

## Peer Review File

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### Reviewer A

**General comments:** This manuscript presents the retrospective study performed by Lee and colleagues in which the outcomes of 25 patients who underwent TV surgery with a lateral thoracotomy and beating-heart technique were analyzed. The authors show good results in the majority of patients. However, I have some points I think need to be addressed:

**Reply:** We appreciate your in-depth review and valuable suggestions.

**Comment 1:** How many surgeons were involved in these surgeries?

**Reply 1:** Two surgeons performed the operations. We have added this comment to the Methods section (page 6, line 93).

**Changes in the text 1:**

*“Finally, the remaining 25 patients operated by 2 surgeons were enrolled for evaluation (Figure S1).”*

**Comment 2:** How did the physicians make the decision to operate someone with or without cardiocirculatory arrest?

**Reply 2:** A patient who needs isolated tricuspid valve surgery is considered a candidate for the beating heart surgery at our institution. The intracardiac shunt is the contraindication for beating heart surgery; thus, preoperative comprehensive echocardiographic evaluation is paramount. We have added the descriptions in the Methods section (page 6, line 98).

**Changes in the text 2:**

*“Indications and feasibility assessment*

*Patients needing isolated TV surgery were the primary candidates for the right mini-thoracotomy beating heart surgery. All candidates underwent computed tomography angiography to assess the feasibility of cannulation for cardiopulmonary bypass. Intracardiac shunt and previous right thoracotomy were regarded as contraindications for this approach.”*

**Comment 3:** What was the criteria for lateral thoracotomy as opposed to sternotomy?

**Reply 3:** Since the beginning of the study period, right mini-thoracotomy has been our

institution's primary approach for isolated tricuspid valve surgery. However, the criteria for this approach are 1) the low likelihood of the right pleural adhesion (especially the absence of right thoracotomy history) and 2) the feasibility of cannulation for the cardiopulmonary bypass. We have updated the Methods section adding the criteria (page 6, line 98).

**Changes in the text 3:**

*"Indications and feasibility assessment*

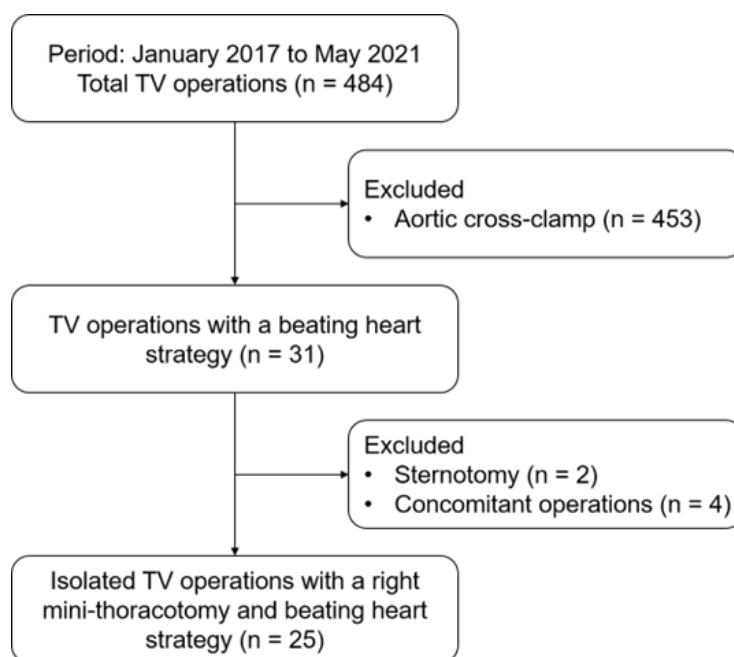
*Patients needing isolated TV surgery were the primary candidates for the right mini-thoracotomy beating heart surgery. All candidates underwent computed tomography angiography to assess the feasibility of cannulation for cardiopulmonary bypass. Intracardiac shunt and previous right thoracotomy were regarded as contraindications for this approach."*

**Comment 4:** A figure should be added where the patient selection/exclusion is included.

**Reply 4:** We agree and have added a study flow diagram for patient selection (page 6, line 93, Figure S1).

**Changes in the text 4:**

*"Finally, the remaining 25 patients operated by 2 surgeons were enrolled for evaluation (Figure S1)."*



**Figure S1** Study flow diagram. TV, tricuspid valve.

**Comment 5:** The authors claim that factors for bad outcomes after TV surgeries is bleeding from a sternotomy is there any specific evidence to support this claim?

**Reply 5:** Thank you for pointing this out. The bleeding issue is always a concern in TR patients, especially with liver dysfunction/cirrhosis-related coagulopathy, which is not uncommon. Theoretically, massive postoperative mediastinal bleeding requiring reoperations and transfusion would predispose to mortality. This presumption and observation were well described in a systematic review by Jacob *et al.* analyzing 19 retrospective studies describing the features of hepatic cirrhosis patients (n = 638) undergoing cardiac surgery. The study described excessive mediastinal bleeding as a severe and frequent postoperative complication. The leading mortality mechanism was multiple reoperations due to postoperative bleeding and infection.

Recent various investigations constantly demonstrated decreased mediastinal bleeding after cardiac surgery with the thoracotomy approach compared with the median sternotomy (Hanedan *et al.*, Kim *et al.*). In this context, the 2019 EACTS/EACTA/EBCP guidelines on cardiopulmonary bypass in adult cardiac surgery recommend minimally invasive heart valve surgery to reduce blood loss and the need for transfusion (class IIb, level of evidence B).

#### *References*

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- Kim DC, Chee HK, Song MG, et al. Comparative analysis of thoracotomy and sternotomy approaches in cardiac reoperation. *Korean J Thorac Cardiovasc Surg* 2012;45:225-9.
- Wahba A, Milojevic M, Boer C, De Somer FMJJ, Gudbjartsson T, van den Goor J, Jones TJ, Lomivorotov V, Merkle F, Ranucci M, Kunst G, Puis L; EACTS/EACTA/EBCP Committee Reviewers. 2019 EACTS/EACTA/EBCP guidelines on cardiopulmonary bypass in adult cardiac surgery. *Eur J Cardiothorac Surg*. 2020 Feb 1;57(2):210-251.

We have added the references in the Discussion section (page 100, line 195).

**Changes in the text 5:**

*“Possible conventional TV surgery-related factors responsible for poor postoperative outcomes are myocardial ischemia associated with cardioplegic arrest and mediastinal/sternal bleeding (13-16).”*

**Comment 6:** Line 199 in the discussion: A surgeon can modify the procedure immediately when the rhythm issue occurs, and this can minimize the postoperative permanent pacemaker insertion. It is supported by the fact that, in the present study, we had only 1 (4.0%) case of permanent pacemaker insertion in a TV replacement patient with a previous history of multiple valvular and coronary surgeries” It would be interesting to compare this to other studies.

**Reply 6:** Thank you for the suggestion. We have added the pacemaker implantation rates of the references in the Discussion section (page 11, line 221; page 12, line 225).

The decreased pacemaker insertion rate with beating heart surgery would be a great subject to investigate; however, such an analysis is beyond the scope of our current paper. We plan to explore it as a separate study with an optimal design to compare after cumulating a sufficient number of patients.

**Changes in the text 6:**

*“The early mortality and pacemaker implantation rates were 7.9% and 1.6%, respectively, with a 5-year survival rate of 81.3%.”*

*“Postoperative pacemaker insertion was needed in 5 patients (10.4%).”*

**Comment 7:** Props to the authors on the great videos.

**Reply 7:** We appreciate your kind comment.

**Changes in the text 7:** None.

**Comment 8:** The results presented here seem to be promising, even though they were made on only 25 patients. Have the authors considered performing a comparison with patients who underwent a TV surgery at their center with sternotomy and the cohort presented in this manuscript?

**Reply 8:** We agree with the need for a comparative study, and it is described in the Discussion section (page 13, line 258). As you pointed out, the small number of patients due to the rarity of isolated TV surgery is a hurdle to the comparative analysis. However, along with the permanent pacemaker topic you suggested (Comment 6), we hope to perform the investigation comparing the thoracotomy and sternotomy with an adequate number of cases shortly. Thank you again for offering such great ideas.

**Changes in the text 8:** None.

## Reviewer B

**General comments:** In this manuscript the authors describe the feasibility of doing TV-repair/ replacement using mini-thoracotomy on beating heart. This is a study from a single institution, with highly limited number of patients (n=25), but the outcome is good and the technique well illustrated through the added videos. There are some issues that need to be discussed:

**Reply:** We appreciate your insightful comments and recommendations.

**Comment 1:** Out of 484 patients, only 25 fulfilled the criteria. Here you have a sincere selection bias that needs to be discussed. How do you select patients suitable for mini-thoracotomy on beating heart. Which preoperative investigations do you need- CT to demonstrate open jugular veins? Calcification of the arteries- how do you select here?

**Reply 1:** Thank you for pointing this out. As you know, in most cases, tricuspid valve surgery is performed concomitantly with other procedures, such as left-side valve surgery, and isolated tricuspid valve surgery is quite rare. Our experiences are not different from this general situation. Thus, we believe the number of isolated tricuspid valve surgeries with mini-thoracotomy is reasonable during the study period from January 2017 to May 2021.

However, the right mini-thoracotomy beating heart strategy has been our institution's primary approach for isolated tricuspid surgery since the beginning of the study period. The criteria for this approach are 1) the low likelihood of the right pleural adhesion (especially the absence of right thoracotomy history) and 2) the feasibility of cannulation for the cardiopulmonary bypass. The cannulation feasibility was routinely assessed with CT angiography, and cannulation configuration was determined; all the patients underwent femoral and jugular cannulations with no need for an alternative cannulation strategy in this study. Meanwhile, the surgeon's discretion might affect the operative strategy selection.

We have added relevant comments in the Methods (page 6, line 98) and Discussion section (page 13, line 254).

### **Changes in the text 1:**

*“Indications and feasibility assessment*

*Patients needing isolated TV surgery were the primary candidates for the right mini-thoracotomy beating heart surgery. All candidates underwent computed tomography angiography to assess the feasibility of cannulation for cardiopulmonary bypass (CPB). Intracardiac shunt and previous right thoracotomy were regarded as contraindications*

*for this approach.”*

*“Even though isolated TV surgery was the primary indication for the right mini-thoracotomy beating heart surgery, as surgeons decide the operative strategy, individual experience, anatomical factors, and surgical risk may have influenced the patient selection.”*

**Comment 2:** When you state that 25 patients were eligible to study- are there other patients which were converted from mini-thoractomy to full sternotomy- then these patients should be included. That means that all patients with an intention to treat through mini-thoractomy and beating heart should be included.

**Reply 2:** You have raised an important point here. However, there was no sternotomy conversion from mini-thoracotomy in this study. Therefore, all the patients intended to treat with the right mini-thoracotomy and beating heart strategy were included in the analysis. We have added a relevant comment in the Result section (page 9. Line 159).

**Changes in the text 2:**

*“There was no sternotomy conversion.”*

**Comment 3:** You state a low number of kidney failure- according to which guidelines do you refer? Any patient on dialysis?

**Reply 3:** Thank you for the clarification. Acute kidney injury meant the situation requiring dialysis. We have revised the term in the Abstract (page 4, line 57) and Table 3.

**Changes in the text 3:**

*“Acute kidney injury requiring dialysis occurred in 3 patients (12.0%), and a permanent pacemaker was required in 1 patient (4.0%).”*

**Comment 4:** I also lack a table on the indication for TV surgery: degeneration of native valve, endocarditis, bioprosthesis degeneration, pacemaker induced retraction of leaflets etc.

**Reply 4:** Thank you for pointing this out. We have added the TV pathologies in the Result section (page 9, line 156).

**Changes in the text 4:**

*“TV pathologies were functional (n = 8), rheumatic (n = 6), degenerative (n = 5), prosthetic valve failure (n = 4), pacemaker-related (n = 2), and traumatic (n = 1).”*

**Comment 5:** Table 1- change so all parameters are in the same style.

**Reply 5:** We apologize for the technical error. We have modified Table 1.

**Changes in the text 5:** Style change only.

**Comment 6:** Misspelling: In the abstract, the sentence “The median length of intensive care unit stay and hospital stay was 1.0 days” should be 1.0 day. Also change in Results section.

**Reply 6:** Thank you for the comment. We have rephrased the sentences in the Abstract (page 4, line 59) and Results section (page 9, line 168), incorporating another reviewer’s opinion.

**Changes in the text 6:**

*“The median lengths of stay in the intensive care unit and hospital were 1.0 day (Q1–Q3, 1.0–2.0) and 9.0 days (Q1–Q3, 6.0–18.0), respectively.”* **Reviewer C**

**General comments:** Authors of the manuscript “Midterm outcomes of isolated tricuspid valve surgery with a mini-thoracotomy and beating heart strategy” present 25 patients who had undergone surgery due to isolated tricuspid valve dysfunction. The paper is interesting, operative techniques have been well written and presented and mid-term outcomes seem to be encouraging.

**Reply:** We appreciate your careful review and comments.

**Comment 1:** However, the paper lacks a description of the underlying disease in patients with isolated tricuspid valve dysfunction. What was the cause of the valve damage? Have there been cases of isolated TV endocarditis? Have there been cases of lead-related tricuspid valve dysfunction?

**Reply 1:** Thank you for pointing this out. The causes were functional, rheumatic, degenerative, prosthetic valve failure, pacemaker-related, and traumatic. However, there was no isolated TV endocarditis in this cohort. We have added the TV pathologies in the Result section (page 9, line 156).

**Changes in the text 1:**

*“TV pathologies were functional (n = 8), rheumatic (n = 6), degenerative (n = 5), prosthetic valve failure (n = 4), pacemaker-related (n = 2), and traumatic (n = 1).”*

**Reviewer D**

**General comments:** A general comment to the authors to start: I commend you on your surgical approach and the superior results you have achieved here.

**Reply:** We appreciate your detailed review and thoughtful suggestions, which improved the article's quality.

**Comment 1:** I have been unable to view the video files to date and will need to see those once these revisions are carried out.

**Reply 1:** We are sorry that you could not view the video. The files, however, are probably fine because other reviewers had no problem playing the videos. It may be the codec problem, so we recommend checking compatibility. Still, we will upload video files again during the revision process, and we hope you can check them out.

**Changes in the text 1:** None.

**Comment 2:** Page 4 Line 59: The median length of intensive care unit stay and hospital stay was 1.0 days (Q1–Q3, 1.0–2.0) and 9.0 days (Q1–Q3, 6.0–18.0), respectively.

Please rephrase to ‘The median length of stay in the intensive care unit and hospital were 1.0 days (Q1–Q3, 1.0–2.0) and 9.0 days (Q1–Q3, 6.0–18.0), respectively.’

**Reply 2:** We have rephrased the sentences in the Abstract (page 4, line 59) and Results section (page 9, line 168), incorporating another reviewer's opinion.

**Changes in the text 2:**

*“The median lengths of stay in the intensive care unit and hospital were 1.0 day (Q1–Q3, 1.0–2.0) and 9.0 days (Q1–Q3, 6.0–18.0), respectively.”*

**Comment 3:** Page 4 Line 61: Estimated freedom from overall mortality, severe tricuspid regurgitation, 62 and significant tricuspid stenosis (i.e., trans-tricuspid pressure gradient  $\geq 5$  mmHg) at 4 years 63 was 89.1%, 94.4%, and 83.3%, respectively.

Can the authors clarify what exactly they mean by ‘estimated’

**Reply 3:** The word ‘estimated’ indicates no specific statistical meaning in this sentence. To avoid confusion, we have removed the term from the Abstract (page 4, line 61).

**Changes in the text 3:**

*“Freedoms from overall mortality, severe tricuspid regurgitation, and significant tricuspid stenosis (i.e., trans-tricuspid pressure gradient  $\geq 5$  mmHg) at 4 years were 89.1%, 94.4%, and 83.3%, respectively.”*

**Comment 4:** In ‘Key Findings’

Mini-thoracotomy beating heart strategy for isolated tricuspid valve (TV) surgery showed favorable early and midterm outcomes.

Please rephrase to ‘Mini-thoracotomy beating heart strategy for isolated tricuspid valve



(TV) surgery demonstrated favorable early and midterm outcomes.’

In ‘Key Findings’

What is known and what is new?

Conventional isolated TV operation is considered high-risk surgery. However, some investigations presented improved outcomes after minimally invasive or beating heart TV surgery.

The present study demonstrated favorable early and midterm outcomes of isolated TV surgery performed with combined minimally invasive (mini-thoracotomy) and beating heart strategies.

I think this message can be phrased more powerfully

One example would be ‘Conventional isolated tricuspid valve interventions carry high morbidity and mortality risks. This study demonstrates superior early and midterm outcomes with a minimally invasive beating heart approach’

In ‘Key Findings’

What is the implication, and what should change now?

Mini-thoracotomy beating heart strategy may be a valuable option for isolated TV operations.

Again, I think this can be better phrased. ‘Our findings demonstrate that this approach offers a superior option in properly selected patients and should be considered’

**Reply 4:** Thank you for your recommendations. We agree and have accordingly updated the Highlight box (page 5, line 72)

**Changes in the text 4:**

*“Highlight box*

*Key findings*

- *Mini-thoracotomy beating heart strategy for isolated tricuspid valve (TV) surgery demonstrated favorable early and midterm outcomes.*

*What is known and what is new?*

- *Conventional isolated tricuspid valve interventions carry high morbidity and mortality risks.*
- *This study demonstrates superior early and midterm outcomes with a minimally invasive beating heart approach.*

*What is the implication, and what should change now?*

- *Our findings demonstrate that this approach offers a superior option in properly selected patients and should be considered.”*

**Comment 5:** Page 6 line 77 ‘However, as stated above, early surgical treatment is rarely executed, resulting in delayed surgery, which is more risky and ineffective’

Please rephrase: However, as stated above, early surgical treatment is rarely carried out resulting in delays and an even further elevated preoperative risk’

It would also be nice to quote the average mortality associated with these operations and an appropriate reference

**Reply 5:** We have revised the sentence and added references in the Introduction section (page 6, line 76).

**Changes in the text 5:**

*“Isolated tricuspid valve (TV) surgery is known to have high mortality and morbidity rates, reaching up to 10% and 31%, respectively, and thus it is not frequently performed (1,2). As with other valvular heart diseases, a timely surgical referral is paramount in TV disease. However, as stated above, early surgical treatment is rarely carried out, resulting in delays and an even further elevated preoperative risk (2,3).”*

**Comment 6:** Page 6 ‘Conventional TV surgery with median sternotomy and arrested heart strategy may predispose major postoperative complications such as bleeding and myocardial ischemia. In this regard, minimally invasive (mini-thoracotomy) beating heart surgery is expected to have several advantages over conventional TV surgery: 1) less bleeding due to no sternotomy with minimal tissue dissection and 2) excellent myocardial protection with no myocardial ischemic time. Our study aims to evaluate the outcomes of the isolated TV operation with a mini-thoracotomy beating heart strategy.

Just a comment here; I think this needs rephrasing; the predominant issue that kills these patients is cardiogenic shock and right heart failure. This should be mentioned with reference to the myocardial protection issue and it should be ranked 1st in priority. Another advantage to your approach is of course avoidance of redo sternotomy and circumferential dissection of the heart which is likely to reduce the risk of bleeding. The order should be changed and the fact that the bleeding is less because so many of these patients are redos emphasised.

**Reply 6:** Thank you for pointing this out. We have revised the paragraphs in the Introduction (page 6, line 81) and Discussion section (page 10, line 195).

**Changes in the text 6:**

*“Conventional TV surgery with median sternotomy and arrested heart strategy may predispose major postoperative complications such as myocardial ischemia and bleeding (4). In this regard, minimally invasive (mini-thoracotomy) beating heart surgery is*

*expected to have several advantages over conventional TV surgery: 1) excellent myocardial protection with no myocardial ischemic time and 2) less bleeding due to no sternotomy with minimal tissue dissection. Our study aims to evaluate the outcomes of the isolated TV operation with a mini-thoracotomy beating heart strategy.”*

*“Possible conventional TV surgery-related factors responsible for poor postoperative outcomes are myocardial ischemia associated with cardioplegic arrest and mediastinal/sternal bleeding (13-16).”*

“

**Comment 7:** Page 10 line 182 ‘As a result, the late surgical referral would worsen the postoperative outcome (11).’

Please change to ‘As a result, delays in referral for surgery worsens postoperative outcomes’

**Reply 7:** We have revised the sentence per your recommendation in the Discussion section (page 10, line 193).

**Changes in the text 7:**

*“As a result, delays in referral for surgery worsen the postoperative outcomes (12).”*

**Comment 8:** Page 10 line 189 ‘Even in severe pericardial adhesion, the adhered pericardium and the RA can be opened en bloc without adhesiolysis with this approach.’ Please change to ‘Even with severe pericardial adhesions, the adhered pericardium and RA can be opened en bloc without adhesiolysis using our approach.’

**Reply 8:** We have accordingly changed the sentence in the Discussion section (page 11, line 208).

**Changes in the text 8:**

*“Even with severe pericardial adhesions, the adhered pericardium and RA can be opened en bloc without adhesiolysis using our approach.”*

**Comment 9:** Page 10 line 189 ‘In addition, the right mini-thoracotomy provides excellent TV exposure (“en face view”) without distorting the heart axis (Video 1).’ Please change to ‘Furthermore, the right mini-thoracotomy provides excellent TV exposure (“en face view”) without distorting the cardiac axis (Video 1).’

**Reply 9:** We have revised the sentence per your suggestion in the Discussion section (page 11, line 202).

**Changes in the text 9:**

*“Furthermore, the right mini-thoracotomy provides excellent TV exposure (“en face view”) without distorting the cardiac axis (Video 1).”*

**Comment 10:** Page 10 line 192 ‘Meanwhile, myocardial ischemia can be minimized by performing beating heart surgery with no aortic cross-clamp.’

Please change to ‘A further benefit is that myocardial ischemia can be minimized by performing the surgery without cross-clamping the aorta.’

**Reply 10:** We have changed the sentence but modified it to rearrange the Discussion paragraphs according to your Comment 6 (page 10, line 197).

**Changes in the text 10:**

*“A benefit of our strategy is that myocardial ischemia can be minimized by performing the surgery without cross-clamping the aorta.”*

**Comment 11:** Just a general comment about the discussion; can the authors please revise the structure of your discussion to directly compare your outcomes; mortality, PPM rate, medium term mortality etc with the studies referenced. I’m very interested to see that the beating heart approach lead you to have such a low PPM rate but I think this should be compared to typical PPM rates. I would like to see your own results put into better context.

**Reply 11:** We appreciate your constructive suggestion. We agree with this and have incorporated your advice throughout the Discussion section (page 11, line 219).

**Changes in the text 11:**

*“Ricci et al. (17) analyzed 64 patients at high risk (EuroSCORE II, 7.3±2.9%) who underwent minimally invasive TV surgery. In the study, 33 patients (51.5%) underwent beating heart surgery. The early mortality and pacemaker implantation rates were 7.9% and 1.6%, respectively, with a 5-year survival rate of 81.3%. Pfannmüller et al. (18) demonstrated 48 patients who underwent isolated TV operations (beating heart surgery, 87.5%) after previous cardiac surgery. The 30-day mortality rate was 0% for elective patients and 4.2% (n=2) for urgent and emergent cases. Postoperative pacemaker insertion was needed in 5 patients (10.4%). The 5-year survival rate was 72.2±10.0% in patients who underwent elective reoperative TV surgery through minimally invasive access. In a multicenter study about isolated TV surgery by Russo et al. (19), there were fewer acute renal failures and strokes in the beating heart strategy compared with the arrested heart strategy. In the beating heart group, 30-day mortality was 5%; the 6-year survival and freedom from cardiac death were 78±5 % and 84±4%, respectively. The 6-year composite cardiac endpoint of cardiac death and reoperation rate was worse in the arrested heart TV surgery group than the beating heart TV surgery group (P = 0.024). Our study included patients who underwent TV operations using both minimally invasive and beating heart strategies. It demonstrated favorable early outcomes (early mortality,*

*4% [n=1]; permanent pacemaker implantation, 4% [n=1]), and mid-term survival was 89.1 % at 4 years (median follow-up, 30.3 months [Q1–Q3, 19.2–43.8]).”*