# Statin use and clinical outcomes in patients with COVID-19: An updated systematic review and meta-analysis

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## ABSTRACT

**Purpose** Observations studies have shown that prior use of statins is associated with a reduced risk of adverse clinical outcomes in patients with COVID-19. However, the available data are limited, inconsistent and conflicting. Besides, no randomised controlled trial exists in this regard. Hence, the present meta-analysis was conducted to provide an updated summary and collate the effect of statin use on clinical outcomes in COVID-19 using unadjusted and adjusted risk estimates.

**Methods** PubMed, Scopus and Web of Science databases were systematically searched using appropriate keywords till December 18 2020, to identify observational studies reporting clinical outcomes in COVID-19 patients using statins versus those not using statins. Prior and in-hospital use of statins were considered. Study quality was assessed using the Newcastle-Ottawa Scale. Unadjusted and adjusted pooled odds ratio (OR) with 95% CIs were calculated.

**Results** We included 14 observational studies pooling data retrieved from 19 988 patients with COVID-19. All the studies were of high/moderate quality. Pooled analysis of unadjusted data showed that statin use was not associated with improved clinical outcomes (OR 1.02; 95% CI 0.69 to 1.50, p=0.94, $I^2$=94%, random-effects model). However, on pooling adjusted risk estimates, the use of statin was found to significantly reduce the risk of adverse outcomes (OR 0.51; 95% CI 0.41 to 0.63, p<0.0005, $I^2$=0%, fixed-effects model).

**Conclusions** Statin use is associated with improved clinical outcomes in patients with COVID-19. Individuals with multiple comorbidities on statin therapy should be encouraged to continue the drug amid the ongoing pandemic.

## INTRODUCTION

The novel coronavirus disease (COVID-19) has scourged the world affecting over 90 million individuals and inflicting more than 2 million casualties in over 200 nations worldwide. With the inception of the pandemic, there has been an explosion of interest in unearthing medicines that can curtail the morbidity and mortality of the disease. However, amid the present circumstances, repurposing existing drugs is a faster and far more economical option than contemplating the development of a whole new drug. Expectedly, multiple existing drugs have been repurposed for use in patients with COVID-19 with variable results. One such drug is statins.[1]

Statins are known for their pleiotropic effects that include their immunomodulatory and anti-inflammatory properties that could, in turn, reduce the risk of cytokine storm in patients with COVID-19.[1–3] Multiple observational studies have shown that prior use of statins is associated with a reduced risk of adverse outcomes in patients with COVID-19.[4–9] On the contrary, other studies showed either no differences in outcomes[10–12] or even adverse outcomes in statin users.[13] There exist two meta-analyses in this regard; while one showed that statin use did not improve the in-hospital outcomes,[14] the other reported a 30% reduction in fatal or severe disease.[3] Although the two meta-analyses were conducted at an almost similar time period, the studies included were highly variable. While Hariyanto and Kurniawan had included several non-indexed and non-peer-reviewed studies (preprints) and did not adjust for inherent confounding factors, Kow and Hasan had used only adjusted data for the meta-analysis. It did not include some of the recently published observational studies particularly looking into clinical outcomes in statin users.[4 6 7 9]

The present meta-analysis was hence conducted to provide an updated summary and collate the effect of statin use on the clinical outcomes in COVID-19 using unadjusted as well as adjusted estimates.

## METHODS

This meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.[15] The protocol has not been registered in any database.

### Search strategy

Two investigators (RP and MB) independently performed a systematic search of the literature across PubMed, Scopus and Web of Science databases from inception to 18 December 2020, using the following keywords interposed with appropriate Boolean operators: "COVID-19" OR "SARS-CoV-2" AND "Statins" OR "HMG-CoA reductase". The language was restricted to English only. The references of relevant reviews and retrieved articles were also screened for pertinent articles. For missing data, the corresponding authors of the potentially eligible studies were contacted wherever possible.

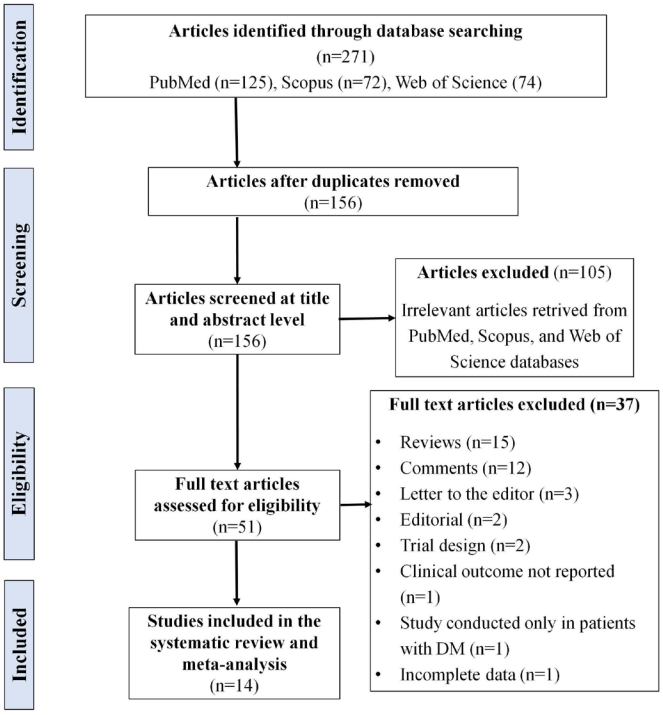


**Figure 1** PRISMA flow chart showing the study selection process. DM, diabetes mellitus; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

### Eligibility and exclusion criteria

Eligibility criteria were set as follows

1. In the absence of randomised controlled trials (RCTs), we planned to include observational studies (cohort or case-control design).
2. Studies should include patients with confirmed COVID-19, a proportion who must have been taking statins prior to or on admission (home medication). Studies reporting the in-hospital use of statins in COVID-19 patients were also included.
3. Studies should report the data comparing the rate of occurrence of the clinical outcome (as the number of 'events') among statin users compared with non-statin users.
4. In addition, studies also reporting the adjusted odds ratio (OR) or hazard ratio (HR) of the reported clinical outcome in statin users as compared with statin non-users were preferred, although it was not a mandatory eligibility criterion.

Exclusion criteria were set as follows

1. Reviews, comments, editorials, letters to the editor.
2. Studies reporting only adjusted OR/HR without delineating the absolute number of events in statin users as compared with non-users.
3. Studies performed only in patients with diabetes mellitus.
4. Incompleteness in data.

### Data extraction

Two investigators (RP and MB) independently scanned titles and/or abstracts to exclude duplicate studies and studies that failed to meet the aforementioned eligibility criteria. Potentially eligible studies were full-text assessed. Any discrepancies between the aforementioned investigators were solved by discussion, consensus or arbitration by a third investigator (UY).

Studies hence selected were reviewed, and the following data were extracted from full-text reports for further assessment: study characteristics, the number of patients using statins, the clinical outcomes reported (severe disease or mortality or both), the covariates included, the number of statin users versus non-users who achieved the reported clinical outcome (ie, the number of events in statin users vs non-users) and the adjusted OR/HR of the reported clinical outcome in statin users as compared with statin non-users.

### Assessment of study quality

The Newcastle-Ottawa Scale (NOS) was used to assess the quality and risk of bias of the included observational studies. The scale assesses three quality parameters, namely, selection, comparability and outcome divided across eight specific items, which slightly differ when scoring case–control and cohort studies.[16] The maximum score on NOS is 9. Any score ≥7 qualifies as high quality with a low risk of bias, while a score <5 is categorised as low quality with a high risk of inherent bias. Any score in between is rated as moderate quality.[17] The assessment of study quality was independently conducted by two investigators (RP and MB). Any discrepancy was solved by a discussion with a third investigator (SB).

### Statistical analysis

Being a dichotomous variable, the difference in the rate of occurrence of the reported clinical outcome (events) in statin users versus statin non-users in COVID-19 patients were calculated using OR with 95% CI after implementation of the Mantel-Haenszel fixed-effects formula. Adjusted estimates (OR or HR) from each study, wherever reported, were also pooled together using the generic inverse variance model with the fixed-effects formula. The OR and HR were pooled separately. Statistical heterogeneity among studies was assessed using $I^2$ statistics. Heterogeneity was quantified as low, moderate and high with upper limits of 25%, 50% and 75% for $I^2$, respectively.[18] In the present meta-analysis, significant heterogeneity was considered when the $I^2$ value was ≥50%, with a $p<0.05$. Outcomes with significant heterogeneity were reanalysed and reported using the random-effects model. The possible sources of significant heterogeneity were addressed through sensitivity analyses. A $p<0.05$ was considered to be statistically significant.

Statistical analysis was performed using the RevMan Version5.4 software.

## RESULTS

After a scrupulous literature search and a meticulous study selection process, we included 14 observational studies in our meta-analysis,[4–9 11–13 19–23] pooling data retrieved from 19 988 patients with COVID-19 (figure 1). The study by Yan *et al* was a case–control study,[11] rest all were retrospective cohort studies. The studies by Zhang *et al* and Rodriguez-Nava *et al* catered to the in-hospital use of statins,[5 19] while all the rest of the studies had reported using statins before or on admission. The primary characteristics of the included studies, along with the NOS scores have been summarised in table 1.

All the studies were of high (n=8) or moderate quality (n=6). Notably, only 10 studies had reported adjusted estimates of the clinical outcome in terms of OR or HR; however, the covariates adjusted for were highly variable across all the studies. The clinical outcomes in the majority of the studies were reported in terms of mortality or intensive care unit admission; however, in the study by Yan *et al*, patient outcomes were reported in terms

**Table 1** Showing characteristics and risk of bias assessment of the included observation studies

| Authors (reference) | No of participants Design Place of study | Clinical outcomes reported | | | Covariates adjusted for | NOS * |
|---|---|---|---|---|---|---|
| | | Statin users | Statin non-users | Adjusted estimate | | |
| Gupta *et al*[4] | 1296† Retrospective multicentre cohort study, USA | In-hospital 30 days mortality 96/648 (14.8%) | 172/648 (26.5%) | OR=0.49 (0.38, 0.63) | Age, male sex, history of atrial arrhythmias, and DM | 8/9 |
| Zhang *et al*[5]‡ | 4305† Retrospective multicentre cohort study, China | Mortality 45/861 (5.2%) | 325/3444 (9.4%) | HR=0.58 (0.43, 0.80) | Age, sex, oxygen saturation at admission | 8/9 |
| Alamdari *et al*[6] | 459 Retrospective single centre cohort study, Iran | Mortality 6/117 (5.1%) | 57/342 (16.7%) | NR | NR | 6/9 |
| Daniels *et al*[7] | 170 Retrospective single centre cohort study, USA | ICU admission or mortality 20/46 (43.5%) | 70/124 (56.5%) | OR=0.29 (0.11, 0.71) | Age, sex, comorbidities (obesity, HTN, DM, CVD, and CKD) | 7/9 |
| De Spiegeleer *et al*[8] | 154 Retrospective multicentre cohort study, Europe | Hospital stay or mortality 6/31 (19.4%) | 31/123 (25.2%) | OR=0.75 (0.24, 1.87) | Age, sex, functional status, DM, HTN | 6/9 |
| Song *et al*[9] | 249 Retrospective single centre cohort study, USA | Mortality 27/123 (21.9%) | 15/126 (11.9%) | OR=0.88 (0.37, 2.08) | Age, sex, race, CVD, COPD, DM, obesity. | 7/9 |
| Yan *et al*[11] | 578 Retrospective multicentre case control Study, China | Severe and critical disease 5/15 (33.3%) | 123/563 (21.8 %) | NR | NR | 5/9 |
| McCarthy *et al*[12] | 247 Multi-centre cohort, USA | ICU admission or mortality 51/107 (47.7%) | 61/140 (43.6%) | NR | NR | 5/9 |
| Krishnan *et al*[13] | 152 Retrospective multicentre cohort study, USA | Mortality 57/81 (70.4%) | 35/71 (49.2%) | NR | NR | 5/9 |
| Rodriguez-Nava *et al*[19]‡ | 87 Retrospective single centre cohort study, USA | Mortality 23/47 (48.9%) | 25/40 (62.5%) | HR=0.38 (0.18, 0.77) | Age, HTN, CVD, severity, invasive mechanical ventilation, and antibiotics (except azithromycin) | 6/9 |
| Nicholson *et al*[20] | 1042 Retrospective multicentre cohort study, USA | Mortality 122/510 (23.9%) | 89/530 (16.8%) | OR=0.502 (0.273, 0.926) | Age, sex, ethnicity, comorbidities, smoking, aspirin, albumin, CRP, PCT and haematological parameters | 7/9 |
| Butt *et al*[21] | 4842 Observational nationwide cohort study, Denmark | All-cause mortality 177/843 (21.0%) | 311/3999 (7.8%) | HR=0.96 (0.78, 1.18) | Age, sex, ethnicity, socioeconomic status and comorbidities | 8/9 |
| Masana *et al*[22] | 2157 Retrospective multicentre cohort study, Spain | Mortality 115/581 (19.8%) | 238/1576 (15.1%) | HR=0.58 § (0.39, 0.89) | Distance, age, sex, smoking status, comorbidities | 7/9 |
| Saeed *et al*[23] | 4252 Retrospective single centre cohort study, USA | Cumulative in-hospital mortality 311/1355 (23.0%) | 782/2897 (27.0%) | HR=0.51 ¶ (0.43, 0.61) | Age, sex, history of AHD, Charlson comorbidity index, presenting vitals, serum glucose, lactic acid, creatinine and intravenous antibiotic use during hospitalisation | 8/9 |

Clinical outcome data reported as n/N (%).
OR/HR presented as ratio (95% CI).
*Risk of bias assesssment was performed using NOS.
†Number of participants after applying propensity score-matching model to minimise differences in baseline characteristics between statin users versus non-statin users.
‡Studies reporting in-hospital use of statins.
§HR calculated 581 statin users and 581 genetic matched statin non-users.
¶HR calculated only for COVID-19 patients with diabetes mellitus (n=2266) with 983 being statin users and 1283 being statin non-users.
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AHD, atherosclerotic heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension; ICU, intensive care unit; NOS, Newcastle-Ottawa Scale; NR, not reported; OSA, obstructive sleep apnoea; PCT, procalcitonin.

of severe and critical disease rather than mortality.[11] The results of the meta-analysis have been summarised under the following heads.

### Pooled analysis using the rate of occurrence of the reported clinical outcome (number of events) in statin users versus statin non-users

The pooled analysis of the data from all the included studies

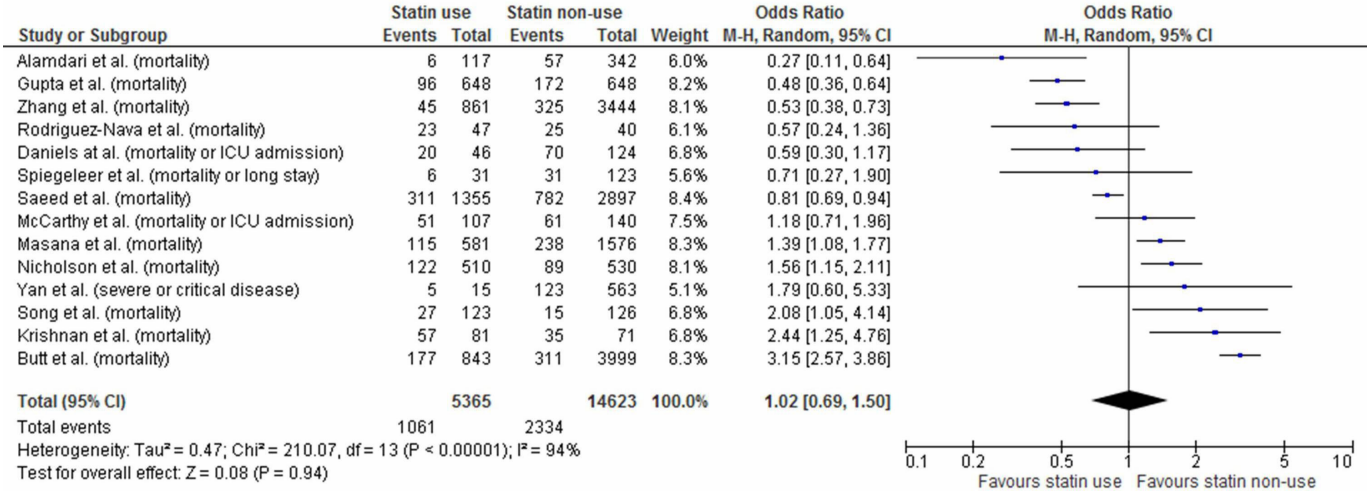


**Figure 2** Forest plot showing the effect (unadjusted) of statin use on clinical outcomes in patients with COVID-19 as compared with non-use of the drug. The reported clinical outcomes of individual studies have been represented in brackets. ICU, intensive care unit; M-H, Mantel-Haenszel.

showed that statin use was not associated with improved clinical outcomes (OR 1.02; 95% CI 0.69, 1.50, p=0.94, $I^2$=94%, random-effects model) (figure 2). We performed a sensitivity analysis after excluding the studies where clinical outcomes were not reported in terms of mortality; likewise, we found that statin use was not associated with improved patient mortality (OR 1.04; 95% CI 0.65, 1.66, p=0.88, $I^2$=96%, random-effects model) (figure 3).

### Pooled analysis using adjusted odds ratios or hazard ratios of the reported clinical outcome in statin users versus statin non-users

Adjusted OR of the reported clinical outcomes in statin users as compared with non-users were reported in five studies involving 2909 patients with COVID-19.[4 7–9 20] Pooled analysis showed that prior statin use was associated with improved clinical outcomes (pooled OR 0.51; 95% CI 0.41, 0.63, p<0.0005, $I^2$=0%, fixed-effects model) (figure 4A). Similarly, covariate-adjusted HR were reported in five studies[5 19 21–23]; however, the adjusted HR was reported by Saeed *et al* only in patients with diabetes mellitus, hence, not included. Pooled adjusted HR also showed that statin use was associated with improved clinical outcomes in COVID-19 patients (pooled HR 0.64; 95% CI 0.64 to 0.93, p=0.02, $I^2$=77%, random-effects model) (figure 4B).

## DISCUSSION

In this updated systematic review and meta-analysis, we found that the use of statins was associated with improved clinical outcomes in patients with COVID-19. Since our meta-analysis had included a large number of COVID-19 patients and we have also provided pooled estimates of ORs and HRs from large-scale studies that have adjusted extensively for multiple potential confounding factors, the findings can be considered fairly reliable and generalisable.

With the inception of the COVID-19 pandemic, repurposing of existing drugs has become a norm. One such drug that has come to the forefront is statins.[1] Apart from their predominant antiatherosclerotic and cardioprotective effects, statins exert a multitude of pleiotropic effects, notably, modulation of immune responses, augmentation of anti-inflammatory processes and alterations of signalling pathways involving cholesterol intermediates. Hence, a number of diseases have been linked to the pleiotropic effects of statins that include inflammatory bowel disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, malignancy and Alzheimer's disease.[2] With regard to infectious diseases, statins have been investigated in AIDS and certain bacterial infections.[24–26]Furthermore, two retrospective cohort studies had reported a reduced risk of influenza death among statin users.[27 28] Likewise, statins use has been

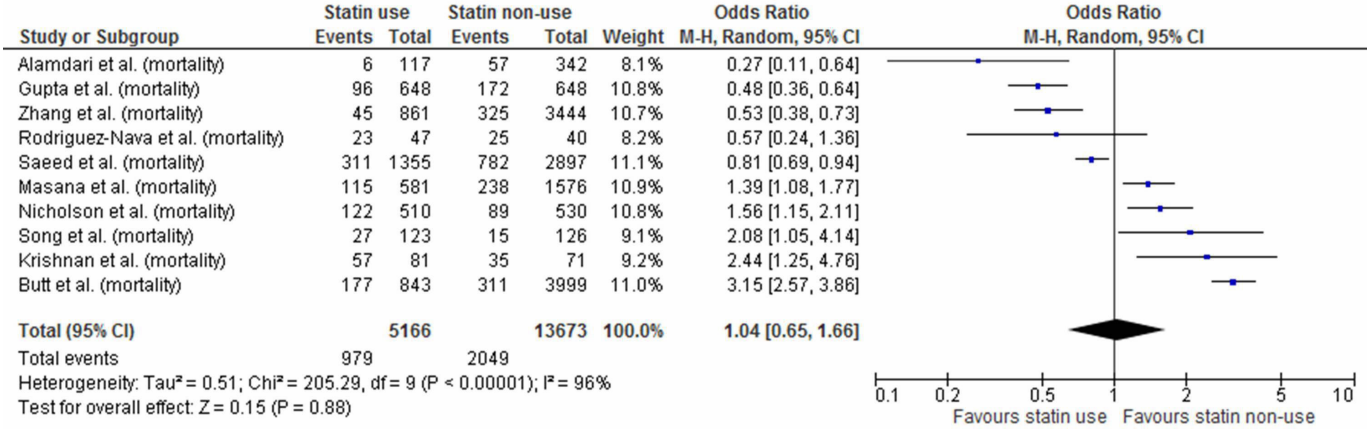


**Figure 3** Forest plot of sensitivity analysis showing the effect (unadjusted) of statin use on mortality in patients with COVID-19 as compared with non-use of the drug. The reported clinical outcomes of individual studies have been represented in brackets. M-H, Mantel-Haenszel.

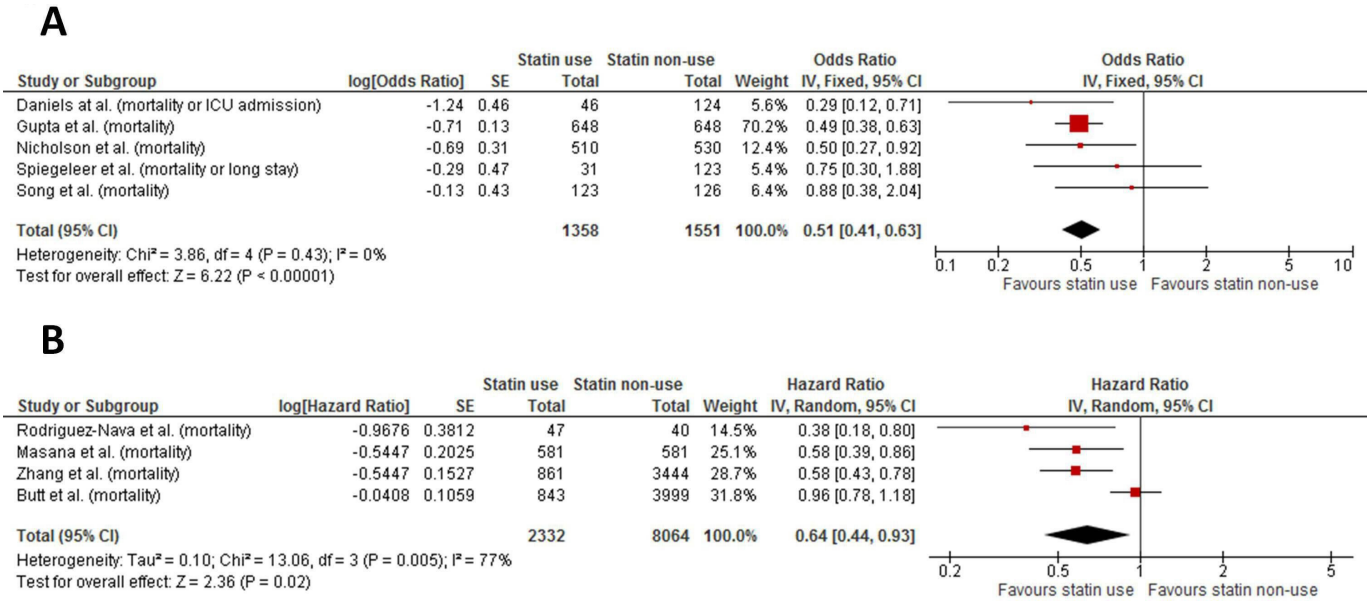


**Figure 4** (A, B) Forest plot showing the effect (adjusted) of statin use on clinical outcomes in patients with COVID-19 as compared with non-use of the drug expressed either as pooled odds ratio (A) or pooled HR (B). The reported clinical outcomes of individual studies have been represented in brackets. ICU, intensive care unit.

found to be associated with a reduced risk of adverse outcomes in patients with COVID-19.[4–9] The data are, however, limited and contradictory with some studies reporting no difference while others showing adverse outcomes in statin users compared with non-users.[10–13]

In the present meta-analysis, we found that statin use was associated with improved clinical outcomes in patients with COVID-19. The benefit was observed even though statin users were more likely to be old and likely to suffer from comorbid conditions, notably, hypertension, diabetes mellitus and ischaemic heart disease, all of which are known to independently increase the risk of adverse outcomes and mortality in COVID-19.[29 30] When adjusted for all potential confounding factors, statins were found to be all the more beneficial, reducing the risk of adverse clinical outcomes by 36%–49%. The data are encouraging and reiterates the need to continue statins in individuals at risk of poor outcomes with COVID-19 (those with multiple comorbidities). Besides, the drug should be continued in patients who had been infected with SARS-COV-2 and should also be pursued as a potent drug even in COVID-19 patients who had prior never been on statins. Atorvastatin as adjunctive therapy in COVID-19 is presently being investigated as a part of an RCT (STATCO19, identifier NCT04380402).

The potential beneficial effect of statins in COVID-19 pertains primarily to the immunomodulatory properties of the drug. The SARS-CoV, the coronavirus responsible for the SARS outbreak in 2003, has been shown to interact with Toll-like receptors on the host cell membrane, thereby increasing the expression of the myeloid differentiation primary response 88 (*MyD88*) gene. This ultimately leads to the activation of the downstream NF-κB pathway thereby triggering inflammation.[31] Statins have been shown to stabilise MyD88 levels following a proinflammatory trigger and, thereby, mitigate activation of NF-κB.[32] Thus, statins might prevent the development of an overwhelming inflammatory response (cytokine storm) in patients with COVID-19.[3] Besides, preclinical studies have shown that statins could directly inhibit the SARS-CoV-2 main protease (Mpro).[33] Statins are also known to upregulate ACE2 expression that might protect against coronavirus-mediated lung injury.[3]

The present study happens to be the most updated meta-analysis, having incorporated all hitherto available observational studies screened from three large databases reporting clinical outcomes in COVID-19 patients using statins. Apart from including a fairly large number of patients in the meta-analysis, we have provided both unadjusted and adjusted estimates of the effect sizes of the clinical outcomes. Nevertheless, the study does have certain limitations. Adjusted estimates were not reported in some studies, hence, they could not be included in the adjusted pooled analysis. In addition, the covariates reported across all the 14 studies were not uniform and the OR/HR derived from various studies was adjusted for different covariates.

## Main messages

- Statin use is associated with reduced risk of adverse outcomes in patients with COVID-19.
- Statins are beneficial despite the fact that patients on statins tend to have multiple comorbidities.
- Individuals with multiple comorbidities on statin therapy should be encouraged to continue the drug amid the ongoing pandemic.

## Current research questions

- What are the mechanistic insights behind the beneficial effect of statins in COVID-19?
- Does there exist any dose–response relationship underlying the beneficial effect of statins in COVID-19?
- Can statin be pursued as an adjunctive therapy even in statin-naïve patients with COVID-19?

Furthermore, most studies do not mention the type and dosage of statin treatment in their studied samples that can be an independent source of potential bias. Besides, most of the studies reporting the preadmission use of statins are silent about whether the drug was continued or discontinued after hospitalisation. Lastly, the association between statin use and improved clinical outcomes might have been confounded by the fact that, more often than not, people with better access to healthcare prior to COVID-19 might have been prescribed statins.

In conclusion, statin use is associated with improved clinical outcomes in patients with COVID-19. Individuals with multiple comorbidities on statin therapy should be advised not to discontinue the drug amid the ongoing pandemic. Besides, statin-treated patients should continue the drug if infected with SARS-CoV-2. The role of statins as an adjunct to standard therapy in statin-naïve COVID-19 patients needs to be further explored.

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