

Peer Review File

Article Information: <https://dx.doi.org/10.21037/apm-22-207>

Comment 1:

Ports of VATS are 3 or 4 ports and ports of RATS are 5 ports. In addition, intercostal spaces are different from each other. The incision of the thoracotomy group of the author is very small. If a metallic retractor was not used, differences in postoperative pain between the two groups may be slight.

Reply 1:

Thank you for your valuable suggestions. We agree with you and have incorporated this suggestion throughout our paper in limitations and results. (see page12 ,line11 and Page13,line5)

Changes in the text:

Thirds, the number of ports and port positions of thoracoscopic surgery are different in the study, it became difficult to compare postoperative pain of RATS and VATS. For this reason, these surgical procedures were not possible to compare postoperative pain in our study.

We were able to improve the postoperative pain in the chronic phase to the same extent as thoracoscopic surgery by making various efforts in thoracotomy surgery.

Comment 2: Is a port needed in most cases of thoracotomy?

Reply 2: Thank you for pointing out the ambiguity of our statement. We use an automatic suture device to cut blood vessels and bronchi. Port is needed in thoracotomy for safe use of automatic suture device. We have reworded the text in the method of Thoracotomy. (see page6 ,line8)

Changes in the text:

The 4th or 5th intercostal space was opened and retracted with a silicon thoracic opener. In some cases, a port was not created for video assistance or using an automatic suture

device to cut blood vessels and bronchi.

Comment 3: In Table 1, diabetes mellitus should be included at least.

Reply 3: Thank you for your valuable suggestions. We added this data.
(see Table1)

Changes in the text:

Past History (%)

Diabetes mellitus 6 (14%) 8 (14%) p=0.7740

Chronic obstructive pulmonary disease 7 (17%) 20 (32%) p=0.1130

Hypertension 16 (38%) 26 (44%) p=1.000

Comment 4: The number of cases in Figure 3 and Figure 4 is small and different. The author included 100 cases in this study. Therefore, all cases should be analyzed.

Reply 4: Thank you for your valuable suggestions. In our study, we could not obtain complete BPI, PST, and FS data from all patients. There were some cases in which the examination was not performed or was interrupted at the discretion of the anesthesiologist. Missing data was left as a missing value. We have included your points as consideration for limitations. (see page 12,line19)

Changes in the text:

Finally, a major limitation of our study is that we did not obtain complete BPI, PST, and FS data in all patients.

Response for the second referee.

Comment 1: Line 27 - please write "single-center" with a hyphen,

Reply 1: We have modified our text as advised (see Page3, line5)

Changes in the text: single-center

Comment 2: Line 47 - I would write this sentence a bit differently: "Patients who undergo thoracotomy may experience post-thoracotomy pain syndrome (PTPS), which is defined by the International Association."

Reply 2:

We have modified our text as advised (see Page4, line1)

Changes in the text:

Patients who undergo thoracotomy may experience post-thoracotomy pain syndrome (PTPS), which is defined by the International Association

Comment 3: Line 65 - it should be "present",

Reply 3: We have modified our text as advised (see Page5, line1)

Changes in the text: We present the following

Comment 4: Line 85 - it should be "the removal",

Reply 4: We have modified our text as advised (see Page5, line19)

Changes in the text:

The main skin incision was 4–5 cm in the intercostal space to enable the removal of the lung from the chest cavity.

Comment 5: Line 112 - "along with the surgical scars.."

Reply 5: We have modified our text as advised (see Page7, line10)

Changes in the text:

PTPS was defined as pain along with the surgical scars with the worst pain score > 3 , which was assessed 3 months after the surgery.

Comment 6: Line 112 - "the worst"

Reply 6: We have modified our text as advised (see Page7, line 7)

Changes in the text:

BPI items, including the worst pain, least pain, average pain, general activities, mood, walking, relationship with other people, sleep, and enjoyment of life, were investigated in each patient. Patients graded each item with scores ranging from 0 (best) to 10 (the worst) at 1 week, 1 month (21–40 days), and 3 months (81–100 days) postoperatively.

Comment 7: Line 116-117 Rewrite: "An epidural catheter was placed in each patient for postoperative pain relief according to the incision site".

Reply 7: We have modified our text as advised (see Page7, line14)

Changes in the text:

An epidural catheter was placed in each patient for postoperative pain relief according to the incision site. Epidural analgesia with fentanyl at 4 mL/h (median, 800 µg; range, 0–1500 µg), diluted with 0.125%–0.25% levobupivacaine, was usually continued for 2 days.

Comment 8: Line 117 - "a rate of" is unnecessary,

Reply 8: We have modified our text as advised (see Page 7, line 14)

Changes in the text:

An epidural catheter was placed in each patient for postoperative pain relief according to the incision site. Epidural analgesia with fentanyl at 4 mL/h (median, 800 µg; range, 0–1500 µg), diluted with 0.125%–0.25% levobupivacaine, was usually continued for 2 days.

Comment 9: Line 119 - "anti-inflammatory",

Reply 9: We have modified our text as advised (see Page7, line14)

Changes in the text:

Oral non-steroidal anti-inflammatory drugs (loxoprofen sodium hydrate, 180 mg) were administered from postoperative day one.

Comment 10: Line 156 - "relationships",

Reply 10: We have modified our text as advised (see Page9, line10)

Changes in the text:

Compared with patients in the thoracotomy group, those in the thoracoscopy group demonstrated significantly lower average pain scores 1 week after the surgery ($p < 0.050$, $d = 0.63$) and lower QOL scores about activities, mood, relationships, and enjoyment in

life during the same period ($p < 0.050$, $d = 0.46$; $p < 0.050$, $d = 0.47$; $p < 0.050$, $d = 0.54$; $p < 0.050$, $d = 0.47$, respectively) (Table 4).

Comment 11: Line 163 - "affects",

Reply 11: We have modified our text as advised (see Page9, line18)

Changes in the text:

PST is reported to be elevated in patients with neurotic disorders, such as diabetic neuropathic foot (13,14), and affects the pain sensation

Comment 12: Line 167 - " would" is unnecessary,

Reply 12: We have modified our text as advised (see Page10, line2)

Changes in the text:

However, correlations were not found between PST and BPI or between PST and QOL. Conversely, these results imply that the individual pain threshold did not affect BPI and might support the obtained BPI and QOL data.

Comment 13: Line 183-184 Rewrite: "In our study, a significant difference between the two groups' pain scores were only observed in the acute phase."

Reply 13: We have modified our text as advised (see Page11, line6)

Changes in the text:

In the chronic phase, the present results demonstrated no difference between the thoracoscopy and thoracotomy groups.

Comment 14: Line 187 - "introducing" instead of " the introduction of",

Reply 14: We have modified our text as advised (see Page11, line3)

Changes in the text:

However, the introduction of a silicon thoracic opener improves the visualization and decreases postoperative pain (23,24).

Comment 15: Line 189 - "avoiding" instead of "avoidance of"

Reply 15: We have modified our text as advised (see Page11, line5)

Changes in the text:

Therefore, avoidance of metal retractors and conventional drains in thoracotomy may be an effective approach to reducing PTPS.

Comment 16: Line 190-192 Rewrite: "In the chronic phase, the present results demonstrated no difference between the thoracoscopy and thoracotomy groups."

Reply 16: We have modified our text as advised (see Page11, line6)

Changes in the text:

In the chronic phase, the present results demonstrated no difference between the thoracoscopy and thoracotomy groups.

Comment 17: Line 210 - "analgesia"

Reply 17: We have modified our text as advised (see Page12, line4)

Changes in the text:

The significance of FS remains to be elucidated. In our study, FS might have affected subjective pain during the postoperative period of epidural analgesia protocol until 2–3 days after the surgery.

Comment 18: Line 211 - "removing"

Reply 18: We have modified our text as advised (see Page12, line5)

Changes in the text:

If FS affects pain or QOL after removing the epidural tube, the effect is deemed preemptive. Factors that affect FS remain to be investigated.

Comment 19: Introduction, please provide 1-2 sentences in the Introduction and

Methodology to explain why the pain sensation threshold (PST) and fentanyl sensitivity (FS) was investigated. As a reader, the purpose of this part of the study is not fully understood by me.

Reply 19: Thank you for your valuable suggestions. We agree with you and have incorporated this suggestion throughout our paper in the introduction. (See Page4, line12 and Page6, line14).

Changes in the text:

Hsu et al. reported that preoperative pressure pain tolerance is significantly correlated with the level of postoperative pain (9). Since PTPS involves chronic pain, it is important to evaluate not only the pain but also the quality of life (QOL) of the patients and investigate whether pain sensation threshold (PST) and fentanyl sensitivity (FS) other than the surgical procedure can be a risk factor for developing chronic pain.

PST for the objective method for assessing pain was measured using a pressure algometer (Baseline Evaluation Instruments: FABRICATION ENTERPRISES, USA) immediately before the induction of general anesthesia by the anesthesiologists.

Comment 20:

The authors clearly described the limitations of their paper. However, there is no discussion of the individual limitations - they are simply listed. I encourage you to discuss the limitations. Moreover - is it not the limitation to evaluate such QoL components as general activities, mood, walking, relationship, or enjoyment of life, but you investigated them in each patient only for pain? Could the decreased value of these parameters also result from the fact that the patient has lost a lung lobe/segment, and its efficiency may be reduced from 6 months to a year, affecting his quality of life?

Reply 20: Thank you for the helpful question. We evaluated the pain related QOL using Brief Pain Index. This questionnaire asks if pain affects activities, mood, walking, relationship, and enjoyment of life. Patients with dementia who do not understand the question are excluded, so it is unlikely that QOL will be affected by symptoms other than pain. Dyspnea may occur depending on the surgical procedure, which may reduce the QOL. It cannot be denied that this study affected QOL due to the difference in the number

of cases of lobectomy and segmentectomy by surgical approach. This content will be added to the limitation. (see page12,line14)

Changes in the text: Forth, we evaluated the pain related QOL using Brief Pain Index. This questionnaire asks if pain affects activities, mood, walking, relationship, and enjoyment of life. Patients with dementia who do not understand the question are excluded, so it is unlikely that QOL will be affected by symptoms other than pain. Dyspnea may occur depending on the surgical procedure, which may reduce the QOL. It cannot be denied that this study affected QOL due to the difference in the number of cases of lobectomy and segmentectomy by surgical approach.

Comment 21: QoL - In my opinion, the description of the methodology for assessing the quality of life is unclear. How was the quality of life assessed? Did you use your own questionnaire, or was the questionnaire standardized? If so, was Cronbach's alpha calculated during its construction?

Reply 21: Thank you for the helpful question. We evaluated the QOL using Brief Pain Inventory (BPI) . This questionnaire was standardized. This questionnaire evaluates how pain affects items activities, mood, walking, relationship, and enjoyment of life on a scale of 0-10 points. For example, if the pain has no effect on mood, it will be 0 points, and if it has a sufficient effect, it will be 10 points. The BPI displayed excellent internal consistency (Cronbach's alpha value of 0.91). We agree with your comment and have incorporated this suggestion throughout our paper in methods.

(see page7,line9)

Changes in the text:

BPI was a standardized questionnaire and displayed excellent internal consistency (Cronbach's alpha value of 0.91).

Comment 22:

Line 126-127 I do not quite understand this sentence. The Shapiro-Wilk test is used to check the normality of the distribution.

Reply 22: Thank you for your valuable suggestions. We have modified our text as advised

(see Page8, line4)

Changes in the text:

The Shapiro-Wilk test was used for normality of the distribution in histogram data of PST or FS.

Comment 23: Line 143 - "respectively" is unnecessary.

Reply 23: We have modified our text as advised (see Page8, line14).

Changes in the text:

The thoracoscopy group consisted of 30 (71%) and 12 (29%) patients who underwent VATS and RATS.

Comment 24: Table 1. I propose to improve readability: if a given variable has a normal distribution, please provide it with a standard deviation; if there is no normal distribution, please give its value together with the first and second quartiles.

Reply 24: Thank you for your valuable suggestions. We added this data. (See Table1)

Surgery time \pm SD (min)	185 \pm 8.0 (92–417)	170 \pm 7.0 (99–382)	p=1.0000
Length of skin incision \pm SD (cm)	5.0 \pm 1.9 (2–6)	9.6 \pm 2.7 (8–10)	p<0.0001
Blood loss \pm SD (mL)	90 \pm 18 (1–800)	77 \pm 21 (1–730)	p=0.6056

Changes in the text:

Response for the third referee.

Comment 1: Given that the objective measures of pain threshold/medication sensitivity were not correlative, more specific conclusions about the role of these or alternative measurements in perioperative care for prediction/personalization of pain trajectory management are required.

Reply1: I think you for your careful reading of my manuscript and for your helpful

suggestions. We have modified our text as advised (see Page13, line7).

Changes in the text:

In this study, PST and FS could not predict patients with PTPS. Future studies are needed to find alternative measurements of pain predictors.

Comment 2: I do agree that thoracotomy patients will benefit from the results of this work but question the usefulness of conducting another RCT on the approaches themselves (as the VIOLET trial is now available) but rather recommend comparing approaches to the management of pain.

Reply1: I think you for carefully reading my manuscript and for your helpful suggestions. We have modified our text as advised (see Page13, line7).

Changes in the text:

In this study, PST and FS could not predict patients with PTPS. Future studies are needed to find alternative measurements of pain predictors. We believe that the results of this study will be beneficial for patients who may undergo thoracotomy. The authors will continue to examine the pain predictors for thoracic surgery.