Author’s response to reviews

Title: Cardiac valve calcification and risk of cardiovascular or all-cause mortality in dialysis patients: A meta-analysis

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Author’s response to reviews:

Mohan Palla (Reviewer 1):

Review of Manuscript:

Methods:

The methodology for systematic review and meta-analysis follows Newcastle-Ottawa Scale (NOS) which is mainly for meta-analysis of observational studies.

This meta-analysis doesn't include all the available data in the literature and the results should be interpreted with caution as there is missing data. This is not an updated meta-analysis. The study performed by Sanchez-Perales C et al reported MI, stroke and/or died from cardiovascular causes in this patient population. Zhe Wang et al did not include this study in the meta-analysis. Please find the citation of the study below.


Reply:

The endpoint of the study by Sanchez-Perales C et al was the occurrence of one or several of the following events in the course of follow-up: MI, stroke or death from cardiovascular causes. This meta-analysis did not include the study, because the study didn’t report the all-cause/cardiovascular mortality in patients with/without valvular calcification. I sent an e-mail to
the author to ask for the correlated data, but I hadn’t received a reply. Thus, we had to exclude the study from this meta-analysis.

Results and Statistics:

In the sub-group analysis performed based on region, only two studies were included in case of the non-Asian studies. But there are total of three studies per author's systematic review. As the author did not present the details of individual studies in sub-group analysis, I cannot point out which study was not included.

Reply:

Seven studies reported the association between CVC and all-cause mortality (Figure 2), two studies (Panuccio et al, Italy and Varma et al, USA) are non-Asian studies, others are Asian studies (1 from Japan, 4 from China).

The author did not mention how the subgroup analyses would explain the observed heterogeneity.

Reply:

We have added the following information in the discussion section.

The inter-study heterogeneity showed decrease after grouping based on the hemodialysis (I2=17.8%) and peritoneal dialysis (I2=0.0%) in the all-cause mortality. Thus, the modes of dialysis may be a source for the inter-study heterogeneity. For the sensitivity analysis, the heterogeneity showed significant decrease after excluding the study reported by Varma et al (I2=12.4%), which may be related the higher heterogeneity as the study was of low quality. Meta-regression analysis revealed region, follow up duration, dialysis modality, being a multicenter study or not, a randomized study or not, a blinded follow up or not were not the major source for the inter-study heterogeneity (all P>0.1). Besides, the number of physicians analyzing echocardiographic recordings served as variable, which also showed no statistical differences (P=0.054). As only a few studies were included, it may be a source for the heterogeneity despite a P value of >0.05. For further analysis, subgroup analysis was performed using the number of physicians as the variable, which revealed significant decrease in the heterogeneity. Thus, single physician may increase the bias, which overestimated the effects of cardiac valve calcification on the all-cause mortality.

For the analysis of cardiovascular mortality, the regions were divided into Asia and non-Asian regions. The heterogeneity in the 5 studies performed in Asia was low (I2=0.0%). Only one study was performed in the non-Asian region, which may be responsible for the heterogeneity. Meta-regression analysis revealed region, follow up duration, dialysis modality, being a multicenter study or not, a randomized study or not, a blinded follow up or not were not the major source for the inter-study heterogeneity (all P>0.1). Besides, the number of physicians analyzing echocardiographic recordings served as variable, which also showed no statistical
difference (P=0.061). As only a few studies were included, it may be a source for the heterogeneity despite a P value of >0.05. For further analysis, subgroup analysis was performed using the number of researchers as the variable, which revealed significant decrease in the heterogeneity (two physicians: HR: 1.890; 95% CI: 1.256–2.845; I² = 9.0%; P = 0.333; one physician: HR: 3.718; 95% CI: 2.624–5.268; I² = 0.0%; P = 0.691). Thus, single physician may increase the bias, which overestimated the effects of cardiac valve calcification on the cardiovascular mortality. In a previous study, Panuccio et al excluded the patients with heart failure, which may increase the heterogeneity. Meta-regression analysis showed heart failure may be a source for the heterogeneity despite a P value of >0.05. In the meta-analysis excluding such study, the heterogeneity showed significant decrease (HR: 3.255; 95% CI: 2.428–4.363; I² = 0.0%; P = 0.492). As heart failure was one of the major causes for the cardiovascular mortality, exclusion of heart failure may underestimate the effects of cardiac valve calcification.

Discussion:

The discussion is poorly written. The authors did not summarize the important findings of their meta-analysis in the beginning of the discussion and I have to jump to conclusion to find out the main findings of the meta-analysis. The discussion should be rewritten.

As the meta-analysis is incomplete, both in main analysis and sub-group analyses, I would not like to point out each and every grammatical error.

The author mentioned in summary (last paragraph) - "this meta-analysis indicates that CVC is independently associated with higher all-cause and cardiovascular mortality in dialysis patients". The independent association cannot be mentioned because the data provided by some studies is not adjusted, the data included in the study is not the raw data (the study included the outcomes measure such as hazards ratio) and the meta-regression analysis is not performed.

Reply:

We have revised the discussion section with care according to your comments.

As mentioned by the reviewers, some of the data were not adjusted and the data were not the original data. We have revised the sentences in the conclusion.

Emmanuel Akintoye (Reviewer 2):

Major

1. It's not clear from the analysis what method was used to pool the estimates together. Is it DerSimonian and Laird, or other methods? This need to be stated

Reply:
We have added the following information in the Statistical analyses section.

Random effect model as described by DerSimonian and Laird was applied in cases of significant heterogeneity (P < 0.10 and I² > 50%), otherwise, a fixed-effect model as described by Mentel-Haenszel was applied.

2. Reference 13 i.e. Varma R et al did not report hazard ratio as study estimates. Was relative risk used for this study in the meta-analysis? This will not be compatible with other studies and analysis with and without this study should be performed. If you decide to include this study, report the summary estimate as HR may not be right except you have a justification for approximating the estimate used as HR

Reply:

The formula is as follows:

\[ O - E = O \times R_t \times R_c / (R_t + R_c) \times z \]

\[ V = O \times R_t \times R_c / (R_t + R_c)^2 \]

Where O stands for death toll, \( R_t \) stands the number of patients with valvular calcification, \( R_c \) stands for the number of patients in the non-calcified group. Then the \( O - E \) and \( V \) were entered into the 1745-6215-8-16-S1 Engauge Digitizer to calculate the HR


3. For reference 17, what I found published is "Risk Factor Analysis of Calcification in Aortic and Mitral Valves in Maintenance Peritoneal Dialysis Patients Kidney Blood Press Res. 2013;37(4-5):488-95" which does not evaluate mortality. Was the article referenced by the author actually got published?

Reply:


The article included in our research is not the one you mentioned. The article is a master dissertation of soochow university, which contains all-cause/cardiovascular mortality in patients with/without valvular calcification.

Link to the article: http://d.wanfangdata.com.cn/Thesis/D504588
4. You will need to conduct a metaregression for all subgroups analysed. You are not able to claim any subgroup difference (e.g. peritoneal vs hemodialysis) without showing that there is statistical significant difference between the subgroups. Hence, discussion of subgroup analysis in the DISCUSSION should based on the result of the metaregression. This point should be address throughout the manuscript

Reply:

Please check the newly added paragraphs in the discussion section.

5. If there is a difference in study result by region (i.e. asia vs non-asia), it will be nice to have critical review of the studies by region to be sure the difference is not actually due to difference in quality of the studies. If this difference cannot be explained by difference in quality, then the authors can speculate on why this difference exist or can leave it to future studies has done already

Reply:

For the correlation between cardiac valve calcification and the all-cause mortality, the heterogeneity in the studies in the asian region showed significant decrease ($I^2 = 0.0\%$). Whereas, in the two studies in the non-asian region, the heterogeneity was large, which may be related to the low quality of the study (Varma et al).

For the correlation between the cardiac valve calcification and the cardiovascular mortality, the whole heterogeneity was 48.5\%. The heterogeneity in the asian region showed obvious decrease ($I^2 = 0.0\%$), the non-asian region study could not explain for the source of heterogeneity. The heterogeneity may be associated with the exclusion of heart failure in the study by Panuccio et al. The prevalence of cardiac valve calcification was 23.27\%, which was obviously lower than the other studies. The risk of cardiovascular mortality (HR 1.48, 95\%CI: 0.86-2.54) was lower than other studies. Therefore, exclusion of the study by Panuccio et al may be the source for the heterogeneity. Heart failure was one of the major causes for the cardiovascular mortality, and exclusion of such parameter may underestimate the effects of CVC on the cardiovascular mortality.

Minor

1. Under the references, ref 16 is incorrectly written as 12

Reply:

It has been revised.
2. In the tables, avoid break in words as much as possible e.g prospective should be one line instead of two lines (with "e" on a different line)

Reply:

Please see the revised tables.