OPEN PEER REVIEW

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Peer Review Report for "A Systematic Review and Meta-analysis of Diabetes Associated Mortality in Patients with COVID-19"

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Review Timeline:

Submit Date:	24 Jan 2021
Revised Date:	1 Jun 2021
Accepted Date:	8 Aug 2021

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0) 1 Mar 2021

Dear AE,
This manuscript does not follow the scientific writing format and has an essential methodological drawback that can mislead the readers.
Major revision:
1- What new value has been added in this study compared to the previous meta-analysis? There are some related meta-analysis studies as follows:
- Shang L, Shao M, Guo Q, Shi J, Zhao Y, Xiaokereti J, Tang B. Diabetes mellitus is associated with severe infection and mortality in patients with COVID-19: a systematic review and meta-analysis. Archives of medical research. 2020 Oct 1;51(7):700-9.
- Palaiodimos L, Chamorro-Pareja N, Karamanis D, Li W, Zavras PD, Chang KM, Mathias P, Kokkinidis DG. Diabetes is associated with increased risk for in-hospital mortality in patients with COVID-19: a systematic review and meta-analysis comprising 18,506 patients. Hormones. 2020 Oct 29:1-0.
2- Title is not supported by findings and findings are not confirmed by title.
3- Different effect sizes such as prevalence, odds ratio, and risk have been expressed by the authors but, each of these effect sizes is suitable for different situations.
4- In table 1, the authors reported study characteristics but did not indicate study designs.
5- Given the small sample size of the studies and the wide confidence interval of their

effect size (for example reference 20-21-24-30-39 ...), how did the studies obtain high-quality scores and good quality by NOS scale?
Minor revision:
6- The reference of the first paragraph is irrelevant.
7- Systematic search, data collection, and data extraction should be done independently by two authors but the search strategy for this meta-analysis was done only by KG.
8- Why did you just search PubMed and DOAJ databases? For optimal searches, authors should search at least Embase, MEDLINE, Web of Science, and Google Scholar.
9- Why did you search randomized controlled trials?
10- In the search of relevant literature, a few search term has been used. Also, the authors need to present search strategy syntax for each database and show the results in Fig. 2.
11- The limited search strategy is a major limitation of this manuscript.
12- Figure 2: Flow diagram. I suggest using the PRISMA Flow chart. How many studies were identified by each database and excluded? Especially in the assessment of the full-texts for eligibility
13- This meta-analysis is included only a few countries.
Thanks.

REFEREE: Reviewer | **Revision (0)** 2 Mar 2021

Dear AE,
- The reason for including Randomized control trials is not clear.
- More explanation is required for Statistical analysis regarding standards in CONSORT guideline.
- There is a mistake in Figure 1(Full-text articles excluded, with reasons (n = 7) Objective results missing (2), insufficient data(6):6+2~=7)
Thanks.

REFEREE: Reviewer | **Revision (0)** 2 May 2021

Dear AE,
I read the manuscript entitled “A systematic review and meta-analysis of Diabetes associated mortality in patients with COVID-19”. Although there are other metanalysis in this subject but because of the importance of this matter and worldwide pandemic and new publications every month, it merits to discuss different aspects of the diseases by different experts.
I have some minor comments as follow:
- Only free full-text articles have been included in the systematic review. Since most papers regarding COVID-19 are free nowadays, it may cause missing a few publications. However, the number of papers missed because of being not free should be reported and mentioned as a limitation in the discussion.
- The authors discussed that “Diabetes carried a slightly higher risk of mortality outside China (OR=1.95, 95% CI: 1.66-2.24) as compared to within China (OR=1.8365 95% CI: 1.3-2).” Since the 95% CIs are entirely overlapped, this view is not supported.

- The sentence of “Diabetes is one of the comorbid conditions found in the elderly patients getting infected with COVID-19. Its prevalence among COVID-19 patients has been on an increase in the last few months.” in the discussion needs at least a reference.
Thanks.

REFEREE: Associate Editor | **Revision** (0) 2 May 2021

Dear EIC,
Three reviewers including clinicians and methodologists reviewed the manuscript. One of them recommended a major revision and two of them asked for a minor revision. I would like to ask the authors to respond to the comments point by point then we can make the decision for publication.
Thanks.

REFEREE: EIC | **Revision** (0) 2 May 2021

Dear Authors,
Based on reviewers' comments the manuscript needs major revision.
Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Reply to the reviewers' comments

Reviewer Number	Original comments of the reviewer	Reply by the author(s)	Changes done on page number and line number
1	*Major revision:* *1- What new value has been added in this study compared to the previous meta-analysis? There are some related meta-analysis studies as following:* *Shang L, Shao M, Guo Q, Shi J, Zhao Y, Xiaokereti J, Tang B. Diabetes mellitus is associated with severe infection and mortality in patients with COVID-19: a systematic review and meta-analysis. Archives of medical research. 2020 Oct 1;51(7):700-9.* *Palaiodimos L, Chamorro-Pareja N, Karamanis D, Li W, Zavras PD, Chang KM, Mathias P, Kokkinidis DG. Diabetes is associated with increased risk for in-hospital mortality in patients with COVID-19: a systematic review and meta-analysis comprising 18,506 patients. Hormones. 2020 Oct 29:1-0.*	1- The sample size of the meta-analysis is larger than the previous ones. We provide a pictorial representation of the mechanism of association of DM with COVID-19. It is the most UpToDate inclusion of the studies and the literature. We assessed both total mortality and diabetes associated mortality. As an Indian author, this is one of the first meta-analysis. *Although there are other metanalysis in this subject but because of the importance of this matter and worldwide pandemic and new publications every month, it merits to discuss different aspects of the diseases by different experts. –* ***As suggested by one of the other reviewers.*** ***The results further adds to the literature and thus increase awareness about control of glycemic levels in diabetics for preventing grave outcomes of COVID-19 in them.***	

	2- Title is not supported by findings and findings are not confirmed by title. *3- Different effect sizes such as prevalence, odds ratio, and risk have been expressed by the authors but, each of these effect sizes is suitable for different situations.*	*Overall it relates to the co-morbid population of the world and thus relates to the public health.* *2-* *The results seem to aptly match the title.* *Title of the article: A systematic review and meta-analysis of Diabetes associated mortality in patients with COVID-19.* *Results:* *A total of 35 studies with 25,934 patients were finally included for meta-analysis. The pooled prevalence of Diabetes mellitus in patients with COVID-19 was 16.8% (n=4381). The overall mortality seen in all the studies were 12.81% (n=3159) and Diabetes associated mortality was 22.14% (n=970). The pooled analysis of 35 studies showed that DM had a significantly higher mortality rate (22.14% vs. 12.81%, p<0.05) with higher odds of death (pooled OR 1.83, 95% CI: 1.61-2.05). The funnel plot was symmetric, thereby indicating a low risk of publication bias.* *3-* *No doubt that the effect size is different in various studies, but as a systematic review and meta-analysis, I have to include all the studies and their individual weightage has been calculated as a part of meta-analysis.*	

	4- In table 1, the authors reported study characteristics but did not indicate study designs. *5- Given the small sample size of the studies and the wide confidence interval of their effect size (for example reference 20-21-24-30-39 ...), how did the studies obtain high-quality scores and good quality by NOS scale?* *Minor revision:* *6- The reference of the first paragraph is irrelevant.*	*4-* Study design has been added in the table for all studies. 5- The sample size of the individual studies was justified as per their facility and duration of the study. Since most of these studies represent individual data of their hospitals, the sample size cannot decide the quality of an individual study as long as they represent the COVID-19 population and report the diabetes associated mortality among them. All the parameters of NOS scale were individually analysed for each study. As far as the wider confidence intervals are concerned, the funnel plot was made which was found to be symmetric, with Egger test showing a p value of 0.268; thereby indicating a low risk of publication bias. So even statistically and subjectively assessing all the studies, they carried low publications bias and had good quality. 6-The reference is removed as advised.	

	7- Systematic search, data collection, and data extraction should be done independently by two authors but the search strategy for this meta-analysis was done only by KG. *8- Why did you just search PubMed and DOAJ databases? For optimal searches, authors should search at least Embase, MEDLINE, Web of Science, and Google Scholar.* *9- Why did you search randomized controlled trials?* *10- In the search of relevant literature, few search term has been used. Also, the authors need to present search strategy syntax for each database and show the results in the Fig. 2.* *11- The limited search strategy is a major limitation of this manuscript.* *12- Figure 2: Flow diagram. I suggest using the PRISMA Flow chart. How many studies were identified by each database and excluded?*	7-Sorry, that was mistyped. It was done by two authors itself independently. Now included the second name there. 8-We considered two databases as minimum for search as they are the most popular. But now as advised, we have covered other databases and extended the table of studies. 9- Sorry. That has been removed from the inclusion criteria, since there was no randomised controlled study in the final table of studies. 10-The search terms have been extended. The syntax is presented. Figure 2 now shows the results. 11- The search strategy has been widely extended and now it does not remain a limitation for the present study. 12- PRISMA is made. Individual database studies searched and excluded has been added. Especially the full texts.	

	Especially in the assessment of the full-texts for eligibility *13- This meta-analysis is included only a few countries.*	We included all studies done in any country.	
2	*- The reason for including Randomized control trials is not clear.* *- More explanation is required for Statistical analysis regarding standards in CONSORT guideline.* *- There is a mistake in Figure 1(Full-text articles excluded, with reasons (n = 7) Objective results missing(2), insufficient data(6):6+2~=7)*	- I have excluded that criteria. Sorry for writing that. Statistical analysis has been elaborated as per CONSORT guidelines -Figure 1 is edited.	
3	*I read the manuscript entitled "A systematic review and meta-analysis of Diabetes associated mortality in patients with COVID-19". Although there are other metanalysis in this subject but because of*	Thank you.	

	the importance of this matter and worldwide pandemic and new publications every month, it merits to discuss different aspects of the diseases by different experts. *I have some minor comments as follow:* *- Only free full-text articles have been included in the systematic review. Since most papers regarding COVID-19 are free nowadays, it may cause missing a few publications. However, the number of papers missed because of being not free should be reported and mentioned as a limitation in the discussion.* *- The authors discussed that "Diabetes carried a slightly higher risk of mortality outside China (OR=1.95, 95% CI: 1.66-2.24) as compared to within China (OR=1.8365 95% CI: 1.3-2)." Since the 95% CIs are entirely overlapped, this view is not supported.* *- The sentence of "Diabetes is one of the comorbid conditions found in the elderly patients getting infected with COVID-19. Its prevalence among COVID-19 patients has been on an increase in the last few months." in the discussion needs at least a reference.*	-Now this has been added in Figure 2 and the limitation section. -That section of the paragraph has been excluded. -The reference has been added.	

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Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Associate Editor | **Revision** (1) 4 Aug 2021

Dear EIC,
With deep discussion with the reviewers, although there are some shortcomings in the systematic review it is not serious and discussed in limitation, and we decided to accept the manuscript because of the importance of the subject and well-performed meta-analysis. By the way, including "diabetes insipidus" in the search strategy does not seem reasonable because its pathophysiology is different from diabetes Mellitus and there are no results regarding this issue in the manuscript. This term should be removed from the search builder.
Warm regards

REFEREE: EIC | **Revision** (1) 8 Aug 2021

Dear Authors,
The manuscript is acceptable for publication in the IJEM.
Thanks.