

Peer Review File

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Reviewer A

This is an original article to explore the risk factors related to MV dysfunction, MV failure, and MV reoperation following repair of the primary mitral valve diseases in children (n=98).

The independent risk factors were, for MV dysfunction (34/98), the mixed MV pathology; for MV failure (20/98), none; for reoperation (9/98), the preoperative LVESVI and \geq moderate MR at 24 hours after the first surgery. The primary pathology, whether MR or MS, was not a determinant of those outcomes.

The major strength of this paper is the details of gathering the retrospective clinical data with lots of effort. The major weakness is the statistical analysis and presentation to pull out the valuable meaning.

The overall impression needs a professional statistician's help to convince the findings.

Comment 1: The variables that did not meet the normal distribution would be presented as median (IQR)—but it seems inconsistent in this paper. For example, the Abstract's line 15 (follow-up duration), Table 1 (LVESVI '52.17±48.54' etc.), Table 4 (Postoperative hospital day, etc.). Subsequently, the non-parametric analysis seems not applied: comparison analysis in two groups with Chi-square or Fisher's exact test (categorical variables) and an independent T-test or Mann–Whitney U test (continuous variables).

Reply 1: Thank you for your suggestion. We have changed the mentioned format into median (IQR). We have also rewritten the use of statistical methods and added the non-parametric analysis. The modified contents are marked in red. (See Abstract—Line 17; See Table 1; See new Table 5; See Section 'Methods'--Statistical analysis, Page 8, Line 10-13).

Changes in the text: We have changed the mentioned format into median (IQR). We have also rewritten the use of statistical methods and added the non-parametric analysis.

Comment 2: One of the critical findings of this paper was "preoperative LVESVI and \geq moderate MR at postoperative 24 hours were independent risk factors for MV reoperation". But \geq moderate MR at 24 hours is the consequence of the initial MV repair, not as one of the risk factors. Moreover, in the MR group (n=76), rather than the " \geq moderate MR at postop 24 hours," the "severe MR at postop 24 hours" seems a better predictor for MV reoperation. Because among the moderate MR (n=16) at 24 hours, 44% of them (7/16) became mild MR, whereas the severe MR (n=6) at 24 hours, 83% of them (5/6) showed persistent severe MR, subsequently underwent a second surgical procedure. Then, why do the authors not use "severe MR at postop 24 hours, rather than (moderate + severe MR) at post 24 hours"? It seems both results from the primary repair, not the risk factors.

Reply 2: Thank you for expressing your opinion. However, we still consider that ' \geq moderate MR at postoperative 24 hours' should be listed as a risk factor. At the end of the mitral valve

repair procedure, we usually perform a transesophageal echocardiography to make sure that the degree of child's mitral regurgitation is controlled below moderate. If the child's MR degree is detected moderate at postoperative 24 hours, we consider that the degree of MR in this child is progressing and is likely to continue to progress to severe during future follow-up. So, \geq moderate MR at 24 hours is not the result from the primary repair. It should be considered as a risk factor. In addition, exactly as you pointed out, 44% (7/16) of patients with moderate MR (n=16) at 24 hours became mild. However, there is still 31.25% (5/16) of patients with moderate MR became severe, which was not a small percentage. Therefore, we think \geq moderate MR (moderate + severe MR) at postoperative 24 hours should be listed as a risk factor.

Changes in the text: No changes in the text

Comment 3: Please consider adding death as the composite outcome variable. And it would be better to use MV dysfunction only (instead of a separate analysis for both MV dysfunction and MV failure).

Reply 3: Thank you for your suggestion. We have added death as the composite outcome variable (See section 'Study endpoints') and described the details of the dead patients (See section 'Results'—Mortality). We have also analyzed the risk factors for death (See Table 8). The modified contents are marked in red. Besides, we have deleted contents about MV failure in the article as suggested.

Changes in the text: We have added death as the composite outcome variable (See section 'Study endpoints'). We have added contents about death and described the details of the dead patients (See section 'Results'—Mortality). We have also analyzed the risk factors for death (See Table 8). The modified contents are marked in red. Besides, we deleted contents about MV failure.

Comment 4: Please add the characteristics of the mixed pathology group.

Reply 4: Thank you for your suggestion. We have added characteristics of the mixed pathology group in new Table 3. We have also made a description in the article. The contents are marked in red. (See new Table 3; See section 'Results'-- Types of MV and classification of mixed MV pathologies)

Changes in the text: We have made a description about the characteristics of the mixed pathology group in section 'Results'-- Types of MV and classification of mixed MV pathologies. Details are displayed in new Table 3.

Comment 5: The number of cases should be reconfirmed. In this paper, 24% (23/98) or 26%(25/98) revealed \geq moderate MR at 24 hours postoperatively (Inconsistent numbers of the \geq moderate MR at postoperative 24 hours: 23 patients in Figure 7; 25 patients in Table 4).

Reply 5: Thank you for pointing out the problem. We have reconfirmed the number of cases. 23 patients revealed \geq moderate MR at 24 hours postoperatively. We have modified the data in new Table 5. The modified contents are marked in red. (See new Table 5)

Changes in the text: We have modified the data in new Table 5 and reconfirmed that 23 patients revealed \geq moderate MR at 24 hours postoperatively.

Here are some specific comments.

1. [Abstract]

1-1. Page 2, Line 4-5: this study's purpose (aim) is to identify the risk factors, not better understand the causes.

Reply 1-1: Thank you for your suggestion. We have revised the statement as required. The modified contents are marked in red. (See section 'Abstract'—Background, Page 2, Line 4-5)

Changes in the text: We have deleted 'to better understand the causes' to 'identify the risk factors'.

1-2. Page 2, Line 8: please consider removing the number of the procedures (112 procedures), and make sure to add the ages and sex.

Reply 1-2: Thank you for your suggestion. We have revised the statement as required. The modified contents are marked in red. (See 'Abstract'—Methods, Page 2, Line 8-10)

Changes in the text: We have removed the number of the procedures and added the ages and sex.

1-3. Page 2, Line 10-12: Among the LV parameters, the preoperative LVESVI was one of the critical risk factors. Therefore, it would be better to use the terminology of the left ventricular volume index instead of the end-diastolic volume index only.

Reply 1-3: Thank you for your suggestion. We have added the left ventricular end-systolic volume index (LVESVI) into the sentence. The modified contents are marked in red. (See 'Abstract'—Methods, Page 2, Line 11-12)

Changes in the text: We have added the left ventricular end-systolic volume index (LVESVI).

1-4. Page 2, Line 15: Follow-up duration should be presented as median [IQR]

Reply 1-4: Thank you for your suggestion. We have revised the statement as required. The modified contents are marked in red. (See 'Abstract'—Results, Page 2, Line 17)

Changes in the text: Follow-up duration is presented as median [IQR].

1-5. Page 3, Line 5-6: "Left ventricular function~~encouraging"—There is insufficient evidence to draw this sentence from this paper. Please consider removing this.

Reply 1-5: Thank you for your suggestion. We agree with your point of view and we have deleted this sentence. (See 'Abstract' section --Conclusion)

Changes in the text: We have deleted the sentence "Left ventricular function~~encouraging" from the paper.

2. [Highlight box]

Page 4, Line 9-15: There is insufficient evidence to draw these sentences. The \geq moderate MR at postoperative 24 hours is not a risk but a result of the primary repair.

Reply 2: Thank you for expressing your opinion. We have answered in the question above. If the child's MR degree is detected moderate at postoperative 24 hours, we consider that the degree of MR in this child is progressing and is likely to continue to progress to severe during future follow-up. So, \geq moderate MR at 24 hours is not the result from the primary repair. It should be considered as a risk factor. In addition, after statistical analysis, we still think the

sentences in Highlight box (Page 4, Line 9-15) are well founded. We have made some changes in the contents, which are marked in red. (See 'Highlight box' section—Page 4, Line 11-19).

Changes in the text: We have made some changes in the contents, which are marked in red. (See 'Highlight box' section—Page 4, Line 11-19).

3. [Methods]

3-1. Page 6, Line 23- Page 7, Line 1: Tachycardia increases the mean pressure gradient, especially in postop and pediatric patients. Was the MS gradient based on the mean pressure gradient (severe >10mmHg) without considering the heart rate?

Reply 3-1: Thank you for your question. In our cohort, MS gradient was based on the mean pressure gradient (severe >10mmHg) with considering the heart rate (such as tachycardia). However, heart rate was well-controlled after operation that it does no significant effect on the measurement of MS degree.

Changes in the text: No changes.

3-2. Page 8: please add the 'multivariable analysis' in the statistical analysis section.

Reply 3-2: The 'multivariable analysis' was already in the statistical analysis section. The contents are marked in red. (See 'Statistical analysis' section—Page 8, Line 15-22; Page 9, Line 1-7).

Changes in the text: No changes

4. [Results]

4-1. Figure 1: It would be helpful to add "the numbers of moderate or severe cases"

Reply 4-1: Thank you for your suggestion. We have added the numbers of moderate and severe cases in Figure 1. (See Figure 1)

Changes in the text: Added the numbers of moderate and severe cases in Figure 1.

4-2. Figure 1. Figure 4B: The MR group (n=76) had severe MS and underwent repair. Figure 4 describes mild, moderate, or severe; does this mean "mild MR, moderate MR, or severe MR"? Any patients with significant MS in the MR group? It would be better to describe MR or MS (not omitting them).

Reply 4-2: Thank you for your suggestion. The mild, moderate, or severe in Figure 4A means mild MS, moderate MS and severe MS. The mild, moderate, or severe in Figure 4B,4C,4D means mild MR, moderate MR and severe MR. Since children with combined MR and MS were assigned to either MR or MS group based on the major lesions, there was no significant MS in the MR group before first operation (only one with severe MR combined with moderate MS). The description of MR and MS in different groups are also added as requested. The contents are marked in red (See section 'Results'--Treatment effects of MS or MR, Page 13, Line 22-23; Page 14, Line 1, Line 7-9, Line 22; Page 15, Line 1, Line 13-14)

Changes in the text: Detailed description of MR and MS has been added.

4-3. Please refine the units throughout the paper (mostly no units; LVEF% does not match 0.704±0.065). And consider the leave decent numbers of decimal places (for example, P-values).

Reply 4-3: Thank you for your suggestion. We have already refined the units. LVEF% was changed into LVEF. As you mentioned, we decided to keep three decimal places after the decimal point for P-value (See new Table 1; See all the values in the entire text)

Changes in the text: We have already refined the units and kept three decimal places after the decimal point for P-value.

4-4. Figure 2~ Figure 7: The median follow-up duration was 18 months (in 89 patients, NR group) or 30 months (in 9 patients, R group). Therefore, the follow-up time (months) up to 100-120 months (X-axis) seems too high.

Reply 4-4: Thank you for expressing your opinion. The median follow-up time of the two groups, 100 and 120, is indeed relatively short, but there are still patients with follow-up time of over 100 months. So I believe it is still necessary to choose the length of the X-axis (100-120 months).

Changes in the text: No changes

4-5. Table 1. And Table 4: Please consider adding another column (n=98) to describe the demographical characteristics of the total cohort. Please add some proper units.

Reply 4-5: Thank you for your suggestion. We have added a column (n=98) in Table 1 and Table 4 and made some modifications in the article. We have also added some proper units. The contents are marked in red (See Table 1 and Table 4; See section 'Results'--Patient characteristics, Page 9, Line 19 & 'Results'--Perioperative data, Page 11, Line 9-18)

Changes in the text: Added a column (n=98) and some proper units in Table 1 and Table 4. Made some modifications in the article.

4-6. Table 1. The LVESVI was indicated as an independent predictor of reoperation. But there was no significant difference in LVESVI between group NR and group R.

Reply 4-6: Thank you for pointing out the problem. After we recalculated the statistics, we found LVESVI not an independent risk factor of MV reoperation (Multivariable analysis: HR=1.016, P=0.167). (See the new Table 7)

Changes in the text: LVESVI was not an independent risk factor of MV reoperation.

Reviewer B

This retrospective study aimed to identify the risk factors associated with mitral valve (MV) dysfunction, failure and reoperation after primary MV disease repair. The study analyzed 112 procedures in 98 patients with primary MR and MS diseases. The results showed that LVESVI before surgery and \geq moderate MV regurgitation at first 24 hours after first surgery were independent risk factors for MV reoperation, while mixed MV pathology was an independent risk factor for MV dysfunction.

Comment 1: Highlight box: some language revisions would be beneficial.

Reply 1: Thank you for your suggestion. We have made some language revisions. The contents are marked in red. (See 'Highlight box'—Page 2, Line 4-6, Line 11-15, Line 18-19)

Changes in the text: We have made some language revisions. (See ‘Highlight box’—Page 2, Line 4-6, Line 11-15, Line 18-19)

Comment 2: Introduction: good introduction to the topic and relevant literature. Although referenced estimates are given for re-operation, no rate is given for incidence of MV dysfunction or failure, which would be a helpful addition to this section.

Reply 2: Thank you for your suggestion. We have added the rate of MV dysfunction in the section. The contents are marked in red (See section ‘Introduction’—Page 5, Line 11-12)

Changes in the text: We have added the rate of MV dysfunction.

Comment 3: Methods: description of methods adequate to replicate study. The section on the Cox regression analysis should be a separate paragraph on its own.

Reply 3: Thank you for your suggestion. We have placed Cox regression analysis in a separate paragraph, and the contents are marked in red. (See section ‘Methods’--Statistical analysis, Page 8, Line 15-22; Page 9, Line 1-7)

Changes in the text: We have placed Cox regression analysis in a separate paragraph, and the contents are marked in red.

Comment 4: Results:

-Include definition of NR acronym (NR: No Reoperation). Same for R.

-Maintain consistency in which group is reported first (NR or R).

Reply 4: Thank you for your suggestion. We have included the definition of NR and R, and the contents are marked in red. (See Section ‘Results’-- Patient characteristics, Page 9, Line 20,21)

Changes in the text: We have included the definition of NR(had no MV reoperations) and R(had MV reoperations).

Comment 5: MR and MS types should be defined in methods section, not results (page 9, line 21). Results for types of MR and MS should stay in results.

Reply 5: Thank you for your suggestion. We have added a new paragraph called ‘MR and MS types’ in methods section to define the MR and MS types. The results for types of MR and MS were still kept in results. The modified contents are marked in red. (See Section ‘Methods’-- MR and MS types; See section ‘Results’—Types of MV and classification of mixed MV pathologies)

Changes in the text: We have added a new paragraph called ‘MR and MS types’ in methods section, and the results for types of MR and MS were still kept in the section ‘Results’-- Types of MV and classification of mixed MV pathologies.

Comment 6: Whenever there is a mention of significant or non-significant, please cite the p-value (e.g. preoperative data section).

Reply 6: Thank you for your suggestion. We have added the p-value in the article when there is a mention of significant or non-significant. The modified contents are marked in red. (See p-value—Page 11, Line 12,14,16,18; Page 13, Line 15;)

Changes in the text: Added the p-value in the article when there is a mention of significant or

non-significant.

Comment 7: Please refrain from discussing results in the results section (page 14, lines 3-6)

Reply 7: Thank you for your suggestion. We have deleted the discussing part in the results section. (See section 'Results'--Treatment effects of MS and MR)

Changes in the text: We have deleted the discussing part in the results section.

Comment 8: Discussion:

-Discuss the mortality cases in the study cohort.

Reply 8: Thank you for your suggestion. We have discussed the mortality cases in the cohort. The modified contents are marked in red. (See section 'Discussion'—Page 20, Line 11-22; Page 21, Line 1-15)

Changes in the text: We have added the discussion of mortality cases.

Comment 9: Discuss the significance of LVESVI as a prognostic indicator, as this was identified as significant factor in the Cox regression analysis.

Reply 9: Thank you for your suggestion. After we recalculated the statistics, we found LVESVI not an independent risk factor of MV reoperation (Multivariable analysis: HR=1.016, P=0.167). (See the new Table 7)

Changes in the text: As we found LVESVI not a prognostic indicator, there is no need for discussion.

Comment 10: Discussion on mixed MV pathology is provided.

Reply 10: We have already provided discussion on mixed MV pathology.

Changes in the text: No changes in the text