23.1% 0.58 [0.38, 0.78] Zhang 2020 -0.6733 0.51 [0.33, 0.78]	Limakanthan 2021	-0.0304	0.1622	5.6%	0.92 [0.96, 0.74]	
B Hazard Ratio Unit No. Hazard Ratio Hazard Ratio Hazard Ratio Hazard Ratio No. No. Statin Users Favours Statin Users Favours Statin Users Favours Statin Users B Hazard Ratio N. Random, 95% CI N. Random, 95% CI <td< td=""><td>Offiakanulari 2021</td><td>-0.1105</td><td>0.1525</td><td>5.0 %</td><td>0.03 [0.00, 1.20]</td><td></td></td<>	Offiakanulari 2021	-0.1105	0.1525	5.0 %	0.03 [0.00, 1.20]	
Heterogeneity: Tau ² = 0.01; Chi ² = 31.94, df = 21 (P = 0.06); P = 34% Interview of a state of the sta	Total (95% CI)			100.0%	0.84 [0.78, 0.92]	•
B Hazard Ratio Hazard Ratio Study or Subgroup log[Hazard Ratio] SE Weight N. Random, 95% CI EI-Solh 2021 0.0198 0.0198 23.7% 1.02 (0.81) (1.29) Haji 2021 -0.5075 0.2069 23.9% 0.60 (0.40, 0.90) Masana 2022 -0.54447 0.2185 23.3% 0.51 (0.33, 0.78)	Heterogeneity: Tau ² =	0.01; Chi ² = 31.94	df = 21	(P = 0.06)	; I ² = 34%	
B Hazard Ratio Hazard Ratio Hazard Ratio Study or Subgroup log[Hazard Ratio] SE Weight V. Random, 95% CI El-Solh 2021 0.0198 0.1198 29.7% 1.02 [0.81, 1.29] Haji 2021 -0.5075 0.2069 23.9% 0.60 [0.40, 0.90] Masana 2022 -0.5447 0.218 23.1% 0.58 [0.38, 0.89] Zhang 2020 -0.6733 0.2168 23.3% 0.51 [0.33, 0.78]	Test for overall effect:	Z = 4.00 (P < 0.000	11)		U.U1 U.1 1 10 100 Equation Station Lineare Equation Man. Station Lineare	
B Hazard Ratio Hazard Ratio Hazard Ratio Hazard Ratio Study or Subgroup log[Hazard Ratio] SE Weinht N, Random, 95% CI N, Random, 95% CI EI-Solh 2021 0.0198 0.1198 29.7% 1.02 [0.81, 1.29] + Haji 2021 -0.5075 0.2069 23.3% 0.60 [0.40, 0.90] + Zhang 2020 -0.6733 0.2168 23.3% 0.51 [0.33, 0.78] +						Favours Statin Osers Favours Non-Statin Osers
B Hazard Ratio Hazard Ratio Hazard Ratio Study or Subgroup log[Hazard Ratio] SE Weight N, Random, 95% Cl N, Random, 95% Cl El-Solh 2021 0.0198 0.1198 29.7% 1.02 (0.81, 1.29) + Haji 2021 -0.5075 0.2069 23.9% 0.60 (0.40, 0.90) + Masana 2022 -0.5447 0.2185 23.3% 0.51 (0.33, 0.78) +						
Study or Subgroup log[Hazard Ratio] Hazard Ratio Hazard Ratio Study or Subgroup log[Hazard Ratio] SE Weight IV.Random, 95% CI IV.Random, 95% CI El-Solh 2021 0.0198 0.1198 29.7% 1.02 [0.81, 1.29] IV.Random, 95% CI Haji 2021 -0.5075 0.2069 23.9% 0.60 [0.40, 0.90] IV.Random, 95% CI Masana 2022 -0.5447 0.2185 23.1% 0.561 [0.38, 0.89] IV.Random, 95% CI Zhang 2020 -0.6733 0.2168 23.3% 0.51 [0.33, 0.78] IV.Random, 95% CI	B					
Study or Subgroup log[Hazard Ratio] SE Weight IV. Random, 95% Cl IV. Random, 95% Cl EI-Solh 2021 0.0198 0.1198 29.7% 1.02 [0.811.129] + Haji 2021 -0.5075 0.2069 23.9% 0.60 [0.40, 0.90] + Masana 2022 -0.5447 0.2185 23.1% 0.58 [0.38, 0.89] + Zhang 2020 -0.6733 0.2168 23.3% 0.51 [0.33, 0.78] +	-				Hazard Ratio	Hazard Ratio
El-Solh 2021 0.0198 0.1198 29.7% 1.02 [0.81, 1.29] Haji 2021 -0.5075 0.2069 23.9% 0.60 [0.40, 0.90] Masana 2022 -0.5447 0.2185 23.1% 0.58 [0.38, 0.89] Zhang 2020 -0.6733 0.2168 23.3% 0.51 [0.33, 0.78]	Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Haji 2021 -0.5075 0.2069 23.9% 0.60 [0.40, 0.90] Masana 2022 -0.5447 0.2185 23.1% 0.58 [0.38, 0.89] Zhang 2020 -0.6733 0.2168 23.3% 0.51 [0.33, 0.78]	El-Solh 2021	0.0198	0.1198	29.7%	1.02 [0.81, 1.29]	-
Masana 2022 -0.5447 0.2185 23.1% 0.58 [0.38, 0.89] T Zhang 2020 -0.6733 0.2168 23.3% 0.51 [0.33, 0.78]	Haji 2021	-0.5075	0.2069	23.9%	0.60 [0.40, 0.90]	
Zhang 2020 -0.6733 0.2168 23.3% 0.51 [0.33, 0.78]	Masana 2022	-0.5447	0.2185	23.1%	0.58 [0.38, 0.89]	
	Zhang 2020	-0.6733	0.2168	23.3%	0.51 [0.33, 0.78]	
Total (95% Cl) 100.0% 0.67 [0.47, 0.97]	Total (95% CI)			100.0%	0.67 [0.47, 0.97]	◆
Heterogeneity: Tau ² = 0.10: Chi ² = 12.21. df = 3 (P = 0.007): P = 75%	Heterogeneity: Tau ² =	0.10: Chi ² = 12.21	df = 3 /P			
Test for overall effect Z = 2.13 (P = 0.03) 0.01 0.1 1 10 100	Test for overall effect:	Z = 2.13 (P = 0.03)	0	0.001/1		0.01 0.1 1 10 100

Figure 4. Forest plots of adjusted odds ratio (**A**) and hazard ratio (**B**) for mechanical ventilation in statin users versus non-users among COVID-19 patients.

Studies reporting hazard ratios—We included four studies containing covariate-adjusted or propensity score-matched hazard ratio data for mechanical ventilation in statin users and non-users [45,60,84,94]. NOS risk of bias analysis show that these studies were in the good category (Supplementary Table S3). The pooled estimate was 0.67 (95% CI: 0.47–0.97), and there was a statistically significant benefit for statin users (Z = 2.13; p = 0.03). The low number of studies precluded the publication bias analyses. Our analysis also revealed heterogeneity in the data ($I^2 = 75\%$). Visual inspection of the data suggest that one study had a quantitatively different effect to others [45]. We performed a sensitivity analysis by sequentially excluding individual studies from the analysis (Supplementary Figure S8). Our analysis revealed that removing the El-Solh et al. (2021) study from the analysis increased the beneficial effect of statins on mechanical ventilation (0.56; 95% CI: 0.44–0.72) and removed the heterogeneity altogether ($I^2 = 0\%$). Exclusion of other studies had no effect on heterogeneity. Taken together, our meta-analysis revealed that statin use reduces the requirement of mechanical ventilation in COVID-19 patients.

4. Discussion

Our meta-analysis of retrospective observational studies is the largest to date. Our results revealed that statin use was associated with lower mortality, reduced ICU admission and reduced requirement for mechanical ventilation. In terms of mortality, our meta-analysis found an overall 28% and 26% lower mortality in statins users, when pooling adjusted odds ratios and hazard ratios, respectively. For ICU admission, we found that statins users were 6% and 24% less likely to be admitted, when pooling adjusted odds and hazard ratios, respectively. Finally, statin users were 16% and 33% (pooled odds ratio and hazard ratio, respectively) less likely to require mechanical ventilation. We focused our meta-analysis on studies that reported covariate-adjusted point estimates and/or propensity score-matched populations. Nevertheless, we found substantial unexplained heterogeneity in our mortality meta-analysis, which was not surprising given the meta-analysis was based entirely on retrospective studies. This limits the certainty of the results of our mortality meta-analysis showed little heterogeneity, thus lending further support for the role that statins may play to mitigate severe COVID-19 outcomes.

The beneficial role of statins in the treatment of COVID-19 is supported by preclinical evidence. Statins have been shown to impair the structure, expression and trafficking of CD147 [110,111], which is used by SARS-CoV2 as a co-receptor to infect cells [112]. Statins are also well known to have anti-inflammatory effects, and this has been suggested to contribute to their beneficial effects on cardiovascular outcomes in general [113]. Statins have been shown to regulate the NLRP3 inflammasome [114]. This may be through inhibition of nuclear factor kappa B (NF-kB) and Toll-like receptor 4 [115,116]. This may reduce the excessive cytokine induction mediated by inflammasomes and NF-kB in COVID-19 patients [117].

There have been several meta-analyses evaluating the association between statin use and COVID-19 outcomes. Interestingly, meta-analyses that included both covariate adjusted and unadjusted point estimates in their summary effect analyses have found mixed effects of statins on COVID-19 outcomes [11,12,18,19,24,118]. Those that used covariate adjusted point estimates all reported beneficial effects of statins on COVID-19 outcomes [10,13–15,17,21–23]. This is not surprising because adverse COVID-19 outcomes have been associated with a wide range of different factors [2]. A recent retrospective study of over 2 million COVID-19 patients in the UK has found factors such as age, male sex, ethnicity, obesity and a number of underlying chronic conditions to be associated with hospital admission and death from COVID-19 [119]. For instance, male patients were approximately 1.5 times more likely to be admitted to hospital and/or die from COVID-19. Obese patients were over twice as likely to be hospitalized. People suffering from hypertension and diabetes were also at significantly increased risk for hospital admission and mortality from COVID-19. Indeed, the use of more than two antidiabetic or antihypertensive drugs was associated with increased mortality from COVID-19 [120]. Therefore, underlying cardiovascular diseases and/or diabetes will have a significant influence on point estimates for mortality and progression to more severe COVID-19 (i.e., ICU admission and requirement for mechanical ventilation). Similarly, mortality and severity point estimates will also be influenced by other confounding factors listed above. We therefore argue that it is crucial to use only multivariable-adjusted point estimates in these meta-analyses. Indeed, the effect of confounding factors are highlighted by the meta-analyses performed by Diaz-Arocutipa et al. (2021) and Scheen (2021) in which the effect of using unadjusted and adjusted point estimates were evaluated. Diaz-Arocutipa et al. (2021) found that the pooled estimate for mortality using unadjusted point estimates was 1.16, while that using adjusted point estimates was 0.67. Importantly, the extent of heterogeneity (assessed by the I^2 statistic) also reduced from 99% to 79% in the unadjusted and adjusted analyses, respectively. This is also consistent with the findings of Scheen (2021), who directly compared the pooled hazard ratio estimates from univariate (unadjusted) and multivariate (adjusted) analyses and found a statistically significant improvement in the hazard ratio for mortality

in the multivariate-adjusted analysis. We also focused our meta-analysis on studies that used propensity score-matched populations. Our sensitivity analysis revealed that the odds ratio or hazard ratio for studies that used propensity score matching was qualitatively and quantitatively similar to those that only reported covariate-adjusted point estimates. Our findings are also consistent with one other systematic review that evaluated propensity score-matched populations [22]. We therefore argue that propensity score matching should always be considered when performing retrospective clinical studies.

Our meta-analysis suffers from a number of limitations. The inclusion of non-randomized retrospective studies will inevitably increase the heterogeneity in our meta-analysis, although such heterogeneity was only observed in the mortality. Our sensitivity analyses did not reveal the causes for this heterogeneity, which limits the certainty in the mortality summary effect estimates. Nevertheless, the heterogeneity for our ICU admission odds and hazard ratio were substantially less ($I^2 = 0\%$ and 57%, respectively), and that for the mechanical ventilation odds ratio was 34%. The substantial heterogeneity seen with the mechanical ventilation hazard ratio was due to one study in particular [45]. This study was based on military veterans and as such was predominantly male (over 90%). Male sex is a known risk factor for the development of severe COVID-19 [2]. It was also not established whether the participants in the statin group in that study were actually taking statin at the time of developing infection with COVID-19. A similar problem exists with many of the studies reporting antecedent statin use. For the unexplained heterogeneity in our mortality meta-analysis, we could speculate on a number of factors. Such heterogeneity could come from the type and dosage of statins used by patients, which may not be clearly stated in some studies. The timing of statin administration may also be a factor. Prior meta-analyses have shown that patients already on statins prior to hospitalization with COVID-19 showed no benefit in terms of mortality, when compared to those where statins were only initiated after hospitalization [9,16]. Many studies we included do not make this distinction, and it can be reasonably assumed that pre-hospitalization statin use would have continued following hospital admission. Furthermore, the duration of statin administration and adherence to this prescription may also show great variation. This is consistent with the high level of heterogeneity in the studies or subgroups that isolated the patients who have been taking stating before hospitalization [9,16]. We therefore believe that studies describing the use of statins after hospitalization provide a more reliable indication that the patient had taken the drug. Another source of variation comes from studies that have evaluated statins as part of a multi-treatment modality for COVID-19, or studies that focused on a particular subgroup of patients (e.g., diabetics, hypertensives or elderly). Finally, heterogeneity will also exist in the criteria for covariate adjustments, propensity score matching and the follow up time for mortality data.

Despite these limitations, our findings are in broad agreement with similar metaanalyses performed, and therefore, the conclusions that can be drawn from our studies are strong and generalizable. Furthermore, the pooled estimates for odds ratios and hazard ratios of our specified outcomes were qualitatively and quantitatively in agreement with each other. Therefore, our findings and those of other well conducted meta-analyses provide strong evidence for the appropriate use of statins to reduce the risk of cardiovascular disease in people who may be at risk of developing COVID-19. Indeed, the use of statins has been advocated for the treatment of Middle East Respiratory Syndrome (MERS) [117,121]. We believe that this is a strong basis on which to conduct well-designed prospective clinical trials to evaluate the de novo use of statins to treat COVID-19. In this study, we excluded retrospective studies on the use of statins specifically for the treatment of COVID-19 because we argue that this can only be appropriately tested using prospective clinical trials. A number of clinical trials are ongoing, and two of these trials have reported their findings. The INSPIRATION-S study is a randomized clinical trial that directly compared the effect of atorvastatin with placebo on mortality and adverse cardiovascular events in 605 COVID-19 patients [122]. The study found no significant differences in the composite outcomes (incidence of mortality and cardiovascular events). However, the authors did note that the

incidence of the primary outcome was lower than expected, and therefore, more subtle effects of statins may not be detectable. Another randomized clinical trial compared the effects of emtricitabine, tenofovir, colchicine and rosuvastatin on 28-day mortality in 994 COVID-19 patients [123]. The study reports that while emtricitabine with tenofovir or colchicine with rosuvastatin did not improve mortality, the combination of the four drugs significantly improved 28-day mortality (HR = 0.53, 95% CI: 0.29–0.96), and reduced the requirement for mechanical ventilation (risk difference = 0.08; 95% CI: 0.11-0.04). However, we note that patient recruitment period for both of these trials overlapped with the roll-out of the different COVID-19 vaccines, which had substantial efficacy to prevent severe COVID-19 and death. Neither of these studies took vaccination status into account during randomization and this may have affected the results. Four ongoing randomized clinical trials will seek to directly evaluate the effects of statin use in COVID-19 patients (NCT02735707, NCT04380402, NCT04952350 and NCT04900155). Others are looking at a combination of drugs, including statins (NCT04472611, NCT04813471, NCT04631536, NCT04466241 and NCT04348695). Interestingly, there are two ongoing randomized clinical trials evaluating the effect of statins on post-COVID-19 syndrome (i.e., "long COVID", NCT04904536 and NCT04801940). We anticipate the results of these ongoing trials with much enthusiasm, and we believe further meta-analysis of the effect of statins on COVID-19 outcomes should focus on randomized clinical trials.

5. Conclusions

The results of our meta-analysis have shown that the use of statins is associated with significantly lower risks of mortality, ICU admission and mechanical ventilation in COVID-19 patients. These studies were based on the antecedent use of statins prior to infection or hospital admission and/or the continued use of statin after hospital admission rather than commencement of statin treatment after developing COVID-19 infection. The use of statin treatment to reduce cardiovascular risk in appropriate patients should be encouraged during the COVID-19 pandemic. Whether it may be beneficial to start statin treatment after developing the infection may be difficult to prove with the ongoing trials because of the rapid changes in the use of vaccinations and effective antiviral drugs and the changes in the SARS-CoV-2 variants.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/ 10.3390/jcm11185454/s1, Figure S1: Funnel plot and asymmetry analysis for mortality odds and hazard ratio, Figure S2: Sensitivity analysis of individual study effect on mortality odds ratio, Figure S3: Sensitivity analysis of studies with or without propensity score matching effect on mortality odds ratio, Figure S4: Sensitivity analysis of individual study effect on mortality hazard ratio, Figure S5: Sensitivity analysis of studies with or without propensity score matching effect on mortality hazard ratio, Figure S6: Funnel plot and asymmetry analysis for ICU admission odds and hazard ratio, Figure S7: Funnel plot and asymmetry analysis for mechanical ventilation odds ratio, Figure S8: Sensitivity analysis of individual study effect on mechanical ventilation hazard ratio, Table S1: Literature search strategy, Table S2: Summary of included studies, Table S3: Newcastle-Ottawa Scale assessment of study quality.

Author Contributions: Conceptualization, D.T.B.-H. and B.T.; methodology, D.T.B.-H. and B.T.; formal analysis, U.-S.L. and C.-F.L.; investigation, U.-S.L. and C.-F.L.; data curation, U.-S.L. and C.-F.L.; writing—original draft preparation, U.-S.L. and C.-F.L.; writing—review and editing, D.T.B.-H. and B.T.; visualization, D.T.B.-H. and B.T.; supervision, D.T.B.-H. and B.T.; project administration, D.T.B.-H. and B.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: Author Brian Tomlinson is an editorial board member of Journal of Clinical Medicine. Author Brian Tomlinson was not involved in the journal's review of, or decisions related to, this manuscript. The other authors declare no conflict of interest.

References

- 1. Dong, E.; Du, H.; Gardner, L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect. Dis.* **2020**, *20*, 533–534. [CrossRef]
- Williamson, E.J.; Walker, A.J.; Bhaskaran, K.; Bacon, S.; Bates, C.; Morton, C.E.; Curtis, H.J.; Mehrkar, A.; Evans, D.; Inglesby, P.; et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020, 584, 430–436. [CrossRef] [PubMed]
- 3. Moore, J.B.; June, C.H. Cytokine release syndrome in severe COVID-19. Science 2020, 368, 473–474. [CrossRef] [PubMed]
- 4. Chen, G.; Wu, D.; Guo, W.; Cao, Y.; Huang, D.; Wang, H.; Wang, T.; Zhang, X.; Chen, H.; Yu, H.; et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J. Clin. Investig.* **2020**, *130*, 2620–2629. [CrossRef] [PubMed]
- 5. Guo, W.; Li, M.; Dong, Y.; Zhou, H.; Zhang, Z.; Tian, C.; Qin, R.; Wang, H.; Shen, Y.; Du, K.; et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab. Res. Rev.* **2020**, *36*, e3319. [CrossRef] [PubMed]
- Dehnavi, S.; Sohrabi, N.; Sadeghi, M.; Lansberg, P.; Banach, M.; Al-Rasadi, K.; Johnston, T.P.; Sahebkar, A. Statins and autoimmunity: State-of-the-art. *Pharmacol. Ther.* 2020, 214, 107614. [CrossRef]
- Ridker, P.M.; Danielson, E.; Fonseca, F.A.; Genest, J.; Gotto, A.M., Jr.; Kastelein, J.J.; Koenig, W.; Libby, P.; Lorenzatti, A.J.; MacFadyen, J.G.; et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N. Engl. J. Med.* 2008, 359, 2195–2207. [CrossRef]
- Ridker, P.M.; Rifai, N.; Clearfield, M.; Downs, J.R.; Weis, S.E.; Miles, J.S.; Gotto, A.M., Jr.; Air Force/Texas Coronary Atherosclerosis Prevention Study, I. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. N. Engl. J. Med. 2001, 344, 1959–1965. [CrossRef]
- Chow, R.; Im, J.; Chiu, N.; Chiu, L.; Aggarwal, R.; Lee, J.; Choi, Y.G.; Prsic, E.H.; Shin, H.J. The protective association between statins use and adverse outcomes among COVID-19 patients: A systematic review and meta-analysis. *PLoS ONE* 2021, 16, e0253576. [CrossRef]
- 10. Diaz-Arocutipa, C.; Melgar-Talavera, B.; Alvarado-Yarasca, A.; Saravia-Bartra, M.M.; Cazorla, P.; Belzusarri, I.; Hernandez, A.V. Statins reduce mortality in patients with COVID-19: An updated meta-analysis of 147 824 patients. *Int. J. Infect. Dis.* **2021**, *110*, 374–381. [CrossRef]
- 11. Hariyanto, T.I.; Kurniawan, A. Statin and outcomes of coronavirus disease 2019 (COVID-19): A systematic review, meta-analysis, and meta-regression. *Nutr. Metab. Cardiovasc. Dis.* 2021, 31, 1662–1670. [CrossRef]
- 12. Hariyanto, T.I.; Kurniawan, A. Statin therapy did not improve the in-hospital outcome of coronavirus disease 2019 (COVID-19) infection. *Diabetes Metab. Syndr.* 2020, 14, 1613–1615. [CrossRef]
- 13. Kollias, A.; Kyriakoulis, K.G.; Kyriakoulis, I.G.; Nitsotolis, T.; Poulakou, G.; Stergiou, G.S.; Syrigos, K. Statin use and mortality in COVID-19 patients: Updated systematic review and meta-analysis. *Atherosclerosis* **2021**, *330*, 114–121. [CrossRef]
- 14. Kow, C.S.; Hasan, S.S. Meta-analysis of Effect of Statins in Patients with COVID-19. *Am. J. Cardiol.* **2020**, *134*, 153–155. [CrossRef] [PubMed]
- 15. Kow, C.S.; Hasan, S.S. The Association Between the Use of Statins and Clinical Outcomes in Patients with COVID-19: A Systematic Review and Meta-analysis. *Am. J. Cardiovasc. Drugs* **2021**, *22*, 167–181. [CrossRef]
- Permana, H.; Huang, I.; Purwiga, A.; Kusumawardhani, N.Y.; Sihite, T.A.; Martanto, E.; Wisaksana, R.; Soetedjo, N.N.M. In-hospital use of statins is associated with a reduced risk of mortality in coronavirus-2019 (COVID-19): Systematic review and meta-analysis. *Pharmacol. Rep.* 2021, 73, 769–780. [CrossRef]
- 17. Scheen, A.J. Statins and clinical outcomes with COVID-19: Meta-analyses of observational studies. *Diabetes Metab.* **2021**, 47, 101220. [CrossRef]
- Vahedian-Azimi, A.; Mohammadi, S.M.; Banach, M.; Beni, F.H.; Guest, P.C.; Al-Rasadi, K.; Jamialahmadi, T.; Sahebkar, A. Improved COVID-19 Outcomes following Statin Therapy: An Updated Systematic Review and Meta-analysis. *Biomed. Res. Int.* 2021, 2021, 1901772. [CrossRef]
- 19. Wu, C.C.; Lee, A.J.; Su, C.H.; Huang, C.Y.; Islam, M.M.; Weng, Y.C. Statin Use Is Associated with a Decreased Risk of Mortality among Patients with COVID-19. J. Clin. Med. 2021, 10, 1450. [CrossRef]
- 20. Wu, K.S.; Lin, P.C.; Chen, Y.S.; Pan, T.C.; Tang, P.L. The use of statins was associated with reduced COVID-19 mortality: A systematic review and meta-analysis. *Ann. Med.* **2021**, *53*, 874–884. [CrossRef]
- Yetmar, Z.A.; Chesdachai, S.; Kashour, T.; Riaz, M.; Gerberi, D.J.; Badley, A.D.; Berbari, E.F.; Tleyjeh, I.M. Prior Statin Use and Risk of Mortality and Severe Disease From Coronavirus Disease 2019: A Systematic Review and Meta-analysis. *Open Forum Infect. Dis.* 2021, *8*, ofab284. [CrossRef] [PubMed]
- Zein, A.; Sulistiyana, C.S.; Khasanah, U.; Wibowo, A.; Lim, M.A.; Pranata, R. Statin and mortality in COVID-19: A systematic review and meta-analysis of pooled adjusted effect estimates from propensity-matched cohorts. *Postgrad. Med. J.* 2022, *98*, 503–508. [CrossRef] [PubMed]
- 23. Pal, R.; Banerjee, M.; Yadav, U.; Bhattacharjee, S. Statin use and clinical outcomes in patients with COVID-19: An updated systematic review and meta-analysis. *Postgrad. Med. J.* 2022, *98*, 354–359. [CrossRef]

- 24. Vahedian-Azimi, A.; Mohammadi, S.M.; Heidari Beni, F.; Banach, M.; Guest, P.C.; Jamialahmadi, T.; Sahebkar, A. Improved COVID-19 ICU admission and mortality outcomes following treatment with statins: A systematic review and meta-analysis. *Arch. Med. Sci.* **2021**, *17*, 579–595. [CrossRef]
- 25. Vahedian-Azimi, A.; Rahimibashar, F.; Najafi, A.; Kidde, J.; Shahriary, A.; Shojaei, S.; Pourhoseingholi, M.A.; Jamialahmadi, T.; Sahebkar, A. Association of In-hospital Use of Statins, Aspirin, and Renin-Angiotensin-Aldosterone Inhibitors with Mortality and ICU Admission Due to COVID-19. In *Identification of Biomarkers, New Treatments, and Vaccines for COVID-19*; Guest, P.C., Ed.; Springer International Publishing: Cham, Switzerland, 2021; pp. 205–214.
- Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021, 372, n71. [CrossRef]
- 27. EPOC. EPOC Resources for Review Authors. Available online: https://epoc.cochrane.org/epoc-resources-review-authors (accessed on 3 August 2022).
- 28. The Cochrane Collaboration. Review Manager (RevMan); Version 5.4; Cochrane: London, UK, 2020.
- 29. Ageno, W.; De Candia, E.; Iacoviello, L.; Di Castelnuovo, A. Protective effect of oral anticoagulant drugs in atrial fibrillation patients admitted for COVID-19: Results from the CORIST study. *Thromb. Res.* **2021**, 203, 138–141. [CrossRef]
- Al Sulaiman, K.; Aljuhani, O.; Korayem, G.; Altebainawi, A.; Al Harbi, S.; Shaya, A.; Badreldin, H.; Kensara, R.; Harthi, A.; Alghamdi, J.; et al. Statins' safety and impact on the clinical outcomes in COVID-19 critically ill patients: A Multicenter, Cohort Study. *Res. Sq.* 2021. [CrossRef]
- Andrews, L.; Goldin, L.; Shen, Y.; Korwek, K.; Kleja, K.; Poland, R.E.; Guy, J.; Sands, K.E.; Perlin, J.B. Discontinuation of atorvastatin use in hospital is associated with increased risk of mortality in COVID-19 patients. *J. Hosp. Med.* 2022, 17, 169–175. [CrossRef]
- 32. Aparisi, A.; Amat-Santos, I.J.; Lopez Otero, D.; Marcos-Mangas, M.; Gonzalez-Juanatey, J.R.; San Roman, J.A. Impact of statins in patients with COVID-19. *Rev. Esp. Cardiol.* **2021**, *74*, 637–640. [CrossRef]
- 33. Basu, A.; Agwu, J.C.; Barlow, N.; Lee, B. Hypertension is the major predictor of poor outcomes among inpatients with COVID-19 infection in the UK: A retrospective cohort study. *BMJ Open* **2021**, *11*, e047561. [CrossRef]
- Bejan, C.A.; Cahill, K.N.; Staso, P.J.; Choi, L.; Peterson, J.F.; Phillips, E.J. DrugWAS: Drug-wide Association Studies for COVID-19 Drug Repurposing. *Clin. Pharmacol. Ther.* 2021, 110, 1537–1546. [CrossRef] [PubMed]
- Bifulco, M.; Ciccarelli, M.; Bruzzese, D.; Dipasquale, A.; Lania, A.G.; Mazziotti, G.; Gazzerro, P. The benefit of statins in SARS-CoV-2 patients: Further metabolic and prospective clinical studies are needed. *Endocrine* 2021, 71, 270–272. [CrossRef] [PubMed]
- Bui, A.N.; Tyan, K.; Giobbie-Hurder, A.; Klein, I.A.; Manos, M.P.; Zubiri, L.; Reynolds, K.; Grover, S.; Weinhouse, G.L.; Ott, P.A.; et al. Impact of COVID-19 on Patients with Cancer Receiving Immune Checkpoint Inhibitors. *J. Immunother. Precis.* Oncol. 2021, 4, 35–44. [CrossRef] [PubMed]
- Byttebier, G.; Belmans, L.; Alexander, M.; Saxberg, B.E.H.; De Spiegeleer, B.; De Spiegeleer, A.; Devreker, N.; Van Praet, J.T.; Vanhove, K.; Reybrouck, R.; et al. Hospital mortality in COVID-19 patients in Belgium treated with statins, ACE inhibitors and/or ARBs. *Hum. Vaccin. Immunother.* 2021, 17, 2841–2850. [CrossRef] [PubMed]
- Cabezon Villalba, G.; Amat-Santos, I.J.; Duenas, C.; Lopez Otero, D.; Catala, P.; Aparisi, A.; Lopez-Pais, J.; Cacho Antonio, C.E.; Candela, J.; Antunez Muinos, P.; et al. Impact of the presence of heart disease, cardiovascular medications and cardiac events on outcome in COVID-19. *Cardiol. J.* 2021, 28, 360–368. [CrossRef]
- Chacko, S.R.; DeJoy, R.; Lo, K.B.; Albano, J.; Peterson, E.; Bhargav, R.; Gu, F.; Salacup, G.; Pelayo, J.; Azmaiparashvili, Z.; et al. Association of Pre-Admission Statin Use With Reduced In-Hospital Mortality in COVID-19. Am. J. Med. Sci. 2021, 361, 725–730. [CrossRef]
- 40. Cho, D.-H.; Choi, J.; Gwon, J.G. Atorvastatin Reduces the Severity of COVID-19: A Nationwide, Total Population-Based, Case-Control Study. *COVID* **2022**, *2*, 398–406. [CrossRef]
- 41. Choi, D.; Chen, Q.; Goonewardena, S.N.; Pacheco, H.; Mejia, P.; Smith, R.L.; Rosenson, R.S. Efficacy of Statin Therapy in Patients with Hospital Admission for COVID-19. *Cardiovasc. Drugs Ther.* **2021**. [CrossRef]
- 42. Chow, R.; Lee, J.; Noh, H.; Lee, J.; Simone II, C.B.; Shin, H.J.; Choi, Y.-G. The association between statin and COVID-19 adverse outcomes: National COVID-19 cohort in South Korea. *Ann. Palliat. Med.* **2022**, *11*, 1297–1307. [CrossRef]
- 43. Daniels, L.B.; Ren, J.; Kumar, K.; Bui, Q.M.; Zhang, J.; Zhang, X.; Sawan, M.A.; Eisen, H.; Longhurst, C.A.; Messer, K. Relation of prior statin and anti-hypertensive use to severity of disease among patients hospitalized with COVID-19: Findings from the American Heart Association's COVID-19 Cardiovascular Disease Registry. *PLoS ONE* 2021, *16*, e0254635. [CrossRef]
- De Spiegeleer, A.; Van Migerode, J.; Bronselaer, A.; Wynendaele, E.; Peelman, M.; Vandaele, F.; Byttebier, G.; De Tre, G.; Belmans, L.; Van De Wiele, C.; et al. Statin Intake and All-Cause Mortality among Older Nursing Home Residents. *Gerontology* 2022, 68, 407–411. [CrossRef] [PubMed]
- El-Solh, A.A.; Lawson, Y.; El-Solh, D.A. All-cause mortality in COVID-19 patients receiving statin therapy: Analysis of veterans affairs database cohort study. *Intern. Emerg. Med.* 2021, 17, 685–694. [CrossRef] [PubMed]
- Espana, P.P.; Bilbao, A.; Garcia-Gutierrez, S.; Lafuente, I.; Anton-Ladislao, A.; Villanueva, A.; Uranga, A.; Legarreta, M.J.; Aguirre, U.; Quintana, J.M.; et al. Predictors of mortality of COVID-19 in the general population and nursing homes. *Intern. Emerg. Med.* 2021, 16, 1487–1496. [CrossRef] [PubMed]

- 47. Fan, Y.; Guo, T.; Yan, F.; Gong, M.; Zhang, X.A.; Li, C.; He, T.; Luo, H.; Zhang, L.; Chen, M.; et al. Association of Statin Use With the In-Hospital Outcomes of 2019-Coronavirus Disease Patients: A Retrospective Study. *Front. Med.* **2020**, *7*, 584870. [CrossRef]
- Greco, S.; D'Amuri, A.; Giorgini, E.; Luciani, F.; Lopreiato, M.; Fortunato, V.; Scopa, A.; Vestita, G.; Capatti, E.; Passaro, A. Role of Statins in Coronavirus-Related Disease (COVID-19): A Retrospective Cohort Study in Northern Italy. *High. Blood Press Cardiovasc. Prev.* 2021, 28, 355–364. [CrossRef]
- Gupta, A.; Madhavan, M.V.; Poterucha, T.J.; DeFilippis, E.M.; Hennessey, J.A.; Redfors, B.; Eckhardt, C.; Bikdeli, B.; Platt, J.; Nalbandian, A.; et al. Association between antecedent statin use and decreased mortality in hospitalized patients with COVID-19. *Nat. Commun.* 2021, *12*, 1325. [CrossRef]
- Ikari, Y.; Matsue, Y.; Torii, S.; Hasegawa, M.; Aihara, K.; Kuroda, S.; Sano, T.; Kitai, T.; Yonetsu, T.; Kohsaka, S.; et al. Association Between Statin Use Prior to Admission and Lower Coronavirus Disease 2019 (COVID-19) Severity in Patients With Cardiovascular Disease or Risk Factors. *Circ. J.* 2021, *85*, 939–943. [CrossRef]
- 51. Kabootari, M.; Habibi Tirtashi, R.; Hasheminia, M.; Bozorgmanesh, M.; Khalili, D.; Akbari, H.; Roshandel, G.; Hadaegh, F. Clinical features, risk factors and a prediction model for in-hospital mortality among diabetic patients infected with COVID-19: Data from a referral centre in Iran. *Public Heal.* **2022**, *202*, 84–92. [CrossRef]
- 52. Kuno, T.; So, M.; Iwagami, M.; Takahashi, M.; Egorova, N.N. The association of statins use with survival of patients with COVID-19. J. Cardiol. 2022, 79, 494–500. [CrossRef]
- Lee, H.Y.; Ahn, J.; Park, J.; Kyung Kang, C.; Won, S.H.; Wook Kim, D.; Park, J.H.; Chung, K.H.; Joh, J.S.; Bang, J.H.; et al. Beneficial Effect of Statins in COVID-19-Related Outcomes-Brief Report: A National Population-Based Cohort Study. *Arterioscler. Thromb. Vasc. Biol.* 2021, 41, e175–e182. [CrossRef]
- Li, W.; Rios, S.; Nagraj, S.; Hajra, A.; Saralidze, T.; Varrias, D.; Mathai, S.V.; Novakovic, M.; Hupart, K.H.; Miles, J.A.; et al. Statin Use in Hospitalized Patients with COVID-19: A Comprehensive Analysis of the New York City Public Hospital System. *Am. J. Med.* 2022, 135, 897–905. [CrossRef] [PubMed]
- 55. Lohia, P.; Kapur, S.; Benjaram, S.; Mir, T. Association between antecedent statin use and severe disease outcomes in COVID-19: A retrospective study with propensity score matching. *J. Clin. Lipidol.* **2021**, *15*, 451–459. [CrossRef] [PubMed]
- Luo, P.; Qiu, L.; Liu, Y.; Liu, X.L.; Zheng, J.L.; Xue, H.Y.; Liu, W.H.; Liu, D.; Li, J. Metformin Treatment Was Associated with Decreased Mortality in COVID-19 Patients with Diabetes in a Retrospective Analysis. *Am. J. Trop. Med. Hyg.* 2020, 103, 69–72. [CrossRef]
- Ma, Y.; Zhang, Y.; Li, S.; Yang, H.; Li, H.; Cao, Z.; Xu, F.; Sun, L.; Wang, Y. Sex Differences in Association Between Anti-Hypertensive Medications and Risk of COVID-19 in Middle-Aged and Older Adults. *Drugs Aging* 2021, *38*, 921–930. [CrossRef] [PubMed]
- Mallow, P.J.; Belk, K.W.; Topmiller, M.; Hooker, E.A. Outcomes of Hospitalized COVID-19 Patients by Risk Factors: Results from a United States Hospital Claims Database. J. Health Econ. Outcomes Res. 2020, 7, 165–174. [CrossRef]
- 59. Maric, I.; Oskotsky, T.; Kosti, I.; Le, B.; Wong, R.J.; Shaw, G.M.; Sirota, M.; Stevenson, D.K. Decreased Mortality Rate among COVID-19 Patients Prescribed Statins: Data from Electronic Health Records in the US. *Front. Med.* **2021**, *8*, 639804. [CrossRef]
- Masana, L.; Correig, E.; Rodriguez-Borjabad, C.; Anoro, E.; Arroyo, J.A.; Jerico, C.; Pedragosa, A.; Miret, M.; Naf, S.; Pardo, A.; et al. Effect of statin therapy on SARS-CoV-2 infection-related mortality in hospitalized patients. *Eur. Heart J. Cardiovasc. Pharmacother.* 2022, *8*, 157–164. [CrossRef]
- 61. McAlister, F.A.; Wang, T.; Wang, X.; Chu, A.; Goodman, S.G.; Diepen, S.V.; Jackevicius, C.A.; Kaul, P.; Udell, J.; Ko, D.T.; et al. Statins and SARS-CoV-2 Infection: Results of a P.Popu.ulation-Based Prospective Cohort Study of 469 749 Adults From 2 Canadian Provinces. J. Am. Hear. Assoc. 2021, 10, e022330. [CrossRef]
- 62. Mehra, M.R.; Desai, S.S.; Kuy, S.; Henry, T.D.; Patel, A.N. Retraction: Cardiovascular Disease, Drug Therapy, and Mortality in COVID-19. *N. Engl. J. Med.* **2020**, *382*, 2582. [CrossRef]
- Meintrup, D.; Borgmann, S.; Seidl, K.; Stecher, M.; Jakob, C.E.M.; Pilgram, L.; Spinner, C.D.; Rieg, S.; Isberner, N.; Hower, M.; et al. Specific Risk Factors for Fatal Outcome in Critically Ill COVID-19 Patients: Results from a European Multicenter Study. *J. Clin. Med.* 2021, 10, 3855. [CrossRef] [PubMed]
- Merzon, E.; Green, I.; Vinker, S.; Golan-Cohen, A.; Gorohovski, A.; Avramovich, E.; Frenkel-Morgenstern, M.; Magen, E. The use of aspirin for primary prevention of cardiovascular disease is associated with a lower likelihood of COVID-19 infection. *FEBS J.* 2021, 288, 5179–5189. [CrossRef]
- Mitacchione, G.; Schiavone, M.; Curnis, A.; Arca, M.; Antinori, S.; Gasperetti, A.; Mascioli, G.; Severino, P.; Sabato, F.; Caracciolo, M.M.; et al. Impact of prior statin use on clinical outcomes in COVID-19 patients: Data from tertiary referral hospitals during COVID-19 pandemic in Italy. *J. Clin. Lipidol.* 2021, *15*, 68–78. [CrossRef] [PubMed]
- 66. Monserrat Villatoro, J.; Mejia-Abril, G.; Diaz Garcia, L.; Zubiaur, P.; Jimenez Gonzalez, M.; Fernandez Jimenez, G.; Cancio, I.; Arribas, J.R.; Suarez Fernandez, C.; Mingorance, J.; et al. A Case-Control of Patients with COVID-19 to Explore the Association of Previous Hospitalisation Use of Medication on the Mortality of COVID-19 Disease: A Propensity Score Matching Analysis. *Pharmaceuticals* 2022, 15, 78. [CrossRef] [PubMed]
- Nateghi, S.; Gomari, M.M.; Hosamirudsari, H.; Behnoush, B.; Razmjoofard, A.; Azimi, G.; Ordookhani, S.; Jafarpour, A.; Faraji, N. A historical cohort study to investigation of statins safety in COVID-19 hospitalized patients. *Therapie* 2021, 77, 453–460. [CrossRef] [PubMed]

- Nicholson, C.J.; Wooster, L.; Sigurslid, H.H.; Li, R.H.; Jiang, W.; Tian, W.; Lino Cardenas, C.L.; Malhotra, R. Estimating risk of mechanical ventilation and in-hospital mortality among adult COVID-19 patients admitted to Mass General Brigham: The VICE and DICE scores. *EClinicalMedicine* 2021, 33, 100765. [CrossRef]
- 69. Oh, T.K.; Song, I.A.; Jeon, Y.T. Statin Therapy and the Risk of COVID-19: A Cohort Study of the National Health Insurance Service in South Korea. *J. Pers. Med.* **2021**, *11*, 116. [CrossRef]
- Pazoki, M.; Chichagi, F.; Hadadi, A.; Kafan, S.; Montazeri, M.; Kazemian, S.; Aminorroaya, A.; Ebrahimi, M.; Ashraf, H.; Hazaveh, M.M.; et al. Association of clinical characteristics, antidiabetic and cardiovascular agents with diabetes mellitus and COVID-19: A 7-month follow-up cohort study. J. Diabetes Metab. Disord. 2021, 20, 1545–1555. [CrossRef]
- 71. Philipose, Z.; Smati, N.; Wong, C.S.J.; Aspey, K.; Mendall, M. Obesity, old age and frailty are the true risk factors for COVID-19 mortality and not chronic disease or ethnicity in Croydon. *medRxiv* 2020. [CrossRef]
- 72. Ramachandran, P.; Perisetti, A.; Gajendran, M.; Jean-Louis, F.; Bansal, P.; Dwivedi, A.K.; Goyal, H. Pre-hospitalization proton pump inhibitor use and clinical outcomes in COVID-19. *Eur. J. Gastroenterol. Hepatol.* **2022**, *34*, 137–141. [CrossRef]
- 73. Ramos-Rincon, J.M.; Perez-Belmonte, L.M.; Carrasco-Sanchez, F.J.; Jansen-Chaparro, S.; De-Sousa-Baena, M.; Bueno-Fonseca, J.; Perez-Aguilar, M.; Arevalo-Canas, C.; Bacete Cebrian, M.; Mendez-Bailon, M.; et al. Cardiometabolic Therapy and Mortality in Very Old Patients With Diabetes Hospitalized due to COVID-19. J. Gerontol. A Biol. Sci. Med. Sci. 2021, 76, e102–e109. [CrossRef]
- 74. Rosenthal, N.; Cao, Z.; Gundrum, J.; Sianis, J.; Safo, S. Risk Factors Associated With In-Hospital Mortality in a US National Sample of Patients With COVID-19. *JAMA Netw. Open* **2020**, *3*, e2029058. [CrossRef] [PubMed]
- Soldevila, L.; Valerio-Sallent, L.; Roure, S.; Perez-Quilez, O.; Mas, M.A.; Miralles, R.; Lopez-Munoz, I.; Estrada, O.; Valles, X. Drug exposure may have a substantial influence on COVID-19 prognosis among residents of long-term care facilities: An exploratory analysis. *Int. J. Infect. Dis.* 2021, 109, 192–194. [CrossRef]
- 76. Song, S.L.; Hays, S.B.; Panton, C.E.; Mylona, E.K.; Kalligeros, M.; Shehadeh, F.; Mylonakis, E. Statin Use Is Associated with Decreased Risk of Invasive Mechanical Ventilation in COVID-19 Patients: A Preliminary Study. *Pathogens* 2020, *9*, 759. [CrossRef] [PubMed]
- 77. Terlecki, M.; Wojciechowska, W.; Klocek, M.; Olszanecka, A.; Stolarz-Skrzypek, K.; Grodzicki, T.; Malecki, M.; Katra, B.; Garlicki, A.; Bociaga-Jasik, M.; et al. Association between cardiovascular disease, cardiovascular drug therapy, and in-hospital outcomes in patients with COVID-19: Data from a large single-center registry in Poland. *Kardiol. Pol.* 2021, 79, 773–780. [CrossRef] [PubMed]
- 78. Tignanelli, C.J.; Bramante, C.T.; Dutta, N.; Tamariz, L.; Usher, M.G.; Ikramuddin, S. Metabolic surgery may protect against admission for COVID-19 in persons with nonalcoholic fatty liver disease. *Surg. Obes. Relat. Dis.* 2021, 17, 1780–1786. [CrossRef]
- Torres-Pena, J.D.; Perez-Belmonte, L.M.; Fuentes-Jimenez, F.; Lopez Carmona, M.D.; Perez-Martinez, P.; Lopez-Miranda, J.; Carrasco Sanchez, F.J.; Vargas Nunez, J.A.; Del Corral Beamonte, E.; Magallanes Gamboa, J.O.; et al. Prior Treatment with Statins is Associated with Improved Outcomes of Patients with COVID-19: Data from the SEMI-COVID-19 Registry. *Drugs* 2021, *81*, 685–695. [CrossRef]
- Umakanthan, S.; Senthil, S.; John, S.; Madhavan, M.K.; Das, J.; Patil, S.; Rameshwaram, R.; Cintham, A.; Subramaniam, V.; Yogi, M.; et al. The protective role of statins in COVID-19 patients: A retrospective observational study. *Transl. Med. Commun.* 2021, 6, 22. [CrossRef]
- Wander, P.L.; Lowy, E.; Beste, L.A.; Tulloch-Palomino, L.; Korpak, A.; Peterson, A.C.; Kahn, S.E.; Danaei, G.; Boyko, E.J. Associations of statin use with 30-day adverse outcomes among 4 801 406 US Veterans with and without SARS-CoV-2: An observational cohort study. *BMJ Open* 2022, *12*, e058363. [CrossRef]
- Wargny, M.; Potier, L.; Gourdy, P.; Pichelin, M.; Amadou, C.; Benhamou, P.Y.; Bonnet, J.B.; Bordier, L.; Bourron, O.; Chaumeil, C.; et al. Predictors of hospital discharge and mortality in patients with diabetes and COVID-19: Updated results from the nationwide CORONADO study. *Diabetologia* 2021, 64, 778–794. [CrossRef]
- Yetmar, Z.A.; Challener, D.W.; Tleyjeh, I.M.; Sohail, M.R.; Cerhan, J.R.; Badley, A.D.; O'Horo, J.C. Association Between Chronic Statin Use and 30-Day Mortality in Hospitalized Patients With COVID-19. *Mayo Clin. Proc. Innov. Qual. Outcomes* 2021, 5, 442–446. [CrossRef]
- Zhang, X.J.; Qin, J.J.; Cheng, X.; Shen, L.; Zhao, Y.C.; Yuan, Y.; Lei, F.; Chen, M.M.; Yang, H.; Bai, L.; et al. In-Hospital Use of Statins Is Associated with a Reduced Risk of Mortality among Individuals with COVID-19. *Cell Metab.* 2020, *32*, 176–187.e174. [CrossRef] [PubMed]
- Zhong, Y.; Zhao, L.; Wu, G.; Hu, C.; Wu, C.; Xu, M.; Dong, H.; Zhang, Q.; Wang, G.; Yu, B.; et al. Impact of renin-angiotensin system inhibitors use on mortality in severe COVID-19 patients with hypertension: A retrospective observational study. *J. Int. Med. Res.* 2020, *48*, 300060520979151. [CrossRef] [PubMed]
- 86. An, C.; Lim, H.; Kim, D.W.; Chang, J.H.; Choi, Y.J.; Kim, S.W. Machine learning prediction for mortality of patients diagnosed with COVID-19: A nationwide Korean cohort study. *Sci. Rep.* **2020**, *10*, 18716. [CrossRef] [PubMed]
- Ayeh, S.K.; Abbey, E.J.; Khalifa, B.A.A.; Nudotor, R.D.; Osei, A.D.; Chidambaram, V.; Osuji, N.; Khan, S.; Salia, E.L.; Oduwole, M.O.; et al. Statins use and COVID-19 outcomes in hospitalized patients. *PLoS ONE* 2021, 16, e0256899. [CrossRef] [PubMed]
- 88. Bergqvist, R.; Ahlqvist, V.H.; Lundberg, M.; Hergens, M.P.; Sundstrom, J.; Bell, M.; Magnusson, C. HMG-CoA reductase inhibitors and COVID-19 mortality in Stockholm, Sweden: A registry-based cohort study. *PLoS Med.* **2021**, *18*, e1003820. [CrossRef]

- Buenen, A.G.; Sinkeldam, M.; Maas, M.L.; Verdonschot, M.; Wever, P.C. Prior use of anticoagulation is associated with a better survival in COVID-19. *J. Thrombolysis* 2021, 52, 1207–1211. [CrossRef]
- Butt, J.H.; Gerds, T.A.; Schou, M.; Kragholm, K.; Phe.elps, M.; Havers-Borgersen, E.; Yafasova, A.; Gislason, G.H.; Torp-Pedersen, C.; Kober, L.; et al. Association between statin use and outcomes in patients with coronavirus disease 2019 (COVID-19): A nationwide cohort study. *BMJ Open* 2020, *10*, e044421. [CrossRef]
- Castagna, F.; Xue, X.; Saeed, O.; Kataria, R.; Puius, Y.A.; Patel, S.R.; Garcia, M.J.; Racine, A.D.; Sims, D.B.; Jorde, U.P. Hospital bed occupancy rate is an independent risk factor for COVID-19 inpatient mortality: A pandemic epicentre cohort study. *BMJ Open* 2022, 12, e058171. [CrossRef]
- 92. Fung, K.W.; Baik, S.H.; Baye, F.; Zheng, Z.; Huser, V.; McDonald, C.J. Effect of common maintenance drugs on the risk and severity of COVID-19 in elderly patients. *PLoS ONE* **2022**, *17*, e0266922. [CrossRef]
- Grasselli, G.; Greco, M.; Zanella, A.; Albano, G.; Antonelli, M.; Bellani, G.; Bonanomi, E.; Cabrini, L.; Carlesso, E.; Castelli, G.; et al. Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. *JAMA Intern. Med.* 2020, 180, 1345–1355. [CrossRef]
- Haji Aghajani, M.; Moradi, O.; Azhdari Tehrani, H.; Amini, H.; Pourheidar, E.; Hatami, F.; Rabiei, M.M.; Sistanizad, M. Promising effects of atorvastatin on mortality and need for mechanical ventilation in patients with severe COVID-19; a retrospective cohort study. Int. J. Clin. Pract. 2021, 75, e14434. [CrossRef] [PubMed]
- 95. Holman, N.; Knighton, P.; Kar, P.; O'Keefe, J.; Curley, M.; Weaver, A.; Barron, E.; Bakhai, C.; Khunti, K.; Wareham, N.J.; et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: A population-based cohort study. *Lancet Diabetes Endocrinol.* **2020**, *8*, 823–833. [CrossRef]
- 96. Kouhpeikar, H.; Khosaravizade Tabasi, H.; Khazir, Z.; Naghipour, A.; Mohammadi Moghadam, H.; Forouzanfar, H.; Abbasifard, M.; Kirichenko, T.V.; Reiner, Z.; Banach, M.; et al. Statin Use in COVID-19 Hospitalized Patients and Outcomes: A Retrospective Study. *Front. Cardiovasc. Med.* **2022**, *9*, 820260. [CrossRef] [PubMed]
- Lala, A.; Johnson, K.W.; Januzzi, J.L.; Russak, A.J.; Paranjpe, I.; Richter, F.; Zhao, S.; Somani, S.; Van Vleck, T.; Vaid, A.; et al. Prevalence and Impact of Myocardial Injury in Patients Hospitalized With COVID-19 Infection. *J. Am. Coll. Cardiol.* 2020, 76, 533–546. [CrossRef] [PubMed]
- Memel, Z.N.; Lee, J.J.; Foulkes, A.S.; Chung, R.T.; Thaweethai, T.; Bloom, P.P. Association of Statins and 28-Day Mortality Rates in Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 Infection. J. Infect. Dis. 2022, 225, 19–29. [CrossRef]
- 99. Oddy, C.; McCaul, J.; Keeling, P.; Allington, J.; Senn, D.; Soni, N.; Morrison, H.; Mawella, R.; Samuel, T.; Dixon, J. Pharmacological Predictors of Morbidity and Mortality in COVID-19. *J. Clin. Pharmacol.* **2021**, *61*, 1286–1300. [CrossRef]
- 100. Peymani, P.; Dehesh, T.; Aligolighasemabadi, F.; Sadeghdoust, M.; Kotfis, K.; Ahmadi, M.; Mehrbod, P.; Iranpour, P.; Dastghaib, S.; Nasimian, A.; et al. Statins in patients with COVID-19: A retrospective cohort study in Iranian COVID-19 patients. *Transl. Med. Commun.* 2021, 6, 3. [CrossRef]
- Rey, J.R.; Merino Llorens, J.L.; Iniesta Manjavacas, A.M.; Rodriguez, S.O.R.; Castrejon-Castrejon, S.; Arbas-Redondo, E.; Poveda-Pinedo, I.D.; Tebar-Marquez, D.; Severo-Sanchez, A.; Rivero-Santana, B.; et al. Influence of statin treatment in a cohort of patients admitted for COVID-19. *Med. Clin.* 2022, 158, 586–595. [CrossRef]
- 102. Saeed, O.; Castagna, F.; Agalliu, I.; Xue, X.; Patel, S.R.; Rochlani, Y.; Kataria, R.; Vukelic, S.; Sims, D.B.; Alvarez, C.; et al. Statin Use and In-Hospital Mortality in Patients With Diabetes Mellitus and COVID-19. *J. Am. Heart Assoc.* 2020, *9*, e018475. [CrossRef]
- Santosa, A.; Franzen, S.; Natman, J.; Wettermark, B.; Parmryd, I.; Nyberg, F. Protective effects of statins on COVID-19 risk, severity and fatal outcome: A nationwide Swedish cohort study. *Sci. Rep.* 2022, *12*, 12047. [CrossRef]
- 104. Shen, L.; Qiu, L.; Wang, L.; Huang, H.; Liu, D.; Xiao, Y.; Liu, Y.; Jin, J.; Liu, X.; Wang, D.W.; et al. Statin Use and In-hospital Mortality in Patients with COVID-19 and Coronary Heart Disease. *Sci. Rep.* **2021**, *11*, 23874. [CrossRef] [PubMed]
- 105. Vila-Corcoles, A.; Satue-Gracia, E.; Vila-Rovira, A.; de Diego-Cabanes, C.; Forcadell-Peris, M.J.; Hospital-Guardiola, I.; Ochoa-Gondar, O.; Basora-Gallisa, J. COVID19-related and all-cause mortality risk among middle-aged and older adults across the first epidemic wave of SARS-CoV-2 infection: A population-based cohort stuJune 2020.dy in Southern Catalonia, Spain, March. *BMC Public Health* 2021, 21, 1795. [CrossRef] [PubMed]
- 106. Volff, M.; Tonon, D.; Bommel, Y.; Peres, N.; Lagier, D.; Agard, G.; Jacquier, A.; Bartoli, A.; Carvelli, J.; Max, H.; et al. Factors Associated with 90-Day Mortality in Invasively Ventilated Patients with COVID-19 in Marseille, France. *J. Clin. Med.* 2021, 10, 5650. [CrossRef]
- 107. Fayol, A.; Livrozet, M.; Pereira, H.; Diehl, J.-L.; Lebeaux, D.; Arlet, J.-B.; Cholley, B.; Carette, C.; Carves, J.-B.; Czernichow, S.; et al. Cardiometabolic Disorders and the Risk of Critical COVID-19 as Compared to Influenza Pneumonia. *J. Clin. Med.* 2021, 10, 4618. [CrossRef]
- 108. Cariou, B.; Goronflot, T.; Rimbert, A.; Boullu, S.; Le May, C.; Moulin, P.; Pichelin, M.; Potier, L.; Smati, S.; Sultan, A.; et al. Routine use of statins and increased COVID-19 related mortality in inpatients with type 2 diabetes: Results from the CORONADO study. *Diabetes Metab.* 2021, 47, 101202. [CrossRef] [PubMed]
- 109. Svensson, P.; Hofmann, R.; Habel, H.; Jernberg, T.; Nordberg, P. Association between cardiometabolic disease and severe COVID-19: A nationwide case-control study of patients requiring invasive mechanical ventilation. *BMJ Open* 2021, 11, e044486. [CrossRef]
- Sasidhar, M.V.; Chevooru, S.K.; Eickelberg, O.; Hartung, H.P.; Neuhaus, O. Downregulation of monocytic differentiation via modulation of CD147 by 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *PLoS ONE* 2017, 12, e0189701. [CrossRef]

- 111. Liang, X.; Yang, L.X.; Guo, R.; Shi, Y.; Hou, X.; Yang, Z.; Zhou, X.; Liu, H. Atorvastatin attenuates plaque vulnerability by downregulation of EMMPRIN expression via COX-2/PGE2 pathway. *Exp. Ther. Med.* **2017**, *13*, 835–844. [CrossRef]
- 112. Wang, K.; Chen, W.; Zhang, Z.; Deng, Y.; Lian, J.Q.; Du, P.; Wei, D.; Zhang, Y.; Sun, X.X.; Gong, L.; et al. CD147-spike protein is a novel route for SARS-CoV-2 infection to host cells. *Signal. Transduct. Target. Ther.* **2020**, *5*, 283. [CrossRef]
- Albert, M.A.; Danielson, E.; Rifai, N.; Ridker, P.M.; Investigators, P. Effect of statin therapy on C-reactive protein levels: The pravastatin inflammation/CRP evaluation (PRINCE): A randomized trial and cohort study. JAMA 2001, 286, 64–70. [CrossRef]
- 114. Parsamanesh, N.; Moossavi, M.; Bahrami, A.; Fereidouni, M.; Barreto, G.; Sahebkar, A. NLRP3 inflammasome as a treatment target in atherosclerosis: A focus on statin therapy. *Int. Immunopharmacol.* **2019**, *73*, 146–155. [CrossRef] [PubMed]
- 115. Holschermann, H.; Schuster, D.; Parviz, B.; Haberbosch, W.; Tillmanns, H.; Muth, H. Statins prevent NF-kappaB transactivation independently of the IKK-pathway in human endothelial cells. *Atherosclerosis* **2006**, *185*, 240–245. [CrossRef] [PubMed]
- 116. Kong, F.; Ye, B.; Lin, L.; Cai, X.; Huang, W.; Huang, Z. Atorvastatin suppresses NLRP3 inflammasome activation via TLR4/MyD88/NF-kappaB signaling in PMA-stimulated THP-1 monocytes. *Biomed. Pharmacother.* 2016, 82, 167–172. [CrossRef] [PubMed]
- 117. Rodrigues-Diez, R.R.; Tejera-Munoz, A.; Marquez-Exposito, L.; Rayego-Mateos, S.; Santos Sanchez, L.; Marchant, V.; Tejedor Santamaria, L.; Ramos, A.M.; Ortiz, A.; Egido, J.; et al. Statins: Could an old friend help in the fight against COVID-19? *Br. J. Pharmacol.* 2020, 177, 4873–4886. [CrossRef] [PubMed]
- 118. Onorato, D.; Pucci, M.; Carpene, G.; Henry, B.M.; Sanchis-Gomar, F.; Lippi, G. Protective Effects of Statins Administration in European and North American Patients Infected with COVID-19: A Meta-Analysis. *Semin. Thromb. Hemost.* 2021, 47, 392–399. [CrossRef]
- 119. Beaney, T.; Neves, A.L.; Alboksmaty, A.; Ashrafian, H.; Flott, K.; Fowler, A.; Benger, J.R.; Aylin, P.; Elkin, S.; Darzi, A.; et al. Trends and associated factors for COVID-19 hospitalisation and fatality risk in 2.3 million adults in England. *Nat. Commun.* 2022, 13, 2356. [CrossRef]
- Collard, D.; Nurmohamed, N.S.; Kaiser, Y.; Reeskamp, L.F.; Dormans, T.; Moeniralam, H.; Simsek, S.; Douma, R.; Eerens, A.; Reidinga, A.C.; et al. Cardiovascular risk factors and COVID-19 outcomes in hospitalised patients: A prospective cohort study. BMJ Open 2021, 11, e045482. [CrossRef]
- 121. Phadke, M.; Saunik, S. COVID-19 treatment by repurposing drugs until the vaccine is in sight. *Drug Dev. Res.* **2020**, *81*, 541–543. [CrossRef]
- 122. INSPIRATION-S Investigators. Atorvastatin versus placebo in patients with COVID-19 in intensive care: Randomized controlled trial. *BMJ* **2022**, *376*, e068407. [CrossRef]
- 123. Gaitan-Duarte, H.G.; Alvarez-Moreno, C.; Rincon-Rodriguez, C.J.; Yomayusa-Gonzalez, N.; Cortes, J.A.; Villar, J.C.; Bravo-Ojeda, J.S.; Garcia-Pena, A.; Adarme-Jaimes, W.; Rodriguez-Romero, V.A.; et al. Effectiveness of rosuvastatin plus colchicine, emtricitabine/tenofovir and combinations thereof in hospitalized patients with COVID-19: A pragmatic, open-label randomized trial. *EClinicalMedicine* 2022, *43*, 101242. [CrossRef]