Peer Review File

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Reviewer A

The paper titled "Screening and identification of hub genes for ischemic cardiomyopathy and construction and validation of a clinical prognosis model using bioinformatics analysis" is interesting. Bioinformatics methods effectively analyzed the DEGs of ICM and successfully constructed a regulatory network of ICM susceptibility genes. ICM is closely related to the changes of ECM and oxidoreductase activity. The genes with significant differences and hub genes obtained by this screening may provide new targets for early ICM diagnosis and treatment. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) The abstract is not sufficient and needs further modification. The research background did not indicate the clinical needs of the research focus.

Reply 1: We have revised the background to indicate the clinical needs of the research focus. See page 2, line 45-46.

2) The "DEG screening results" section in the results is too simplistic. Suggest adding bioinformatics analysis results for this section.

Reply 2: We have revised the the results of the abstract. See page 2, line 53-63.

3) What is the greatest advantage of the clinical prognosis model in this study? What is the biggest problem we are facing? It is suggested to add relevant content to the discussion.

Reply 3: We have added it in the discussion. See page 8, line 262-267 and page 10, line 335-336.

4) It is suggested to increase the function research of differential genes.

Reply 4: We have discussed it as a limitation in discussion section. See page 10, line 319-324.

5) The bioinformatics analysis in this study is too simple. It is recommended to conduct IPA analysis on the data, which may be more meaningful.

Reply 5: We have discussed it as a limitation in discussion section. See page 10, line 319-324.

6) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as "Analysis of susceptibility genes and myocardial infarction risk correlation of ischemic cardiomyopathy based on bioinformatics, PMID: 36245596". It is recommended to quote the article.

Reply 6: We have cited the paper and revised the introduction. See page 3-4, line 100-107, and reference 15.

7) It is recommended to add in vivo and in vitro experimental validation of the results of this study.

Reply 7: We have discussed it as a limitation in discussion section. See page 10, line 319-324.

Reviewer B

1) First of all, my major concern for this study is the very small sample sizes of healthy myocardial and ICM myocardial tissues, resulting in unstable findings on the biomarkers. My further question is the specificity of the identified biomarkers since the controls are only healthy persons, not persons with other heart diseases.

Reply 1: We have discussed these as a limitation in the discussion section. Thanks. See page 10, line 319-324.

2) Second, the background did not describe the knowledge gaps and what the potential clinical significance of this research focus is. The methods need to specify the validation process including the validation sample and statistical methods for assessing the classification accuracy. The results need to provide data to indicate the accuracy levels of the identified biomarkers. The conclusion should not have comments on the significance of the findings only, please provide the comments on the clinical implications of findings.

Reply 2: We have revised the abstract according to your suggestion. We thank for your help. See page 2, line 41-69.

3) Third, in the introduction, the authors need to extensively review what has been known on the biomarkers in ICM, analyze the limitations of prior studies and knowledge gaps, and clearly indicate the needs for the current analysis.

Reply 3: We have added reference 15 in the revised version. See page 3-4, line 100-107.

4) Fourth, in the methodology, non-significant differences between the two groups are meaningless, since the sample sizes are very small. The authors need to explain on the feasibility of this study by using such a small sample. The authors need to describe the test of the external validity by using an independent sample. Please describe the calculation of AUC and its threshold values for a good classification model.

Reply 4: We used Table 1 to indicates the basic information of two groups. Moreover, we have added the calculation of AUC and its threshold values for a good classification model in the method section. See page 4, line 129-130.

5) Finally, please consider to review several related papers: 1. Biffi M, Loforte A, Folesani G, Ziacchi M, Attinà D, Niro F, Pasquale F, Pacini D. Hybrid transcatheter left ventricular reconstruction for the treatment of ischemic

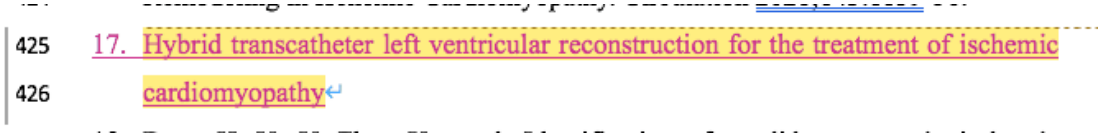
cardiomyopathy. Cardiovasc Diagn Ther 2021;11(1):183-192. doi: 10.21037/cdt-20-265. 2. Zhang N, Yang C, Liu YJ, Zeng P, Gong T, Tao L, Li XA. Analysis of susceptibility genes and myocardial infarction risk correlation of ischemic cardiomyopathy based on bioinformatics. J Thorac Dis 2022;14(9):3445-3453. doi: 10.21037/jtd-22-1060. 3. Ferrell BE, Jimenez DC, Ahmad D, Malkani K, Rosen JL, Gaw G, Plestis KA, Guy TS, Massey HT, Tchantchaleishvili V. Surgical ventricular reconstruction for ischemic cardiomyopathy—a systematic review and meta-analysis of 7,685 patients. Ann Cardiothorac Surg 2022;11(3):226-238. doi: 10.21037/acs-2021-ami-17.

Reply 5: We have reviewed the above papers and added some in the revised version. We thank for your help. See reference 15 and 17.

Reviewer C

1. Reference

This reference is incomplete. Please revise.



Reply: We have revised it. See page 12, line 403.

2. References 15 and 20 are the same. Please delete one of them and update the citations in the paper.

Reply: We have deleted it. Thanks.

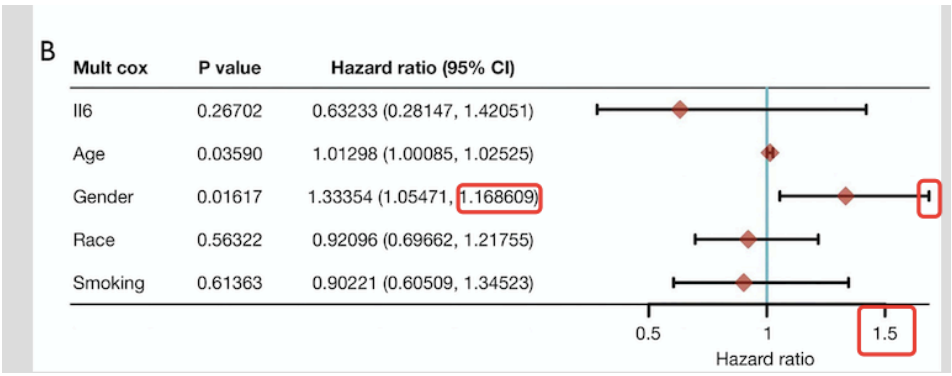
3. The authors mentioned "studies...", while only one reference was cited. Change "Studies" to "A study" or add more citations. Please revise. Please number references consecutively in the order in which they are first mentioned in the text.

Mounting studies have shown that lncRNA can target and bind miRNA to play its role as ceRNA, that is, lncRNA can affect the expression of protein-coding genes by competitively binding miRNA, thus reducing the degradation of protein-coding genes (22).

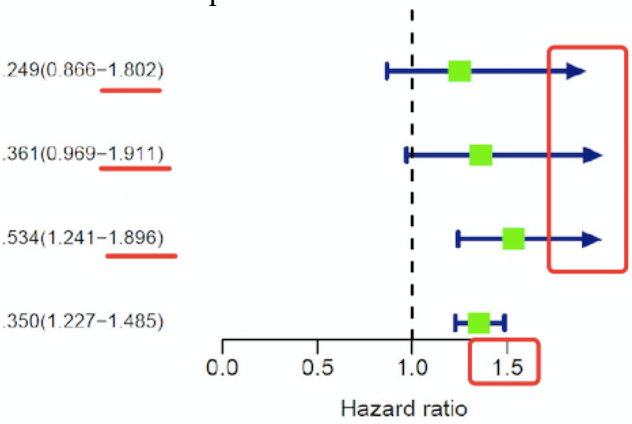
Reply: We have revised it. See page 8, line 265.

4. Figure 6B

To standardize the results, the part that exceeds the horizontal coordinates should be indicated by arrows, or please extend the X-axis.



Here is an example:



Reply: Attached files please find the figure 6.

5. Figure 7

Please unify the word. *IL6 or IL-6?* Please have a thorough check.

253 *Sqstm1*, *Nos2*, *IL6*, *RHOA*, and *Zfp36* genes in the ICM group are lower than those in
254 the blank control group and the difference was statistically significant (P<0.05). *RHOA*
255 and *Stat3* were identified as the key genes controlling the occurrence and development
256 of ICM (*Figure 7*).

Reply: We have unified it. Thanks.