Author’s response to reviews

Title: Short- and long-term outcomes in infective endocarditis patients: a systematic review and meta-analysis

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Author’s response to reviews:

Authors reply to reviewers comment;

Dear Editor,

Thank you for giving this opportunity to review our work again and to submit to the recognized and reputable journal. We have tried to address the comments provided by reviewers accordingly. Herewith we attached the reply below.

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Reviewer reports:

Mahmoud Diab (Reviewer 1): The authors conducted a systemic review and meta-analysis to examine short-term and long-term outcomes of IE patients. They included 34 out of 4,466 articles in the systemic review and 28 in the meta-analysis. They found a significant increase in mortality in IE patients undergoing long-term treatment 27.7% compared to IE patients undergoing short-term treatment 19.9%. The authors concluded that a significant increase in mortality was found in IE patients undergoing long-term treatment than short-term treatment.

General Comments

This manuscript addresses an interesting topic (short-term and long-term outcomes in infective endocarditis patients: a systemic review and meta-analysis). However, there are serious issues with the methodology of this study. (see below for details).

Specific comments:

1. The authors did not define the long-term and short-term treatment in the methods. It is unclear what they mean with these terms. It is crucial to define these two different treatment strategies, especially if the final conclusion is based on these treatment strategies.

Authors reply

Dear reviewer

Thank you for your comment

Short and long term treatment is changed into “outcomes” which is the appropriate terminology.

2. There is no data about the preoperative patient’s characteristics, incidence of neurological complications, echocardiographic findings (vegetation, abscess, valvular insufficiencies), surgical therapy and indications for surgery. It is expected that there is heterogeneity among the 34 studies included in this review and meta-analysis which could cause bias in the results. The
authors did not mention if there was such heterogeneity and if there was some, how they deal with it.

Dear reviewer

The echocardiographic findings are presented in the form of valvar involvement (mitral aortic, others---), the frequency of patients receiving surgical care is also mentioned. In addition neurological complications were stated under “other complications” as it is few cases tp stand alone. Furthermore, the level of herogeneity is calculated and controlled by running the analysis on random effect model.

3. The studies included were conducted over a very wide interval between 1984 and 2016. There have been big advances in diagnostic tools, medical therapies and surgical techniques during this period which could lead again to bias.

Dear reviewer

Information on the above parameters (vegetation, Echocardiography-----) was not complete to include on the manuscript and actually our aim is to determine the long and short term mortality, we found that these background information remain to be supplementary. Considering the wide interval and associated bias in results, we removed studies published before 2000. For the rest of the studies we try to control bias by doing a random effect model and subgroup analysis.

Asim Cheema (Reviewer 2):

This study by Abegaz et al is conducted as a systematic review and meta-analysis of short vs long term outcomes for patients with IE from 1984-2016. The author includes 28 studies in meta-
analysis; 11 prospective and 17 retrospective studies with 21,920 participants. All the included studies looked at medical and surgical treatments. The results show significant increase in long term mortality 27.7% (95% CI: 20.9-34.5; p<0.001) compared to than short-term treatment 19.9%, (95% CI: 17.5-22.3; p<0.001)

Major consideration:

- The authors have tried to address several questions from a heterogeneous population and in the process the "message" of the paper is lost. They have made comparisons of short and long term mortality, short and long term treatment, rate of complications in IE (not certain if they are short term or long term), incidence of IE in drug users and HIV patients (Is this incidence or risk factor presence (prevalence) in patients diagnosed with IE).

Dear reviewer

Our aim is to independently estimate the long and short term outcomes, comparison is made between short and long term outcome. The rate of complications was determined as “overall incidence" not separated into long or short. Drug use is presented as prevalence of risk factor. HIV is not included in the risk factor list.

- The numbers added for various groups do not add up to 100%, i.e, aortic and mitral valve IE, only 10% of patients have acquired left sided IE, native + prosthetic IE do not add up to 100%, similarly, the type of pathogen do not add up to 100%.
Dear reviewer

Thank you for your comments

The sum of aortic and mitral valves are not necessarily 100% since there are other valves affected. The same is true for left side IE, native and prosthetic. We have made a change as well on the manuscript.

- An inclusion exclusion criterion needs more clarification for studies where surgical intervention was undertaken out of total sample but for which patient population?

Dear reviewer

Patients were included if both medical and surgical care was carried out.
- As mentioned by the author age was not limited but no study included children or pediatric population. This makes the statement for limitation of age unjustified and leads to selection bias.

Dear reviewer

Thank you for your deep insight to this term. We have corrected accordingly.

All retrieved studies focused on adults
- Short versus long term treatment for IE needs to be defined clearly in the study.
Dear reviewer

Short and long term treatment for IE is not our aim. Therefore, we have changed this term in the manuscript.

- According to the author, number of studies for long term outcome is 13 (12 references provided in brackets) whereas 10 year, 5 year and 1 year studies number sum up to 28. Should the two match?

Dear reviewer

Thank you for your suggestion

According to the revision we included 14 studies in the long term outcome. Therefore, the discrepancy in the number of studies has been solved. However, one study can report a 1, 5, or 10 year outcome. Hence, the sum of number of studies that report 1, 5, 10 outcome might not be necessarily 14.

Results

- Author has mentioned 34 studies were included but 6 did not meet criteria for meta-analysis. In summary table 34 studies are tabulated with only 2 studies showing * that have not been included in meta-analysis.
Dear reviewer

Thank you

As per your comments we looked at the studies again. We undertook a thorough review and only 25 studies were included for both systematic review and meta-analysis.

- In demographics section author has mentioned nearly half of respondents 9169 (41.96%) were NVE and 1554 (7.12%) PVE. What about the rest of the patients? Also, the numbers provided for NVE and PVE in cardiac involvement in IE cases are different. Please clarify the discrepancy.

Dear reviewer

The frequency of NVE and PVE is corrected based on the number of studies reported. But, the rest of the studies didn’t report as such at all. Therefore, the sum of the NVE and PVE is not necessarily equal to the total sample size. Based on the new data 8496 (37.95%) had native valve IE. Prosthetic valve IE was identified in 1414 (6.32%), IE due to intravenous drug use was reported in 1077 (4.81%) subjects. Other patients 11,395 (50.91%) had either mixed type or unspecified IE.

- For valve involvement; 1355 (6.21%) patients had MV and 1720 (7.8%) patients had AV involvement which seems low with a data set of 21, 920 patients. Rest of the data should be mentioned in the study.

Dear reviewer

Thank you for your concern

The frequency of MV and AV is low because the combination of valves were found to be affected. According to the revised data, we have got the following evidence. Around 1974 (8.8
\( \%) \) were having mitral valve affection IE, whereas, 2,162 (9.7\%) aortic valve involvement, and combination of valves 18,241(81.5\%).

- For risk difference among gender, which group is significant should be mentioned in the section along with the discussion section.

Dear Reviewer

We have found that males are at high risk of IE than females do, 4:1 ratio. We put this finding in the result and discussion part.

- No analysis performed for confounding factors like age or causative microorganism.

Dear reviewer

Factors such as types of strains or pathogens are separately analyzed.

- Analysis should also be performed with exclusion of heavy studies like Terhag el al 2013 with 7603 and Chia-Jen et al 2010 with 8494 in order to prevent "drowning" effect of others studies.

Dear reviewer

We conducted analysis by excluding these studies and we found no different in the result.

- With 21, 920 patients in total MV 1355 (6.21\%) and AV 1720 (7.8\%) involvement seems like a low number. A detail of valvular involvement from included studies can help in better understanding of IE.
Dear reviewer

We discussed this question above.


Dear reviewer

We included the above study. Thank you for supplementing our search.

Minor considerations:

- All results should be expressed as N (%)

Dear reviewer

We have tried to include both frequency and percentages.

- Tables should be added for baseline characteristics and demographics for similarities/comparison between the studies

- Native valve percentage should be corrected

- Forest plots need proper labeling.
Dear Reviewer

We believe that Information that is included in the “overview of studies” contains most important data to compare studies based on sociodemographic and clinical characteristics. We added data on primary and secondary outcomes in the table. We draw forest plots and label them again.

- Author has mentioned funnel plots in manuscript. Please add it to appendix 2. Also, risk of bias summary table should be included as most of the studies are retrospective studies.

Dear reviewer

We did the forest plot and included in the paper.

- There are several spelling mistakes in tables/text that need to be corrected.

Dear reviewer

We address the grammatical and spelling errors. As for the risk of bias, we expect there could be bias and for this we evaluated the quality of studies and attached along with other documents. In addition we also put funnel plot in the manuscript. We hope it is understood that bias and heterogeneity can be reduced by random effect which we utilized during analysis.
Thank you

José M Tolosana (Reviewer 3):

Authors described in this meta-analysis the short-term and long term outcomes in infective endocarditis patients. The manuscript is well written, however there are some issues that have to be solved:

1. The first end point of the meta-analysis is to compare short term treatment vs. long term treatment outcomes in patients with IE. However, short term treatment and long-term treatment of IE were not defined in methods.

Dear reviewer

Thank you for your valuable comment in this regard

We removed the word “treatment” to avoid confusion

2. Authors concluded: "A significant increase in mortality was found in IE patients undergoing long-term treatment than short-term treatment". However, the discussion of the manuscript was focused on short term and long term mortality of IE. The conclusion of the study should be explained in the discussion.

Thank you for your valuable comment on this point

Since we didn’t do comparison based on short and long term treatment, we have changed the conclusion accordingly.

4. As secondary end-points, renal, cardiac and thromboembolic complications were analysed. The definitions of these complications should be explained.

Dear reviewer

We included a detailed definition of secondary outcomes under methods.

4. Author included in this meta-analysis d retrospective studies with few patients. This fact may cause confusion. I suggest to exclude these small retrospective studies from the meta-analysis.
Dear reviewer

Thank you for your valuable advice

We remove studies below 50 sample size from the meta-analysis.

5. Figures: For each study, there is a graphic that explain the RR and 95% of C.I. However the graphic which summarize the overall RR and 95% of the C.I. was wrong in all figures.

Dear reviewer

Thank you for your comment

The graphic which represent the overall RR is drawn in large rectangle which encompass the lower and the upper limit and the point estimate. We clearly indicate this in the new figures.