Statins reduce mortality in patients with COVID-19: an updated meta-analysis of 147 824 patients

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ARTICLE INFO

ABSTRACT

Objectives: There is conflicting evidence about the efficacy of statin use in regard to clinical outcomes in patients with coronavirus disease 2019 (COVID-19). A systematic review and meta-analysis was performed to examine the effect of statin use on mortality in COVID-19 patients.
Methods: The electronic databases were searched, from inception to March 3, 2021. Unadjusted and adjusted effect estimates with their 95% confidence intervals (95% CI) were pooled using random-effects models.
Results: Twenty-five cohort studies involving 147 824 patients were included. The mean age of the patients ranged from 44.9 to 70.9 years; 57% of patients were male and 43% were female. The use of statins was not associated with mortality when applying the unadjusted risk ratio (uRR 1.16, 95% CI 0.86–1.57; 19 studies). In contrast, meta-analyses of the adjusted odds ratio (aOR 0.67, 95% CI 0.52–0.86; 11 studies) and adjusted hazard ratio (aHR 0.73, 95% CI 0.58–0.91; 10 studies) showed that statins were independently associated with a significant reduction in mortality. Subgroup analyses showed that only chronic use of statins significantly reduced mortality according to the adjusted models.
Conclusions: The use of statins was found to be associated with a lower risk of mortality in COVID-19 patients based on adjusted effects of cohort studies. However, randomized controlled trials are still needed to confirm these findings.

1. Introduction

The current coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory coronavirus 2 (SARS-CoV-2), remains a major public health problem across the globe, despite the availability of vaccines (Hamed et al., 2021). Consequently, there is a continuing need for effective pharmacological therapies that reduce the morbidity and mortality of patients with COVID-19.

Statins are widely used drugs in current medical practice. Given their lipid-lowering effect, these drugs are a mainstay in the treatment of patients with dyslipidemia and atherosclerosis-related diseases (Adhyaru and Jacobson, 2018). Recently, statins have emerged as a potential new therapy for patients with COVID-19 due to their pleiotropic effects (Oesterle et al., 2017). However, there are conflicting data about the utility of statins in COVID-19 patients (Masana et al., 2020; Saeed et al., 2020; Zhang et al., 2020). Therefore, a systematic review and meta-analysis was performed to examine the effect of statin use on mortality in COVID-19 patients.

2. Methods

This review was reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement (Moher et al., 2009).

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Table 1
Characteristics of included studies

Study	Country	Population	Sample size	Age, years[a]	Sex	Comorbidities	Definition of the use of statins	Use of statins
Saeed, 2020	USA	Hospitalized patients with COVID-19	4252	65 ± 16	M: 47% F: 53%	Hypertension (72%), diabetes (53%), lung disease (28%)	Use of statins during hospitalization	32%
Alamdari, 2020	Iran	Hospitalized patients with COVID-19	459	61.8 ± 11.9	M: 70% F: 30%	Hypertension (47%), diabetes (25%), grade 2 obesity (8%), CAD (40%), CKD (22%), chronic liver disease (6%), COPD (29%), cancer (11%), immunocompromised (23%)	Drug history of statin use	25%
Masana, 2020	Spain	Consecutive hospitalized patients with COVID-19	2157	67 (54–78)	M: 57% F: 43%	Hypertension (50%), diabetes (23%), obesity (27%), hyperlipidemia (38%), CAD (9%), stroke (6%), HF (8%), chronic live disease (3%), cancer (11%)	Use of statins in the previous year	27%
Rossi, 2020	Italy	Consecutive patients with COVID-19 and a pre-existing chronic CVD	71	Statins: 71 (64–92) No statins: 73 (63–90)	M: 57% F: 43%	Hypertension (71%), diabetes (76%), hypercholesterolemia (95%), obesity (40%), COPD (19%), CAD (56%), stroke (36%), HF (52%), CKD (17%)	Patients taking statins	59%
Rodríguez, 2020	USA	Hospitalized patients with COVID-19 admitted to the ICU	87	68 (58–75)	M: 64% F: 36%	NR	Users of atorvastatin	54%
Song, 2020	USA	Hospitalized patients with COVID-19	249	62 (51–75)	M: 57% F: 43%	Hypertension (49%), obesity (40%), diabetes (33%), CVD (28%), liver disease (5%)	Chronic use of statins	49%
Selçuk, 2020	Turkey	Consecutive hospitalized patients with hypertension and COVID-19	113	56.9 ± 13.7	M: 52% F: 48%	Hypertension (100%), diabetes (42%), chronic lung disease (20%), CKD (11%), CAD (25%), HF (8%), cancer (4%)	In-hospital use	18%
Krishnan, 2020	USA	Consecutive patients with COVID-19 who required mechanical ventilation	152	66 ± 13	M: 62% F: 38%	Hypertension (73%), hypercholesterolemia (61%), diabetes (65%), CAD (15%), COPD (15%), cirrhosis (1%), CKD (14%)	Pre-admission use of statins	53%
Cariou, 2020	France	Hospitalized patients with COVID-19 and diabetes	2449	70.9 ± 12.5	M: 64% F: 36%	Hypertension (80%), diabetes (100%), dyslipidemia (49%), HF (12%), liver cirrhosis (3%), COPD (10%)	Statin use before hospitalization	49%
Bifulco, 2020	Italy	Hospitalized patients with COVID-19	541	65.1 ± 13.7	M: 63% F: 37%	Hypertension (50%), diabetes (24%), COPD (13%), dyslipidemia (21%), CVD (21%)	Use of statins at admission	22%
Mallow, 2020	USA	Outpatients and inpatients with COVID-19	21 676	64.9 ± 17.2	M: 53% F: 47%	Hypertension (68%), diabetes (42%), COPD (21%), severe CVD (55%), HF (16%), immunosuppression (9%), obesity (14%), liver disease (4%)	Use of statins during hospitalization	24%
Zhang, 2020	China	Hospitalized patients with COVID-19	13 981	Statins: 66 (59–72) No statins: 57 (45–67)	M: 49% F: 51%	Hypertension (34%), diabetes (16%), CAD (8%), stroke (3%), chronic liver disease (2%), CKD (3%)	Use of statins during hospitalization	9%
Daniels, 2020	USA	Hospitalized patients with COVID-19	170	59 ± 19	M: 58% F: 42%	Hypertension (44%), diabetes (20%), CVD (21%), obesity (56%), CKD (18%), cancer (14%), asthma (8%)	Use within the 30 days prior to hospital admission	27%
Butt, 2020	Denmark	Danish citizens who were examined at a hospital	4842	54 (25–75)	M: 47% F: 53%	Hypertension (19%), diabetes (9%), HF (4%), AF (7%), stroke (4%), CAD (9%), cancer (10%), CKD (5%), COPD (5%), liver disease (2%)	At least one redeemed prescription of a statin in the 6 months prior to diagnosis	17%
Grasselli, 2020	Italy	Consecutive patients with COVID-19 admitted to the ICU	3988	63 (56–69)	M: 80% F: 20%	Hypertension (41%), diabetes (13%), dyslipidemia (14%), cancer (8%), CKD (2%), COPD (2%), liver disease (2%)	Home intake of long-term use of statins	62%
Oh, 2021	Korea	Patients with COVID-19, regardless of their hospitalization status	7780	NR	NR	NR	Continuous prescription of statins over >30 days	NR
Lee, 2021	Korea	Hospitalized patients with COVID-19	10 448	44.9 ± 19.8	M: 40% F: 60%	Hypertension (21%), diabetes (18%), CAD (6%), HF (3%), stroke (4%), COPD (14%), CKD (1%), cancer (4%)	Filled prescription with >60% of the proportion of days covered during 3 months before the diagnosis of COVID-19	5%
Ahlstrom, 2021	Sweden	Patients with COVID-19 admitted to the ICU	1981	61 (52–69)	M: 74% F: 26%	Hypertension (50%), diabetes (26%), stroke (3%), CKD (4%), COPD (4%), CAD (7%), obesity (6%)	History of dispensed drugs	26%
Peymani, 2021	Iran	Hospitalized patients with COVID-19	150	54.7 ± 4.3	M: 58% F: 42%	Hypertension (29%), diabetes (21%), CVD (1%), respiratory disease (13%), CKD (17%)	History of statin therapy and still used statin at the time of hospitalization	50%
Mitacchione, 2021	Italy	Consecutive hospitalized patients with COVID-19	842	64 (61–77)	M: 62% F: 38%	Hypertension (45%), diabetes (17%), dyslipidemia (24%), CAD (13%), AF (9%), HF (5%), CKD (7%), COPD (7%), stroke (4%), cancer (8%), obesity (9%)	Taking statins for at least 1 month before hospital admission	21%

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Table 1 (*continued*)

Study	Country	Population	Sample size	Age, years[a]	Sex	Comorbidities	Definition of the use of statins	Use of statins
Rosenthal, 2020	USA	Outpatients and inpatients with COVID-19	64 781	56.1 ± 19.9	M: 49% F: 51%	Hypertension (47%), diabetes (28%), HF (9%), myocardial infarction (6%), stroke (4%), CKD (14%), dyslipidemia (29%)	In-hospital use	19%
Fan, 2020	China	Hospitalized patients with COVID-19	2147	NR	M: 48% F: 52%	Hypertension (33%), CAD (8%), diabetes (14%), stroke (3%), COPD (2%), chronic hepatic dysfunction (3%), CKD (3%), cancer (2%)	Used statins prior to admission and continued their use during hospitalization	12%
Aparisi, 2021	Spain	Hospitalized patients with COVID-19	840	68.1 ± 14.7	M: 51% F: 49%	Hypertension (50%), diabetes (19%), prior heart disease (9%), CKD (7%), COPD (9%)	Use prior to admission	35%
Gupta, 2021	USA	Hospitalized patients with COVID-19	2626	Statins: 70 (63–79) No statins: 62 (49–76)	M: 57% F: 43%	Hypertension (54%), diabetes (37%), CAD (12%), HF (10%), CKD (14%), liver disease (3%), stroke (8%)	Prescription of statins as a home medication	36%
Nicholson, 2021	USA	Consecutive hospitalized patients with COVID-19	1042	64 (53–75)	M: 57% F: 43%	Hypertension (56%), diabetes (42%), CAD (17%), CKD (17%), COPD (12%), cancer (16%)	Chronic use of statins	49%

AF, atrial fibrillation; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; F, female; HF, heart failure; ICU, intensive care unit; M, male; NR, not reported.

[a] Data are mean ± standard deviation or median (interquartile range).

2.1. Search strategy

A search was performed in the following six electronic databases: Embase, PubMed, Web of Science, Scopus, CENTRAL, and Cochrane COVID-19 register. The search was conducted from inception to November 25, 2020, and was updated on March 3, 2021, and included, but was not limited to, the following keywords and their combinations: hydroxymethylglutaryl-CoA reductase inhibitors, statin, COVID-19, and SARS-CoV-2. The complete search strategy is shown in **Supplementary Material** Table S1. There were no restrictions on language or publication year. In addition, a hand-search of reference lists of included articles was also performed to identify further eligible studies.

2.2. Eligibility criteria

Cohort studies and randomized controlled trials that evaluated the effect of statins on mortality in COVID-19 patients diagnosed by reverse transcription PCR were included. Case reports, case series, reviews, abstracts, and editorials were excluded.

2.3. Study selection

All articles from the electronic search were downloaded into EndNote X8 and duplicates were removed. The title and abstract were assessed independently by three review authors (MSB, PC, and AAY) to identify potentially eligible studies. Two review authors (BMT and AAY) independently screened the full-text and recorded reasons for the exclusion. Any disagreement on title/abstract and full-text selection was resolved by a third review author (CDA).

2.4. Exposure and outcome

The use of statins was defined as chronic (i.e., before hospital admission) or in-hospital administration (i.e., during hospitalization) of any type and dose of a statin. The outcome of interest was mortality. All author-reported definitions of mortality were used.

2.5. Data extraction

Data from each included study were extracted independently by two review authors (BMT and IB) using a standardized data extraction form that had been piloted previously. Any disagreement was resolved by a third review author (CDA). If additional data were required, the corresponding author was contacted by e-mail to request this information. The following information was extracted: name of the first author, publication year, country, sample size, population, age, sex, comorbidities, use of statins, and mortality. If available, unadjusted and adjusted effect estimates were extracted.

2.6. Risk of bias assessment

The risk of bias of cohort studies was evaluated using the Newcastle–Ottawa Scale (NOS). Each article was classified as follows: high risk of bias (0–4 points), moderate risk of bias (5–7 points), and low risk of bias (8–9 points). Three review authors (MSB, PC, and BMT) independently assessed the risk of bias and any disagreement was resolved by a third review author (CDA).

2.7. Statistical analysis

All meta-analyses were performed using a random-effects model with an inverse-variance method. Between-study variance (tau-square, τ^2) was estimated using the Paule–Mandel method. Unadjusted risk ratios (uRR), adjusted odds ratios (aOR), and adjusted hazard ratios (aHR) with their 95% CI were pooled for the assessment of the effect of statins on mortality. Heterogeneity among studies was evaluated using the chi-square test (threshold $P < 0.10$) and the I^2 statistic. Heterogeneity was defined as low if $I^2 < 30\%$, moderate if $I^2 = 30$–60%, and high if $I^2 > 60\%$. Subgroup analyses were conducted according to the timing of statin use (chronic versus in-hospital). Funnel plots were used to assess publication bias and the Egger's test was performed to measure asymmetry of funnel plots only if 10 or more studies were included. All meta-analyses were conducted using the 'meta' package from R 3.6.3. A two-tailed $P < 0.05$ was considered statistically significant.

3. Results

3.1. Study selection

The electronic search strategy initially identified 857 articles. After the removal of duplicates, 409 articles remained. Following the screening of studies by title/abstract, 359 articles were excluded. After the full-text assessment of 50 articles, 25 articles were excluded. Thus a total of 25 studies (all cohorts) were finally selected (Ahlström et al., 2021; Alamdari et al., 2020; Aparisi et al., 2021; Bifulco et al., 2020; Butt et al., 2020; Cariou et al., 2020;
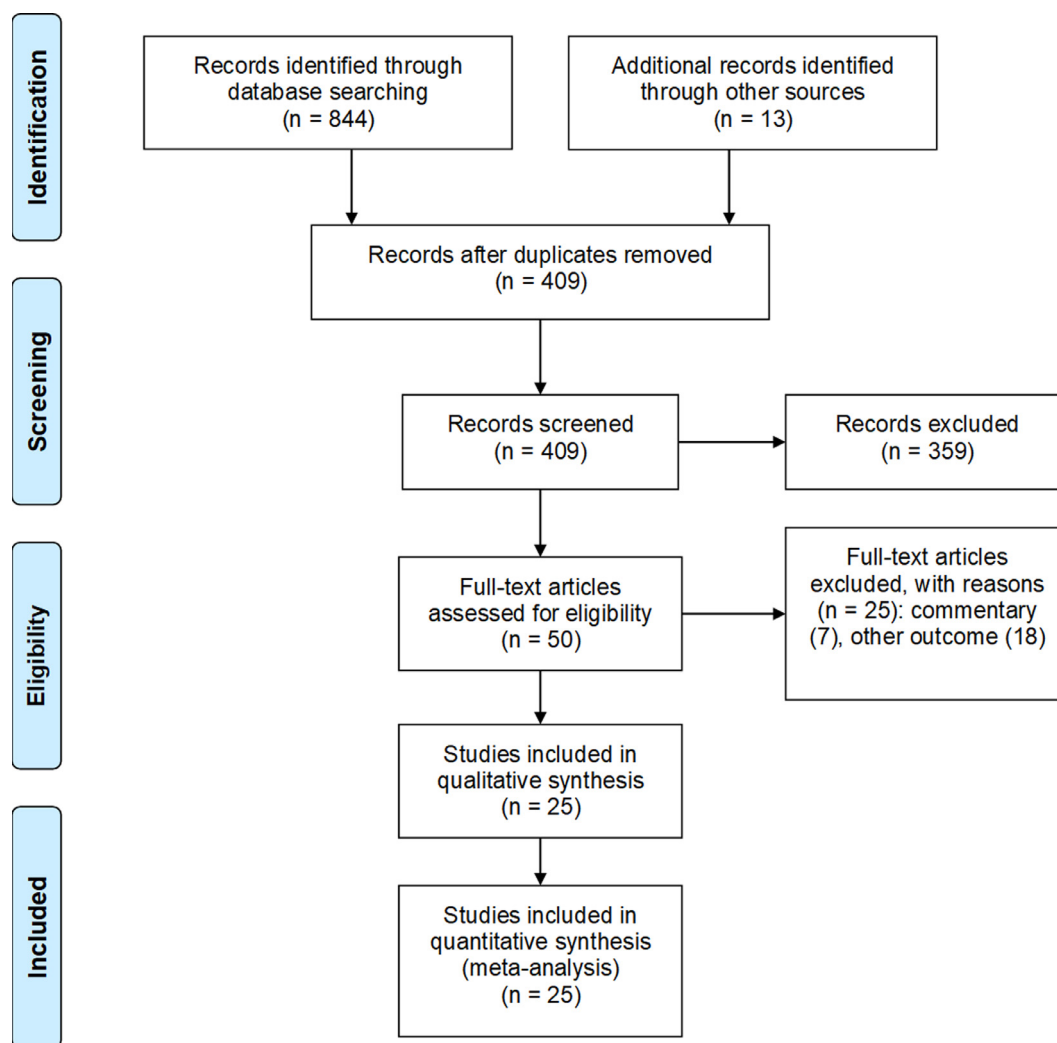
Figure 1. Flow diagram of study selection.

Daniels et al., 2020; Fan et al., 2020; Grasselli et al., 2020; Gupta et al., 2021; Krishnan et al., 2020; Lee et al., 2021; Mallow et al., 2020; Masana et al., 2020; Mitacchione et al., 2021; Nicholson et al., 2021; Oh et al., 2021; Peymani et al., 2021; Rodriguez-Nava et al., 2020; Rosenthal et al., 2020; Rossi et al., 2020; Saeed et al., 2020; Selçuk et al., 2020; Song et al., 2020; Zhang et al., 2020) (Figure 1).

3.2. Study characteristics

The main characteristics of the 25 included studies (147 824 patients) are summarized in Table 1. The mean age of the patients ranged from 44.9 to 70.9 years; 57% of patients were male and 43% were female. Overall, 32% of patients had received statins. Twenty studies reported chronic use of statins and five studies reported in-hospital use. The type of statin was reported in only eight studies. The most common types were atorvastatin (71%), rosuvastatin (13%), and simvastatin (13%). Most studies were from the United States of America ($n = 9$) and Italy ($n = 4$). The most frequent comorbidities were hypertension (51%), dyslipidemia (41%), and diabetes (33%). The majority of studies ($n = 17$) only included hospitalized patients. However, four studies included outpatients and hospitalized patients and four studies included only patients admitted to the intensive care unit (ICU). The adjusted effect esti-

mates and adjusted variables for each individual study are shown in **Supplementary Material** Table S2.
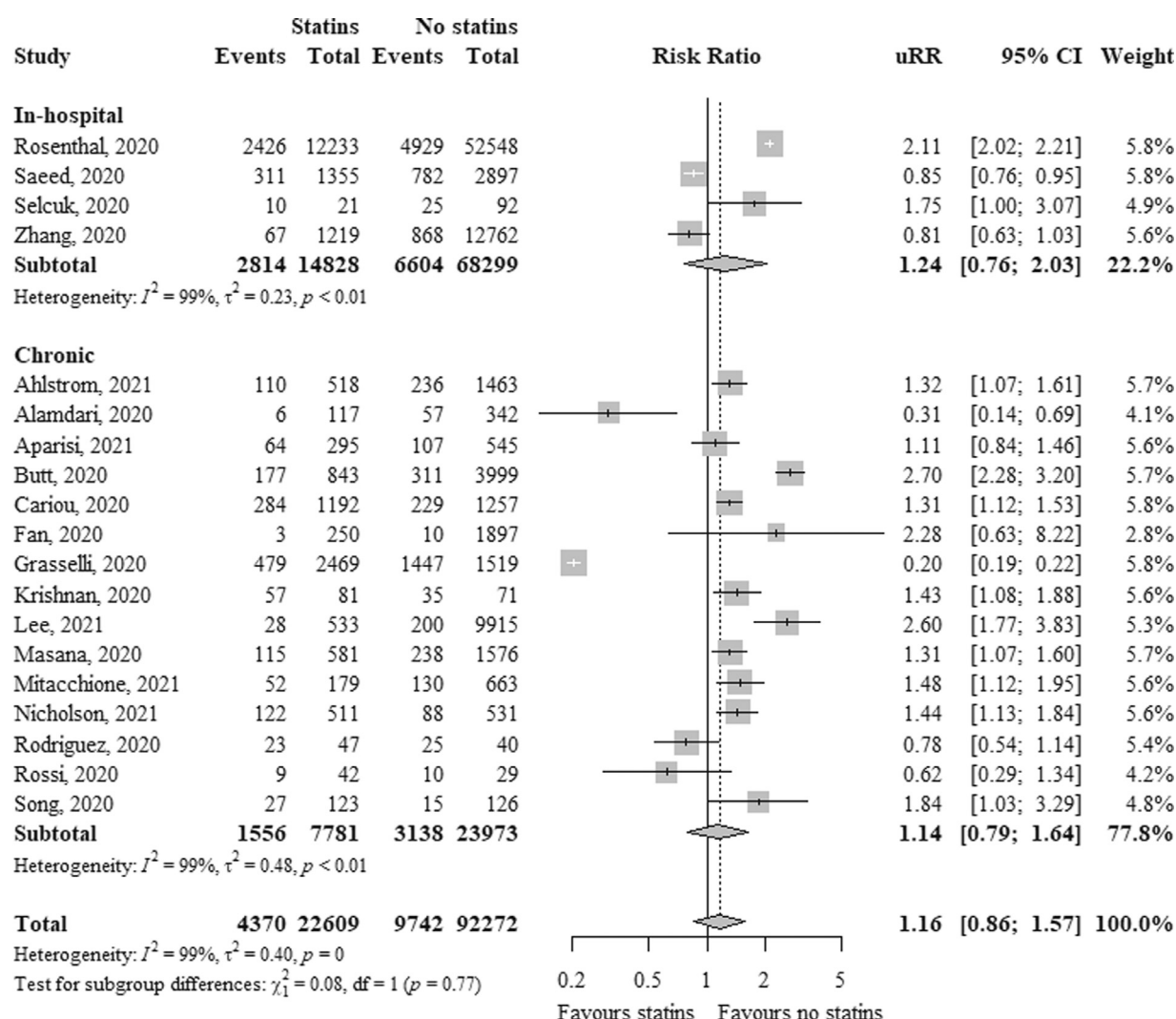
3.3. Risk of bias assessment

The NOS evaluation scored 18 studies as having a low risk of bias, six studies as having a moderate risk of bias, and one study as having a high risk of bias (**Supplementary Material** Table S3).

3.4. Mortality

In 19 studies (114 881 patients), the use of statins was not significantly associated with mortality in COVID-19 patients (uRR 1.16, 95% CI 0.86–1.57; $I^2 = 99\%$) (Figure 2). The funnel plot did not show asymmetry (**Supplementary Material** Figure S1) and the Egger's test was not significant ($P = 0.66$).

In 11 studies (102 996 patients), the use of statins was significantly associated with lower mortality in COVID-19 patients (aOR 0.67, 95% CI 0.52–0.86; $I^2 = 79\%$) (Figure 3). The funnel plot did not show asymmetry (**Supplementary Material** Figure S2) and the Egger's test was not significant ($P = 0.42$).

In 10 studies (44 033 patients), the use of statins was significantly associated with lower mortality in COVID-19 patients (aHR 0.73, 95% CI 0.58–0.91; $I^2 = 64\%$) (Figure 4). The funnel plot showed asymmetry (**Supplementary Material** Figure 3), sug-

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Study	Statins Events	Statins Total	No statins Events	No statins Total	Risk Ratio	uRR	95% CI	Weight
In-hospital								
Rosenthal, 2020	2426	12233	4929	52548		2.11	[2.02; 2.21]	5.8%
Saeed, 2020	311	1355	782	2897		0.85	[0.76; 0.95]	5.8%
Selcuk, 2020	10	21	25	92		1.75	[1.00; 3.07]	4.9%
Zhang, 2020	67	1219	868	12762		0.81	[0.63; 1.03]	5.6%
Subtotal	**2814**	**14828**	**6604**	**68299**		**1.24**	**[0.76; 2.03]**	**22.2%**
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 0.23$, $p < 0.01$								
Chronic								
Ahlstrom, 2021	110	518	236	1463		1.32	[1.07; 1.61]	5.7%
Alamdari, 2020	6	117	57	342		0.31	[0.14; 0.69]	4.1%
Aparisi, 2021	64	295	107	545		1.11	[0.84; 1.46]	5.6%
Butt, 2020	177	843	311	3999		2.70	[2.28; 3.20]	5.7%
Cariou, 2020	284	1192	229	1257		1.31	[1.12; 1.53]	5.8%
Fan, 2020	3	250	10	1897		2.28	[0.63; 8.22]	2.8%
Grasselli, 2020	479	2469	1447	1519		0.20	[0.19; 0.22]	5.8%
Krishnan, 2020	57	81	35	71		1.43	[1.08; 1.88]	5.6%
Lee, 2021	28	533	200	9915		2.60	[1.77; 3.83]	5.3%
Masana, 2020	115	581	238	1576		1.31	[1.07; 1.60]	5.7%
Mitacchione, 2021	52	179	130	663		1.48	[1.12; 1.95]	5.6%
Nicholson, 2021	122	511	88	531		1.44	[1.13; 1.84]	5.6%
Rodriguez, 2020	23	47	25	40		0.78	[0.54; 1.14]	5.4%
Rossi, 2020	9	42	10	29		0.62	[0.29; 1.34]	4.2%
Song, 2020	27	123	15	126		1.84	[1.03; 3.29]	4.8%
Subtotal	**1556**	**7781**	**3138**	**23973**		**1.14**	**[0.79; 1.64]**	**77.8%**
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 0.48$, $p < 0.01$								
Total	**4370**	**22609**	**9742**	**92272**		**1.16**	**[0.86; 1.57]**	**100.0%**
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 0.40$, $p = 0$								
Test for subgroup differences: $\chi_1^2 = 0.08$, df = 1 ($p = 0.77$)					0.2 0.5 1 2 5			
					Favours statins Favours no statins			

Figure 2. Forest plot showing the unadjusted risk ratio between statin use and mortality in COVID-19 patients. (uRR, unadjusted risk ratio; CI, confidence interval.)

gesting publication bias that was confirmed by the Egger's test ($P = 0.03$).

3.5. Subgroup analyses

Subgroup analysis by the timing of statin use (chronic versus in-hospital) revealed that only chronic use of statins significantly reduced mortality in COVID-19 patients according to the adjusted models (Figures 2–4). Moreover, no significant differences were found between the subgroups.

4. Discussion

This study found that the use of statins was significantly associated with a lower risk of mortality compared to non-statin users based on adjusted estimates. In addition, the subgroup analyses showed that only chronic use of statins was associated with a significant risk reduction in mortality. The risk of bias was low to moderate in almost all studies.

Several pathways are involved in the pathogenesis of COVID-19. SARS-CoV-2 enters into cells using angiotensin-converting enzyme 2 (ACE2), which is expressed ubiquitously, with predominance in the lungs, heart, kidneys, and vascular system (Hossain et al., 2020). ACE2 plays a key role in the renin–angiotensin system (RAS)

by negatively regulating RAS activation and attenuating the harmful effects of angiotensin II (Samavati and Uhal, 2020). After viral entry, a robust local and systemic inflammatory response is elicited leading, in some cases, to an overproduction of proinflammatory cytokines (Hossain et al., 2020). Furthermore, there are compelling data showing that COVID-19 patients exhibit a hypercoagulable state, as evidenced by a high incidence of thrombotic complications in these patients (Abou-Ismail et al., 2020).

Statins are a class of lipid-lowering agents that act primarily by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (Adhyaru and Jacobson, 2018). Statins have also been shown to have other pleiotropic effects, whereby they act through many mechanisms independent of low-density lipoprotein cholesterol reduction, including anti-inflammatory, antioxidative, anti-thrombotic, and immunomodulatory functions (Oesterle et al., 2017). In addition, statins significantly increased the ACE2 expression in the heart and kidney in an animal model of atherosclerosis, suggesting a positive effect on RAS balance (Tikoo et al., 2015). Although the clinical significance of the pleiotropic effects of statins remains controversial, there is evidence of clinical benefits in a diversity of diseases such as respiratory viral infections, bacterial pneumonia, and venous thromboembolism, among others (Oesterle et al., 2017). Furthermore, statins, especially pitavastatin, could exert a direct antiviral effect by interacting with the main protease enzyme of SARS-CoV-2 (Reiner et al., 2020). Overall,
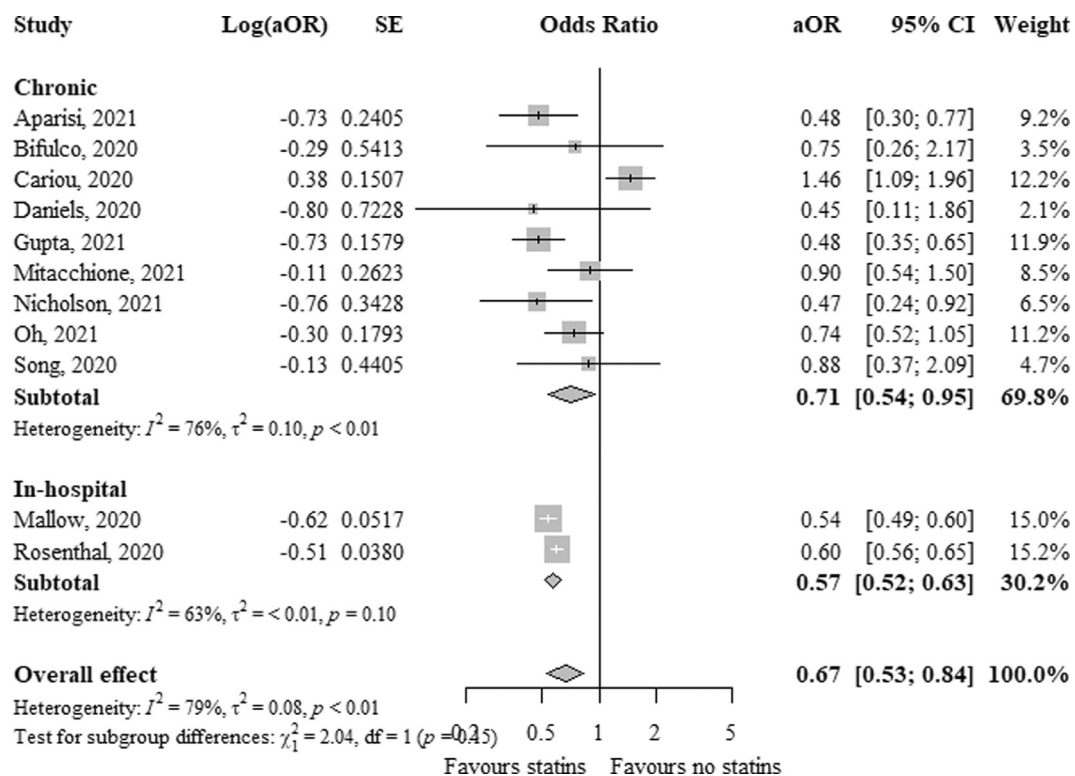
Figure 3. Forest plot showing the adjusted odds ratio between statin use and mortality in COVID-19 patients. (aOR, adjusted odds ratio; CI, confidence interval.)
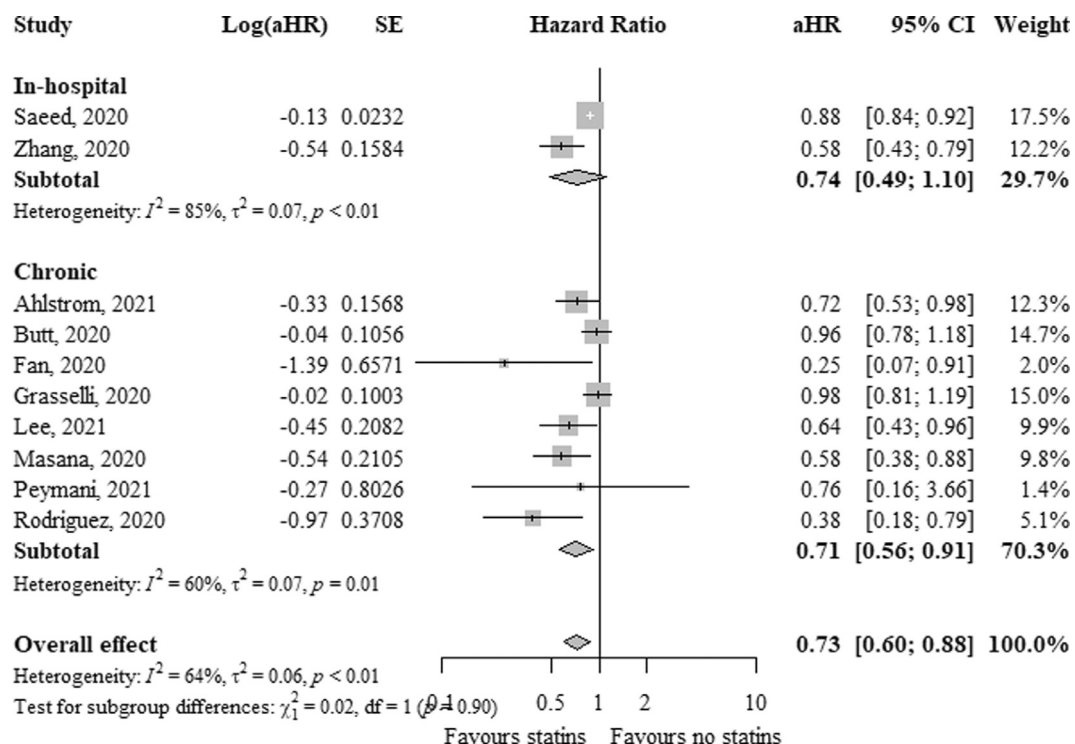

Figure 4. Forest plot showing the adjusted hazard ratio between statin use and mortality in COVID-19 patients. (aHR, adjusted hazard ratio; CI, confidence interval.)

these mechanisms are the different targets where statins could act directly or indirectly during SARS-CoV-2 infection explaining their beneficial effect.

The distinction between the chronic and in-hospital use of statins is an important issue to highlight. In the subgroup analyses, it was found that only patients with chronic use had independently

lower mortality. This suggests that prolonged exposure to statins would be required to manifest their beneficial effects in patients with COVID-19. However, these results should be considered only hypothesis-generating, since a detailed description about the timing of statin use was lacking in almost all studies. It is not known whether patients who reported pre-admission use of statins con-

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tinued to receive them during their hospitalization. Moreover, in the cases that reported in-hospital use, it is not clear whether it was initiated de novo or was a continuation of previous use. In the only two studies that reported continued use of statins during hospitalization (Fan et al., 2020; Oh et al., 2021), only one reported a significant reduction in mortality in COVID-19 patients (Fan et al., 2020). Therefore, randomized controlled trials are needed to clarify whether the de novo or continued administration of statins has a favorable impact in these patients.

There are few previously published systematic reviews examining the effect of statin use in COVID-19 patients (Hariyanto and Kurniawan, 2020; Pal et al., 2021; Permana et al., 2021). Two reviews (Pal et al., 2021; Permana et al., 2021) concluded that statin use was associated with a significant reduction in mortality or ICU admission. In contrast, one review concluded that statins did not improve in-hospital outcomes. The largest review was performed by Permana et al. (Permana et al., 2021), which only included 13 studies involving 52 122 patients. In addition, it was the only review that evaluated chronic and in-hospital use of statins; however, it only combined unadjusted estimates. Compared to these reviews, the present study included substantially more studies and patients. Furthermore, a significant number of adjusted estimates were pooled.

This study has some limitations. First, given that only observational studies were evaluated, there is still a risk of residual confounding that could alter the results. Second, heterogeneity was high in all estimates. Possible reasons for heterogeneity include sample size, types and timing of statins, and heterogeneous populations, among others. Third, there is a risk of misclassification about the timing of statin use (chronic versus in-hospital) due to a lack of detailed information. Finally, some studies included outpatients and others included only ICU patients. This difference in disease severity could be a potential source of selection bias, affecting the pooled effect estimates.

In conclusion, this review found that statins significantly reduce mortality in COVID-19 patients based on adjusted estimates of cohort studies. The subgroup analysis revealed that only patients who were chronically treated with statins had a significant benefit. However, large randomized controlled trials are still needed to confirm these findings.+

Declarations

Funding: None.
Ethical approval: Not applicable.
Informed consent: Not applicable.
Data availability: Data are available from the corresponding author upon reasonable request.
Conflict of interest: The authors declare that there is no conflict of interest.

Author contributions

Carlos Diaz-Arocutipa: participated in database search, study review, data analysis, and manuscript preparation. Beatriz Melgar-Talavera: participated in database search, study review, and manuscript preparation. Ángel Alvarado-Yarasca: participated in database search, study review, and manuscript preparation. María M. Saravia-Bartra: participated in database search, study review, and manuscript preparation. Pedro Cazorla: participated in database search, study review, and manuscript preparation. Iván Belzusarri: participated in database search, study review, and manuscript preparation. Adrian V. Hernandez: participated in study review and manuscript preparation.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2021.08.004.

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