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).

Pal R, *et al. Postgrad Med J* 2022; 98:354–359. doi: 10.1136/postgradmedj-2020-139172

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.

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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.*[18] *In the present meta-analysis, significant heterogeneity was considered when the I^2 value was ≥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).

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