

Peer Review File

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**Reviewer Comments**

The article “Adverse factors and postoperative neuropathic pain in challenging video-assisted thoracoscopic surgery” by Homma and colleagues looked at reasons for long durations (<5 hours) of conventional multiport VATS (CVATS) procedures and for switching surgical procedure from CVATS to thoracotomy – both events were classified as challenging VATS. The authors further assessed the number of patients reporting neuropathic pain following challenging VATS. Out of 911 initially recruited patients, 35 cases were identified as challenging VATS, with 21 having operation durations of 5 plus hours and 14 cases were switched from VATS to thoracotomy. Complications that were reported as potentially causing challenging VATS were severe adhesions, air leak, change in body position of the patient, large tumors, bronchoplasty/angioplasty, and bleeding. In each of the two groups (i.e. long surgery duration and procedural switch) about 71% of patients reported post-surgical neuropathic pain. The authors concluded that in certain cases it may be better to advise for thoracotomy, rather than performing CVATS with a high risk of becoming challenging VATS, in order to prevent or lower the patients’ risk of complications, including the development of neuropathic pain.

While it is important to carefully consider the indication for different surgical procedures, including those for thoracotomy over VATS, I do see several issues with this article that would have to be addressed in order to increase the interpretability of the results and, consequently, increase the potential impact of it.

Major issues with the submitted article:

1) The study is largely under-analyzed and, as a result, many of the conclusions were not sufficiently supported by the presented data.

For the following conclusions that were discussed within the discussion and abstract, statistical analyses are needed to be added to test whether your conclusion is justified:

a. “VATS  $\geq$  5 hours and conversion from 1 VATS to thoracotomy were complicated by postoperative neuropathic pain.” (abstract, page 3): To come to this conclusion we would need to know how many of the non-challenging VAT patients developed neuropathic pain. Is the number/percentage indeed higher in the population that was investigated here?

**Reply:** We added the data as advised. Please see (Page 9, line 17-19)

**Changes in the text:** The number of patients who experienced postoperative neuropathic pain was significantly higher in the challenging VATS group than the suitable VATS group (71.4% vs. 22.0%;  $P < 0.0001$ ).

b. “Body position changes were dependent on the surgical strategy, and bronchoplasty

or angioplasty and bleeding depend on the surgeon skills.” (discussion, page 9): How can you come to this conclusion when surgeon (or surgeon's training level) wasn't taken into consideration within the analysis?

**Reply:** We added as advised. Please see (Page 11, line 19-24) and (Page 17, line 11-16).

**Changes in the text:** For surgeons who have a lot of experience with VATS bronchoplasty or angioplasty, these procedures are not necessarily challenging. However, for surgeons with little experience, they are more challenging than thoracotomy. Individual surgeon volume, surgeon age, and surgeon technical skills affected surgical outcome (13-15). Therefore, operator-related factors depend on an institution, but patient-related factors are considered common between institutions. And, we added references:

(13) Harrison S, Sun T, Kamel MK, et al. Do individual surgeon volumes affect outcomes in thoracic surgery? *Eur J Cardiothorac Surg* 2019;56:770-7.

(14) Tsugawa Y, Jena AB, Orav EJ, et al. Age and sex of surgeons and mortality of older surgical patients: observational study. *BMJ* 2018;25:361:k1343. doi: 10.1136/bmj.k1343

(15) Stulber JJ, Huang R, Kreutzer L, et al. Association between surgeon technical skills and patient outcomes. *JAMA Surg* 2020;155:960-8.

c. “If a patient has severe intrathoracic adhesions, the operation took 78 min longer and the patient was at risk of more complications, as compared to patients without severe adhesions.” (discussion, page 9): This conclusion should be supported by the appropriate statistics - where these patients really at a higher risk of complications?

**Reply:** Our previous data has been already shown. Please see reference #16 (Page 17, line 17-18).

**Changes in the text:** “2020;12:4224-32.”

d. “Intraoperative intervention to stop air leak needed longer time.” (discussion, page 10): it would be nice to see this interpretation supported by statistics - was the operative time indeed longer in patients with air leak than in those without?

**Reply:** We added the data as advised. Please see (Page 12, line 24-25)

**Changes in the text:** “(average time 74 minutes, range 48-148 minutes)”.

e. “This is because the incidence of air leak often decreases due to postural change from a lateral position to a supine position” (discussion, page 10): This can probably be tested statistically within your data - are position changes associated with the occurrence of air leak?

**Reply:** We modified as advised. This is empirical comment, and this study does not

quantitatively evaluate all cases. Please see (Page 13, line 2)

**Changes in the text:** This is because we often experienced the incidence of air leak often decreases due to postural change from a lateral position to a supine position or under spontaneous breathing after extubation.

- f. “This can probably be tested statistically within your data - are position changes associated with the occurrence of air leak?” (discussion, page 10): When was this procedure added. If it was added after the recruitment had started, then this change in procedure has to be taken into consideration and included in your statistics. Compare neuropathic pain for patients operated with this added procedure and those without it.

**Reply:** We added as advised. Please see (Page 7, line 22-24), (Page 8, line 1-8) and (Page 10, line 12-13).

**Changes in the text:**

1. When a subxiphoid incision was needed, the incision was immediately performed after resection of the specimen in the hemilateral decubitus position. After the specimen was delivered, the patient was returned to the lateral decubitus position and the intrathoracic operation was resumed. The subxiphoid wound was sutured in the supine position after the intrathoracic operation completion.
  2. For air leaks, an intraoperative sealing test was routinely performed. If air leaks were detected, the fibrin glue plus poly glycolic acid sheet and/or free pericardial fat pad suturing were performed (7,8). Free pericardial fat pad suturing was carried out, when moderate to severe air leaks were detected. If severe air leak was continued after the supine position or after extubation despite these procedures, the patient was returned to the lateral position and then the above procedure was repeated.
  3. All four cases of air leak after extubation were complicated by neuropathic pain, but there were no cases of intractable pain.
- g. “Neuropathic pain in patients who underwent CVATS was unlikely to be intractable than in those in whom CVATS was converted to thoracotomy.” (discussion, page 10): When you compare groups, this needs to be supported by stats. Do you think your numbers are high enough to come to a robust conclusion?

**Reply:** We added the data as advised. Please see (Page 9, line 19-22)

**Changes in the text:** There were no significant differences between VATS for  $\geq 5$  hours group and conversion to thoracotomy group in the following measured variables: postoperative neuropathic pain (71.4% vs. 71.4%;  $P=1.00$ ) and intractable pain (9.5% vs. 21.4%;  $P=0.37$ ).

- h. “The incidence of intraoperative complications from VATS pulmonary resection performed during night hours was significantly higher than that from VATS performed during working hours” (discussion, page 11): If the authors think this is

an important factor, why not including the time of surgery (or maybe day time versus night time) as a factor and investigate whether it did make a difference for the number of complications?

**Reply:** We added as advised. Please see (Page 5, line 14-15) and (Page 14, line 18-22)

**Changes in the text:**

1. Long-time surgery began on day time. No elective surgery was performed at night except for emergency surgery.
2. Although stress was not evaluated in this study, prolonged surgery, night surgery, and emergency surgery will generally be stressful, not just for nurses, but for everyone as well. Time management should be kept in mind to provide better surgery to patients. The elective surgery should start on day time, and no night surgery should perform except for emergency surgery. There are no nighttime emergency surgery cases in our challenge VATS cases.

i. “This study has several limitations. First, the study has the inherent limitations related to its retrospective design and two-center setting” (discussion, page 11): The authors could statistically test whether results differed for the two centres.

**Reply:** We added as advised. Please see (Page 13, line 13-16).

**Changes in the text:** The challenging VATS for  $\geq 5$  hours cases were significantly more common in one hospital (4.6% vs 1.2%;  $P=0.0019$ ). This was because there were more cases requiring subxiphoid incision than in another hospital. Conversion to thoracotomy were no difference (1.4% vs. 1.6%;  $P=1.00$ ) between two centers.

- 2) Within the methods, certain details were missing to allow for reproducibility or to allow the reader to understand the study better:
  - a. Describe your 'calculations' (methods, page 7) - What statistical tests were run? Which factors were considered within your tests?

**Reply:** We added as advised. Please see (Page 9, line 4-10)

**Changes in the text:** For univariate analysis, inter-group differences were evaluated using the non-parametric Wilcoxon rank-sum test. The  $\chi^2$  or Fisher's exact test was used to compare categorical variables when necessary. Significance was defined as  $P<0.05$ . All reported P-values were two-sided. Continuous variables were presented as mean  $\pm$  standard deviation for normally distributed data and median with interquartile range for non-normally distributed data. Categorical variables were presented as n (%). All statistical analyses were performed using JMP version 12.0 (SAS Institute, Inc., Cary, NC, USA).

b. “The overall responsibility for the quality of all the procedures for a given patients was controlled by the chief surgeon in accordance with sufficient quality requirements.” (methods, page 4): State what you mean by sufficient quality requirements.

**Reply:** We added as advised. Please see (Page 5, line 20-23)

**Changes in the text:** All treatment plans were finalized by the chief surgeon. The chief surgeon gave instructions if a resident was behind in the procedure, and if that did not proceed in the same scene, the chief surgeon performed the operation instead. Also, if the chief surgeon judged that the procedure was very dangerous, the surgeon was replaced by the chief surgeon.

c. “We used validated neuropathic pain screening tools such as the Leeds Assessment of Neuropathic Symptoms and Signs...” (methods, page 6): ‘Such as’ implies that other tools than those mentioned here could have been used. Please provide a complete list of neuropathic pain tools that were used for this study.

**Reply:** We erased “Such as” and modified “S-LANSS”. Please see (Page 8, line 5).

**Change in the text:** S-LANSS

d. Please provide more information on the Leeds Assessment of Neuropathic Symptoms and Signs. Further, please provide more information on the time points of neuropathic pain assessments and the levels of pain patients report.

**Reply:** We added as advised. Please see (Page 8, line 6-10).

**Changes in the text:** The S-LANSS score is an evaluation method to identify pain of predominantly origin, as distinct from no nociceptive pain, without the need for clinical examination. A total score of 12 or higher is evaluated as suggesting pain of predominantly neuropathic origin. We routinely used the S-LANSS score to evaluate postoperative neuropathic pain.

3) Some of the conclusions/statements within the discussion need further explanation or were beyond the scope of the article:

a. “For nurses, 30-40% of operation room nurses were mentally stressed during surgery. Among scrub nurses, endoscopic surgery was related to their mental stress (24). Excessive long working hours has become a social problem. Long working hours is a risk factor of coronary heart disease and stroke (25). Proper time management is an important aspect for a leadership (26). In cases where surgery requires longer operation time, it may be necessary to secure a short break during surgery to restore concentration (27).” (discussion, page 11): While this might be a generally important point the direct relation to the assessed data is unclear. The stress caused for nurses by long working hours seems beyond the scope of this article and was not further assessed within the analysis.

**Reply:** We modified as advised. Please see (Page 14, line 18-22).

**Changes in the text:** Although stress was not evaluated in this study, prolonged surgery, night surgery, and emergency surgery will generally be stressful, not just for nurses, but for everyone as well. Time management should be kept in mind to provide



better surgery to patients. The elective surgery should start on day time, and no night surgery should perform except for emergency surgery. There are no nighttime emergency surgery cases in our challenge VATS cases.

b. “In this study, patients with challenging CVATS more frequently developed postoperative neuropathic pain (71.4%), as compared with our previous data (25.9%).” (discussion, page 10): How do you explain the difference?

**Reply:** We added the data. Please see (Page 13, line 24-25).

**Changes in the text:** In this study, patients with challenging CVATS more frequently developed postoperative neuropathic pain (71.4% vs. 22.0%;  $P < 0.0001$ ), as compared with the suitable VATS. Even with CVATS approach, long-time surgery was considered a risk factor for postoperative neuropathic pain.

c. “For tumors with minimum diameter of  $\geq 5$  cm, thoracotomy was suitable because the operation duration was shortened and an exact incision length was required; although, CVATS could have be performed.” (discussion, page 10): Explain the second part of the sentence further (“although, CVATS could have be performed”) as it seems to be in contrast to the point made within the first part of this sentence.

**Reply:** We corrected them as advised. Please see (Page 13, line 7-12).

**Changes in the text:** For tumors with minimum diameter of  $\geq 5$  cm, thoracotomy was suitable because the intercostal space is about one cm, and an certain extract incision would be required for large tumor delivery. Intrathoracic manipulation was possible even with CVATS, but good surgical field would be difficult. In particular, good surgical field around the hilum would be hard to obtain. Therefore, operation duration with thoracotomy might be shorter than CVATS for tumors with minimum diameter of  $\geq 5$  cm.

e. “we must reflect on whether VATS approach is better for such patients.” (discussion, page 9): Please elaborate on the ‘better’ - better than what?

**Reply:** We modified them. Please see (Page 12, line 8-9).

**Changes in the text:** we must reflect on whether VATS approach is better than thoracotomy in severe intrathoracic adhesions cases.

e. “On the contrary, the aforementioned patient-related factors could fairly contribute to the success of CVATS.” (discussion, page 9): I am unclear about the exact point of this sentence; please clarify what you mean by “on the contrary” - in contrast to what? Further, make it more explicit how you think that complications would be positively associated with the surgery's success ('contribute to the success')? Especially reading the lines below it rather sounds like the patient-related factors stated here are rather associated with further complications, not with success.

**Reply:** We decided the sentence was unnecessary and deleted them. Please see (Page 12, line 1).

4) Overall, the quality of the article could be improved by carefully proof-reading it and being fully checked for grammar and language.

**Reply:** We added. Please see (Page 15, line 21-22).

**Changes in the text: Acknowledgements.** We would like to thank Editage ([www.editage.com](http://www.editage.com)) for English language editing.

Minor issues:

1) Within the introduction it is stated that the development of minimally invasive approaches – such as VATS - can lead to the development of post-surgical pain, whereas the literature cited here (4, 5) found thoracotomies as a risk factors, VATS were not mentioned. Justify how you came to the assumption that specifically VATS might be a source for post-operative pain. I am not saying this is wrong, I would just like the authors to provide the appropriate citations for their argument.

**Reply:** We added as advised. Please see (Page 4, line 13-18).

**Changes in the text:** We previously reported that risk factors for neuropathic pain were preoperative use of hypnotic medication, thoracotomy, and duration of surgery  $\geq 2.5$  hours, and VATS was a negative association with postoperative neuropathic pain (4). Pregabalin (50 mg / day) had a significant preventive effect on postoperative neuropathic pain after thoracic surgery. Nevertheless, 19.6% of patients had postoperative neuropathic pain (5). Longer VATS could be a risk factor for postoperative neuropathic pain, even with pregabalin, because duration of surgery  $\geq 2.5$  hours was also a significant factor in thoracotomy (4). That is, although minimally invasive surgery is often discussed only by the size or number of incisions, operation time is also an important factor.

2) Please provide units for measures displayed within table 1 and 2 (bleeding and operation duration).

**Reply:** We corrected them. Please see Table 1 and 2.

3) In addition to merely stating the limitations it would be nice to describe the authors' efforts to address and deal with them.

**Reply:** We added as advised. Please see (page 15, line 2-3).

**Changes in the text:** However, the number of 995 cases is not small and is considered to be worth considering.

4) In order to better understand the discussion on imaging techniques for diagnostics

prior to surgery, please state within the methods what preoperative diagnostic assessments were used - what are the standard procedures at the involved hospitals?

**Reply:** We added as advised. Please see (Page 6, line 8-12).

**Changes in the text:**

***Preoperative imaging test***

In all cases, a simple chest X-rays and Computed tomography (CT) were performed before surgery. In the case of malignant tumors, contrast-enhanced CT, cerebral magnetic resonance imaging, and positron emission tomography were also performed unless renal dysfunction with eGFR <50 ml / min or uncontrolled diabetes.