Peer Review File

Article Information: https://dx.doi.org/10.21037/cdt-22-140

Review Comments:

Reviewer A:

Chichareon et al retrospectively evaluated 598 consecutive patients with severe rheumatic mitral stenosis who underwent percutaneous balloon mitral valvuloplasty (PBMV) using Inoue balloon technique from 2003 to 2020 at a single tertiary center in Thailand. 49 (8.2%) patients had moderate MR and 549 had less-than-moderate MR. They report that PBMV success and mid-term outcomes (composite of all cause death, mitral valve surgery or re-PBMV) were not different in patients with moderate mitral regurgitation (MR) and less than moderate MR. The intriguing findings were that the MR severity in patients with moderate MR group was either unchanged or even improved after PBMV. Median Wilkins score was 8 in both the groups with similar maximum balloon size of PBMV.

The results may be important and add to the current body of literature. However, there are certain limitations some of which have been mentioned by authors including single center retrospective review and small sample size of patients with moderate MR.

Another major limitation of the study is the echocardiographic assessment of MR severity by the authors. The authors used semi-quantitative assessment of the MR using color doppler instead of using quantitative and objective parameters that are currently used in clinical practice. Also none of the semi-quantitative parameters that were used are mentioned in the paper. Please consider mentioning them.

We thank the reviewers and editors for having evaluated our manuscript. In **bold** we have the text of our rebuttal; in *italic* and *blue* the inserted text in the revised manuscript.

The ACC/AHA guidelines for valvular heart disease recommended the use of Sellar's criteria based on left ventriculography or Doppler echocardiography to assess MR severity before PBMV(1). We assessed the severity of MR based on the color flow jet area of MR and the distance of MR jet in left atrium(2, 3). According to the American Society of Echocardiography (ASE) Guidelines, this method is considered as qualitative rather than quantitative(3), therefore, we have modified the text in the method section (page 4, line 125-127).

"Severity of mitral and tricuspid regurgitation were assessed *with qualitative Doppler based on the color flow jet area and the distance of regurgitant jet in the atrium(2, 3).* The severity was graded as follows; none or trivial (0), mild (1+), moderate (2+), moderate to severe (3+) or severe (4+)(4).

A paragraph acknowledging the limitation on echocardiographic assessment of MR severity has been added to the manuscript.

"The qualitative Doppler method was used in our study to assess MR severity. Although it was acknowledged as the method to assess MR severity before rheumatic MS intervention by the 2020

ACC/AHA guidelines on valvular heart disease(1), other quantitative methods which are currently used in practice such as vena contracta width or proximal isovelocity surface area are more accurate and objective.(3)"

The procedural success was numerically lower 69.4% vs 79.2% between moderate MR vs less-than-moderate MR group respectively, which was statistically non-significant with adjusted OR 0.65, 95% CI 0.32-1.29, p=0.22. This could be related to small a sample size. Also, what was the non-adjusted OR?
The non-adjusted odd ratio of moderate MR vs. less-than-moderate MR for procedural success was 0.59 (0.31-1.13), p = 0.11.
We have added the non-adjusted odd ratio in the results (page 7, line 215-216).

"Moderate MR before PBMV was not associated with lower chance of PBMV success (Moderate MR vs. less than moderate MR before PBMV; *non-adjusted OR 0.59 (0.31-1.13), p = 0.11,* adjusted OR 0.65, 95% CI 0.32-1.29, p = 0.22)."

Minor points:
1. There are a lot of grammatical errors in the paper.
The revised manuscript has been checked by an English native speaker. Grammatical errors have been corrected.

2. The authors should mention in the abstract that there were 49 patients with moderate MR in the cohort.
The number of patients with moderate MR in our study has been added in the abstract.
"Forty-nine patients (8.2%) had moderate MR before PBMV."

3. How many patients had mitral valve assessed with planimetry vs pressure half time?
MVA before PBMV was assessed with planimetry in 591 patients. Information of pressure half-time MVA were used in 6 patients. There was 1 patient whom neither planimetry or pressure half-time MVA were not available.
We have provided table below in the supplement.

Method of MVA assessment *before* PBMV	Number of patients
Planimetry	591
No planimetry, pressure half-time method used	6
Neither planimetry nor pressure halftime available (missing information on MVA before PBMV)	1

Of the 598 patients in the study, post PBMV MVA was assessed with planimetry in 581 patients. No information on MVA after PBMV was available in 17 patients. The reasons for missing MVA after PBMV were mainly patients undergoing emergency surgery due to peri-procedural complications
We have provided table below in the supplement.

MVA after PBMV

Method of MVA assessment *after* PBMV	Number of patients

Planimetry	581
No information of MVA after PBMV	17
Emergency surgery	15
MVR	13
MVR + surgery for tamponade	1
Surgery for tamponade	1
Stroke immediately after PBMV	1
Moderate to severe MR, no surgery	1

4. Is there a long-term echocardiographic follow up? if not please mention in the study limitations.

We have acknowledged this limitation in manuscript (page 12, line 387-388).

"Long-term echocardiographic data and symptoms burden at follow-up were not systematically recorded in our database."

5. What were pre and post procedural mitral valve areas in each group?

Table below shows pre- and post-PBMV mitral valve area in each group.

This information has been added to table 1 in the manuscript.

Characteristics	Overall	Pre-PBMV mitral regurgitation severity		
		Less than moderate (n = 549)	Moderate (n = 49)	p value
Mitral valve area before PBMV (cm2), mean (SD)	0.92 (0.24)	0.91 (0.24)	1.01 (0.22)	0.01
Mitral valve area after PBMV (cm2), mean (SD)	1.57 (0.27)	1.57 (0.27)	1.59 (0.23)	0.57

The following text has been added to the results section of the manuscript.

Line 190-191, page 6

"Pre-PBMV MVA was assessed with planimetry in 591 patients (98.8%) (supplementary table 1)."

Line 202-203, page 6

"The mean MVA before PBMV was 0.91 cm2 and 1.01 cm2 in the less-than-moderate MR and the moderate MR group respectively (p = 0.01)"

Reviewer B:

This is a well-written article, on an interesting topic. The authors seek to assess safety and efficacy of percutaneous balloon mitral valvuloplasty in patients with severe rheumatic MS but with concurrent moderate mitral regurgitation.

We thank the reviewers and editors for having evaluated our manuscript. In **bold** we have the text of our rebuttal; in *italic* and *blue* the inserted text in the revised manuscript.

Questions to be addressed:

1. In this study, a small proportion of patients included (<9%) had moderate mitral regurgitation. In patients who were then classified as "less than moderate", what proportion were classified as trivial, mild, borderline moderate?

The detail of MR severity before PBMV is provided in the table below.

Severity of pre-PBMV MR	Number of patients
None or trivial (0)	334
Mild (1+)	215
Moderate (2+)	49
Moderate to severe (3+)	0
Severe (4+)	0

We have added the number of patients with no or trivial MR or mild MR in the results section (page 6, line 195-196).

Of the 549 patients with less than moderate MR, 334 patients had no or trivial MR, whereas 215 patients had mild MR.

- It may be hard to draw definitive conclusions regarding outcomes in such a small proportion of patients, although results from this study would be encouraging.

We fully agree with the reviewer that the results of our study are encouraging. A recent systematic review showed that minority of the cases who underwent PBMV had more than mild MR(5). The number of rheumatic MS patients with moderate MR in our study are relatively small, however, the number is larger than in previous studies(6-9). As the first reviewer has mentioned, our results would be important and will add up to the body of current literature.

2. In borderline cases, was transoesophageal echocardiography used to definitively evaluate severity of mitral stenosis and mitral regurgitation pre-PBMV?

Transesophageal echocardiography was used to assess left atrial thrombus before PBMV in all cases. In addition, MR was re-assessed with TEE if its severity was borderline by transthoracic echocardiography.

We have added this information in the method section (page 4, line 135).

"Transesophageal echocardiography was used to assess left atrial thrombus before PBMV *and to definitively evaluate severity of MR in borderline cases*."

3. Is there an estimated complicated rate for "new or acute deterioration of MR is a common complication of PMV" on page 4, 3rd paragraph, line 2, as well as "in the majority of patients with worsened MR after PMBV" in page 10, 1st paragraph, line 2.

We have added the incidence of new or acute deterioration of MR and reference in the manuscript.

The following sentence has been added to the introduction.

"Approximately one-fifths of patients underwent PBMV developed new MR after the procedure(10)."

The following sentence has been added to the discussion.

The incidence of MR occurred immediately after PBMV was 19.9% in a recent meta-analysis.

4. What were the objective echocardiographic measurements that was used to grade mitral regurgitation severity in this study?

The ACC/AHA guidelines for valvular heart disease recommended Doppler echocardiography to assess MR severity before PBMV(1). We assessed the severity of MR with qualitative Doppler method based on the color flow jet area of MR and the distance of MR jet in left atrium.
According to the American Society of Echocardiography (ASE) Guidelines, this method is considered as qualitative rather than quantitative, therefore, we have modified the text in the method section (page 4, line 125-127).

"Severity of mitral and tricuspid regurgitation were assessed *with qualitative Doppler based on the color flow jet area and the distance of regurgitant jet in the atrium(2, 3).* The severity was graded as follows; none or trivial (0), mild (1+), moderate (2+), moderate to severe (3+) or severe (4+)(4)."

A paragraph acknowledging the limitation on echocardiographic assessment of MR severity has been added to the manuscript.

"The qualitative Doppler method was used in our study to assess MR severity. Although it was suggested as the method to assess MR severity before rheumatic MS intervention by the 2020 ACC/AHA guidelines on valvular heart disease, other quantitative methods which are currently used in practice such as, vena contracta width or proximal isovelocity surface area, are more accurate and objective."

5. Was information regarding burden of symptoms (NYHA classes, exercise tolerance etc) assessed in this study?

The NYHA class at baseline before PBMV was assessed in 585 patients (97.8%).

Characteristics	Overall	Pre-PBMV mitral regurgitation severity		
		Less than moderate (n = 549)	Moderate (n = 49)	p value
Functional class before PBMV				0.72

I	2.4 (14)	2.2 (12)	4.1 (2)
II	52.3 (306)	52.4 (281)	51.0 (25)
III	42.9 (251)	43.1 (231)	40.8 (20)
IV	2.4 (14)	2.2 (12)	4.1 (2)

This information has been added to the table 1.
The information regarding burden of symptoms were, unfortunately, not available at the follow-up.

We have acknowledged this issue in the limitation section (page 12, line 387-388).
"Long-term echocardiographic data and symptoms burden at follow-up were not systematically recorded in our database."

6. In the group of patients with pre-PBMV with moderate MR, who subsequently had worsened MR, how severe was the post-PBMV MR and what were the symptoms from this?

In the group of moderate MR before, 7 patients subsequently had worsened MR (14.29%). All 7 patients had moderate to severe MR after PBMV. None of these patients had severe MR. Neither in-hospital stroke or emergency surgery occurred in these 7 patients.
This information has been added to the results section (page 7, line 207-211).

In the group with moderate MR before PBMV, 7 patients (14.29%) developed moderate to severe MR after PBMV. Neither severe MR required emergency surgery nor in-hospital stroke occurred in these 7 patients. The proportion of patients with worsening MR after PBMV in the less-than-moderate MR group was 41.8%.

Minor corrections:
1. Grammatical issues:
- page 4, 2nd paragraph, 4th line - "being less invasive"
- page 5, 1st paragraph, 7th line - "ethics committee"
- consistency of presentation e.g. page 7, results section, 1st paragraph - "eighty four percent" should be in numerical format
- page 10, last paragraph, 1st line - "is considered a contraindication"

These issues have been corrected accordingly

"The Ethic*s* committee of the faculty of medicine, Prince of Songkla University approved study protocol with the waiver of informed consent."
"The majorities were female (84%) with *an overall mean age and body mass index of 41.7 years and 23.1 kg/m2 respectively*"
"Although MR more than mild is considered as *a* contraindication for PBMV by the ESC guidelines,…"

2. Please include numbers and percentages in the results section.

Numbers and percentages were included in the results section.