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

Rimesh Pal 1, Mainak Banerjee 2, Urmila Yadav 3, Sukrita Bhattacharjee 4

ABSTRACT
Purpose Observational 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 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, I²=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, I²=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 scoured 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, amidst 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.
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. 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. 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 (UY).

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 was 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 model. The possible sources of significant heterogeneity were reanalysed and reported using the random-effects model. The tool 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 Version 5.4 software.

RESULTS
After a scrupulous literature search and a meticulous study selection process, we included 14 observational studies in our meta-analysis, pooling data retrieved from 19 988 patients with COVID-19 (figure 1). The study by Yan et al was a case–control study, 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, 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 of...
of severe and critical disease rather than mortality. The results of the meta-analysis have been summarised under the following heads.

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

<table>
<thead>
<tr>
<th>Authors (reference)</th>
<th>No of participants</th>
<th>Design</th>
<th>Place of study</th>
<th>Clinical outcomes reported</th>
<th>Covariates adjusted for</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gupta et al⁹</td>
<td>1296</td>
<td>Retrospective multicentre cohort study, USA</td>
<td>In-hospital 30 days mortality</td>
<td>Age, male sex, history of atrial arrhythmias, and DM</td>
<td>8/9</td>
<td></td>
</tr>
<tr>
<td>Zhang et al⁷</td>
<td>4305</td>
<td>Retrospective multicentre cohort study, China</td>
<td>Mortality</td>
<td>Age, sex, oxygen saturation at admission</td>
<td>8/9</td>
<td></td>
</tr>
<tr>
<td>Alamdari et al⁸</td>
<td>459</td>
<td>Retrospective single centre cohort study, Iran</td>
<td>Mortality</td>
<td>Age, sex, comorbidities (obesity, HTN, DM, CVD, and CKD)</td>
<td>7/9</td>
<td></td>
</tr>
<tr>
<td>McCarthy et al⁶</td>
<td>247</td>
<td>Multi-centre cohort, USA</td>
<td>ICU admission or mortality</td>
<td>Age, sex, functional status, DM, HTN</td>
<td>6/9</td>
<td></td>
</tr>
<tr>
<td>Krishnan et al⁷</td>
<td>154</td>
<td>Retrospective multicentre cohort study, Europe</td>
<td>Hospital stay or mortality</td>
<td>Age, sex, smoking, aspirin, albumin, CRP, PCT and haematological parameters</td>
<td>5/9</td>
<td></td>
</tr>
<tr>
<td>De Spiegeleer et al⁸</td>
<td>294</td>
<td>Retrospective single centre cohort study, USA</td>
<td>Mortality</td>
<td>Age, sex, race, CVD, COPD, DM, obesity.</td>
<td>7/9</td>
<td></td>
</tr>
<tr>
<td>De Spiegeleer et al⁹</td>
<td>578</td>
<td>Retrospective multicentre case control Study, China</td>
<td>Severe and critical disease</td>
<td>NR</td>
<td>5/9</td>
<td></td>
</tr>
<tr>
<td>Krishnan et al⁷</td>
<td>152</td>
<td>Retrospective multicentre cohort study, USA</td>
<td>Mortality</td>
<td>NR</td>
<td>5/9</td>
<td></td>
</tr>
<tr>
<td>Rodriguez-Nava et al⁸⁴</td>
<td>87</td>
<td>Retrospective single centre cohort study, USA</td>
<td>Mortality</td>
<td>Age, HTN, CVD, severity, invasive mechanical ventilation, and antibiotics (except azithromycin)</td>
<td>6/9</td>
<td></td>
</tr>
<tr>
<td>Nicholson et al⁰⁴</td>
<td>1042</td>
<td>Retrospective multicentre cohort study, USA</td>
<td>Mortality</td>
<td>Age, sex, ethnicity, comorbidities, smoking, aspirin, albumin, CRP, PCT and haematological parameters</td>
<td>7/9</td>
<td></td>
</tr>
<tr>
<td>Butt et al⁴⁰</td>
<td>4842</td>
<td>Observational nationwide cohort study, Denmark</td>
<td>All-cause mortality</td>
<td>Age, sex, ethnicity, socioeconomic status and comorbidities</td>
<td>8/9</td>
<td></td>
</tr>
<tr>
<td>Masana et al⁴²</td>
<td>2157</td>
<td>Retrospective multicentre cohort study, Spain</td>
<td>Mortality</td>
<td>Distance, age, sex, smoking status, comorbidities</td>
<td>7/9</td>
<td></td>
</tr>
<tr>
<td>Saeed et al⁴³</td>
<td>4252</td>
<td>Retrospective single centre cohort study, USA</td>
<td>Cumulative in-hospital mortality</td>
<td>Age, sex, history of AHD, Charlson comorbidity index, presenting vitals, serum glucose, lactic acid, creatinine and intravenous antibiotic use during hospitalisation</td>
<td>8/9</td>
<td></td>
</tr>
</tbody>
</table>

Clinical outcome data reported as n/N (%).

OR/HR presented as ratio (95% CI).

*Risk of bias assessment 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 only for COVID-19 patients with diabetes mellitus (n=2266) with 983 being statin users and 1283 being 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.

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.

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
showed that statin use was not associated with improved clinical outcomes (OR 1.02; 95% CI 0.69, 1.50, p=0.94, I²=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, I²=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, I²=0%, fixed-effects model) (figure 4A). Similarly, covariate-adjusted HR were reported in five studies5 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, I²=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
found to be associated with a reduced risk of adverse outcomes in patients with COVID-19. 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.

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. 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. Statins have been shown to stabilise MyD88 levels following a proinflammatory trigger and, thereby, mitigate activation of NF-κB. Thus, statins might prevent the development of an overwhelming inflammatory response (cytokine storm) in patients with COVID-19. Besides, preclinical studies have shown that statins could directly inhibit the SARS-CoV-2 main protease (Mpro). Statins are also known to upregulate ACE2 expression that might protect against coronavirus-mediated lung injury.

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.
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 predadministration use of statins are silent about whether the drug was continued or discontinued after hospitalization. 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-naive COVID-19 patients needs to be further explored.

Contributors RP and MB are the primary authors. RP, MB, UY and SB had helped in data collection. All the authors approved the final version of the manuscript.

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Competing interests None declared.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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REFERENCES

Dear Editor

We thank the editor and the reviewer for their constructive comments and letting us revise our manuscript. We have addressed the queries put forward by the reviewer and have re-updated our systematic review and meta-analysis to include all the recently published studies. We believe that the manuscript has been enriched all the more.

FORMATTING AMENDMENTS
Required amendments will be listed here (if any); please include these changes in your revised version:
1. Table 1 not embedded
   - Kindly embed your table (should be editable). Tables should be placed in the main text where the table is first cited. Tables must be cited in the main text in numerical order. Please note that tables embedded as Excel files within the manuscript are NOT accepted. Do not upload your table separately.
   - Please make sure that your Tables are on editable format.

Response: Thank you for the suggestion. We have added Table 1 in the main text in MS word format.

REVIEWERS COMMENTS:

Reviewer: 1

Comments to the Author
The authors report a systematic review and meta-analysis of non-experimental studies of the association between statin use pre-illness and outcomes of COVID-19 illness. The material states that the PRISMA guidelines were followed although a check-list wasn't provided. It doesn't appear that the material was registered with a SR/MA database, and if this was the case it should be explicitly stated.

Response: We thank the reviewer for the suggestion. We have added a PRISMA checklist.
The index systematic review and meta-analysis was not registered in any SR/MA database, which we have now clearly mentioned in the revised manuscript (page 6, line 131-132).
The title of the material should include the phrase 'Systematic review' and the phrase 'Up-to-date' is misleading as it implies that this is a sort of sequential meta-analysis (which it is not).

**Response:** Thank you for the insightful comment. We have modified the title as advised and have replaced the term up-to-date by the term “Updated” (page 1, line 1-2). Besides, we have included all the recent observational studies by extending out literature search till December 18, 2020 (page 6, line 137).

In the planned analysis section the software used should generally be the last sentence.

**Response:** Thank you for the suggestion. We have modified as advised by the reviewer (page 9, line 203).

The important omission from this section and subsequently is that the approach to heterogeneity is not stated. This is very important as there is considerable heterogeneity in the study outcomes such that a random effects estimate has very wide confidence intervals and is not statistically significant at the nominated type I error rate. Generally this should be approached by a pre-specified meta-regression in relation to study-level co-variates. Leave-one-out approaches will not be sufficient here. The authors therefore overstate the evidence supporting the association between pre-illness statin use and COVID-19 outcomes. It is possible to reproduce the meta-analysis shown in Figure 1 however what the authors have omitted is the random effects estimate; estimated using the R-package meta (function metabin) of 0.89 (95% CI 0.59 to 1.34), P=0.57. The order of the Forest plot is not useful; generally this should be in rank order of the point estimates rather than alphabetical order of the first-named author. If this was a sequential meta-analysis then it should be in date order of data acquisition although it is likely all studies have been published only in the last six months. Heterogeneity has clearly accrued because the outcomes are a mix of ICU admission and mortality however other forms of study-level co-variates have not been pursued. Although the authors have attempted some form of sensitivity analysis by showing an analysis of adjusted analyses this is only a small sub-set of all the studies.
Response: Thank you for the insightful comments. We agree with the reviewer. However, we would like to discuss the issues in details.

We have addressed our approach to heterogeneity in details (page 8-9, line 195-201) as outlined below:

“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.\(^\text{18}\) In the present meta-analysis, significant heterogeneity was considered when the $I^2$ value was $\geq 50\%$, with a p value <0.05. Outcomes with significant heterogeneity were reanalyzed and reported using the random-effects model. The possible sources of significant heterogeneity were addressed through sensitivity analyses.”

Hence, as suggested by the reviewer, we have applied the random-effects model for outcomes with significant heterogeneity, while outcomes without significant heterogeneity were analyzed using fixed-effects model. As anticipated by the reviewer, using the random-effects model, the unadjusted pooled analysis did not show any significant association between statin use and clinical outcomes in COVID-19 (Figure 2). However, the adjusted pooled analysis did show significant benefits in clinical outcomes with statin use (Figure 4A, 4B).

Indeed, as stated by the reviewer, part of the heterogeneity has been accrued because of the variable clinical outcomes reported across various studies. Among the 14 studies included, 10 had reported clinical outcomes as mortality, 2 in terms of mortality or ICU admission, 1 in term mortality of long hospital stay and 1 term of severe and critical disease. Thus, mortality was a part of clinical outcome in all but 1 study (Yan et al). Hence, we have performed a sensitivity analysis by excluding the study by Yan et al. which we have represented in Figure 3.

The reviewer’s comment regarding meta-regression is indeed well taken. However, we would like to highlight the fact that covariates involved in all the 14 studies are highly variable. The myriad of covariates involved in all the studies is another major source of heterogeneity. We have mentioned the same in the limitation section of the manuscript as well (page 15, line 325-327).

Considering the multiple covariates involved across all the studies, selecting the appropriate covariates for meta-regression was difficult. Hence, we selected five covariates for meta-regression which is expected to affect clinical outcomes: age, male sex, prevalence of diabetes mellitus, prevalence of hypertension and prevalence...
of cardiovascular disease/ischemic heart disease. **Even then we could retrieve the raw data on the aforementioned covariates from only 7 studies** (Gupta et al., Zhang et al., De Spiegeeler et al., Song et al., Butt et al., Masana et al. and Saeed et al). In rest of the 7 studies, the aforementioned covariates were not separately mentioned in the articles and could not be retrieved even on personal communication with the corresponding authors via emails.

We did try to perform meta-regression using the Comprehensive Meta-analysis software V3. However, with only 7 studies, the software could not perform meta-regression with all the five covariates. Meta-regression could be performed and scatterplots could be generated with individual covariate separately, however, that would not have been reflective of the actual adjusted estimates. Hence, we have not included the same in the manuscript.

Instead, we have provided pooled adjusted estimates in the manuscript. We have pooled together the adjusted odds ratio or hazard ratios reported in the individual studies using the generic inverse variance method (GIMV) (odds ratio and hazard ratios being pooled separately). These pooled estimates are a reliable measure of the adjusted effect of statin use on clinical outcomes in COVID-19. **Hence, instead of meta-regression (which is not possible with data available from only 7 studies), we have provided pooled adjusted estimates using the GIMV.** However, if the reviewer feels that meta-regression data is necessary, we would incorporate the same using each of the five selected covariates separately.

**As suggested by the reviewer, we have arranged the studies in rank order of the point estimates in the Forest Plots.**

As these are non-experimental studies then the reasons for prescription of statins may be surrogates for other factors that are associated with mortality outcomes; for example those people with better access to health care before illness may have been prescribed statins which is a potent alternative explanation for the association.

**Response:** Thank you for the insightful suggestion. We have mentioned the same in the limitation section of the manuscript (page 15, line 331-334).