Author’s response to reviews

Title: Multi-level transcriptome sequencing identifies COL1A1 as a candidate marker in human heart failure progression

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Paper ID: BMED-D-19-00719R2

Revised Title: Multi-level transcriptome sequencing identifies COL1A1 as a candidate marker in human heart failure progression.

We again appreciated the critical comment from one reviewer. We have addressed it during the third revision. The changed text is labeled in red in the revised manuscript. We also revised some text (highlighted in red) to make caution of our results/conclusion to the readers. In the third revised manuscript, we also acknowledged the reviewers whose valuable comments helped us improve the quality of this manuscript.

Our point-to-point response to the reviewers’ comments were also described in the “Response to reviewers” file.

Thank you very much!
Response to reviewers

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Revised Title: Multi-level transcriptome sequencing identifies COL1A1 as a candidate marker in human heart failure progression.
We again appreciated the critical comment from one reviewer. We have addressed it during the third revision. The changed text is labeled in red in the revised manuscript. In the third revised manuscript, we also acknowledged the reviewers whose valuable comments helped us improve the quality of this manuscript.

Responds to the reviewer’s comments:
Reviewer #1 Peter Van Der Meer: I still think that 139 patients are too little to draw robust conclusions, also given the fact that there is no validation cohort. This limitation should be clearly mentioned.
Response: We again thank this reviewer for the high standard of scholarship. In revision, we followed your advice and revised the manuscript to clearly state this limitation, we added this limitation in the Discussion section according to your suggestion (page 21, lines 24-26 and page 22, lines 1-8): “Readers should take caution of the results in our study because the sample size is still relatively small. We used 30 patients (21 HF and 9 healthy donors, all heart tissue samples) for discovery by a multi-omics approach. Our top gene (COL1A1) identified in the 30 discovery cohort samples was further validated by immunohistochemistry staining in the same cohort and qRT-PCR using another independent cohort (20 HF and 9 healthy donors), and an additional 139 cohort patients for evaluation of plasma COL1A1 content. This size of heart failure cohort for potential biomarker discovery is smaller than some of the previous studies of HF [54, 55]. It is due to the fact that all the HF patients, including the 139 HF cohort, were all received heart transplantation, which is different from the previous studies [55]. Considering this limitation, our findings need further validation by recruiting more HF patients with related clinical data and additional functional work to illustrate specific roles of plasma COL1A1 level on HF progression in the future.”

We also revised some text (highlighted in red) to make caution of our results/conclusion to the readers. For example, in the Abstract (page 2, lines 23-25), we revised “Our results suggested that COL1A1 might be a plasma biomarker of HF and associated with HF progression, especially to predict the 1-year survival from HF onset to transplantation.” On page 4, lines 7-9, we revised “Interestingly, the COL1A1 content in plasma was found to contribute to the progression of HF, suggesting that it might be a potential plasma biomarker to predict the heart transplantation (HTx) within 1-year from HF onset.” On page 17, line 7, we stated “COL1A1 as a potential fibrotic marker for HF progression.” On page 18, line 1, we stated “Experimental validation of COL1A1 as a potential biomarker in HF progression.” On page 19, lines 13-15, we revised “Taken together, our data indicated that the plasma COL1A1 content (greater than 256.5 ng/ml) might be used as a potential biomarker of HF progression, especially 1 year after onset of HF.” Page 21, lines 14-16, we revised “Our results indicated that the plasma COL1A1 content could be a potential biomarker to distinguish the malignant process of HF within 1-year after HF.
diagnosis with higher diagnostic efficiency than longer survival condition (Additional file 8: Table S8).”
Thank you for your advice again!

Reviewer #2
No more comments to respond.

Reviewer #3
No more comments to respond.