Peer review file
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Reviewer A

Comment 1:
Furthermore, I cannot really understand why the investigators assessed PONV specifically after thoracoscopic partial pulmonary resections and not for example thoracoscopic pulmonary resections in general.
One explanation could be the duration of the procedure, which is significantly shorter in partial resections and could play a role in PONV
Reply:
We have modified our text as advised (see Page 6, line 94-95).
Thoracoscopic pulmonary wedge resection (TPWR) is a surgical procedure that can maintain lung function and is less physically invasive to a patient than lobectomy.

Comment 2:
In the conclusions of the abstract, the sentence in lines 68-69 should be rephrased.
Reply:
We have modified our text as advised (see Page 5, line 75).
The optimal cut-off value for PONV was 3.58 μg/kg/hr.

Comment 3:
Line 82, replace `were` with `have been` identified and also cite the paper from which these results were extracted.
Reply:
We have modified our text as advised (see Page 6, line 90-93).
Duration of anesthesia, use of opioids, inhalation anesthesia, no antiemetic prophylaxis, surgery over 60 min, gynecological surgery, laparoscopic surgery, and cholecystectomy have been identified as surgical and anesthetic risk factors of PONV [2-4, 9, 10].

Comment 4:
Line 84, replace `maintain` with `preserve` and remove `predictive`, similar mistakes exist throughout the text.
Reply:
We have modified our text as advised (see Page 6, line 94-96).

Thoracoscopic pulmonary wedge resection (TPWR) is a surgical procedure that can preserve lung function and is less physically invasive to a patient than lobectomy. However, the risk factors of PONV following TPWR remain unclear.

Reply:

We deleted `predictive` in the text.

Comment 5:

Is there any literature comparing PONV after lung surgery with other types of procedures and if yes, what did they show? How do you justify the fact that only partial pulmonary resections were analyzed.

Reply:

We have modified our text as advised (see Page 6, line 94-98).

Thoracoscopic pulmonary wedge resection (TPWR) is a surgical procedure that can preserve lung function and is less physically invasive to a patient than lobectomy. However, the risk factors of PONV following TPWR remain unclear. To our knowledge, this investigation is the first literature to evaluate multiple risk factors for PONV after TPWR.

Comment 6:

In the surgical indication paragraph, (lines 101-108). The test from the end of line 104 and until the end of the paragraph is not necessary.

Reply:

We have modified our text as advised (see Page 7, line 113-115).

Surgical indication

The indications for TPWR included suspected adenocarcinoma in situ or minimally invasive adenocarcinoma, insufficient tolerance for anatomical pulmonary resection, and suspicious metastatic disease near the visceral pleural lesion.

Comment 7:

Line 123, the calculation of smoking index needs some further clarification (cigarettes per day x years of smoking)

Reply:

We have modified our text as advised (see Page 8, line 132-133).

Smoking index was calculated as follows: cigarettes per day × years of smoking.

Comment 8:

In line 124, a mistake that exists many times throughout the paper (text and tables) is `Experience of cancer chemotherapy`, which, in my opinion, should be replaced with `history` or `past medical history` of chemotherapy.

Reply:

We have modified our text as advised (see Page 8, line 131-132).

We collected the following patient data: age, sex, body mass index, smoking index, history of cancer chemotherapy, plasma creatinine, and spirometry test results.

We also replaced `experience` with `history` in all other sentences.

Comment 9:

In the results section: The sentence in lines 153-155 should be before the sentence in lines 151-153. This sequence would follow the study flow chart.

Reply:

We have modified our text as advised (see Page 10, line 165- Page 11, line 168).

Sixty patients were excluded due to the following: 19 patients underwent thoracotomies, 32 had benign tumors, 6 had a pneumothorax, and 3 had incomplete data. Finally, 160 patients were reviewed. A total of 27 patients (16.9%) were in the P group, and 133 patients (83.1%) were in the N group (Figure 1).

Comment10:

In line 154, rather than `6 had pneumothorax`, `6 patients were operated for pneumothorax`

Reply:

We have modified our text as advised (see Page 10, line 165- Page 11, line 167).

Sixty patients were excluded due to the following: 19 patients underwent thoracotomies, 32 patients had benign tumors, 6 patients had a pneumothorax, and 3 patients had incomplete data.

Comment11:

In line 156, it is stated that the median duration from cancer chemotherapy to surgery was 526 +/- 1036 days. First of all, maybe it would be better to write it in years or months.

Reply:

We have modified our text as advised (see Page 11, line 169-171).

The median duration from cancer chemotherapy to surgery was 17.5 ± 34.5 months

(range 0–169 months).

Comment12:
Line 163, on which POD was chest drain re-insertion needed?
- Discussion section, line 192, 80% of surgical patients undergoing general anesthesia developed PONV, but only in specific subgroups with 4 out of 4 risk factors.
Reply:
We have modified our text as advised (see Page 11, line 174-179).
Class I complications according to the Clavien–Dindo classification [17] were as follows: prolonged air leakage (drainage period of ≥ 7 days) in 2 patients, both of whom needed reinsertion of chest drains for air leakage on 2 postoperative day (POD), and cerebral infarction on POD1 in 1 patient. Class IIIb complications included subglottic laryngitis requiring emergent tracheostomy on POD2 in 1 patient.
Reply:
We have modified our text as advised (see Page 13, line 206-208).
Approximately twenty years ago, PONV was observed in 30%, and it is up to 70% in high-risk patients undergoing general anesthesia [18].

Comment13:
The take home message is that the analysis identified the dose of fentanyl (per kg /hr) as the strongest risk factor for PONV following thoracoscopic partial pulmonary resections
Regarding the tables, they are rather sizable and confusing.
I would suggest to separate Table 1 into 2. The first will include patient characteristics, sparing spirometry values. Then a second table with operative/peri-operative data
The same applies for Table 2.
Reply:
We separated Table 2 into 2 tables. We deleted Table 1 according to Reviewer B.

Reviewer B

Comment 1:
Overall lower rate of PONV than I had expected. How was PONV determined to be present and when were patients asked? Retrospective studies would be expected to have a lower PONV rate than prospective studies. Assessing PONV in the recovery room would be expected to yield lower rates than PONV after 24h. How was it decided

whether or not to treat PONV?

Reply:

We have modified our text as advised (see Page , line 148- Page 10, line 151).

PONV was determined when awakening from anesthesia. The surgery team and nursing staff evaluated PONV every hour for 6 hours after surgery and every 3 hours until the next morning after 6 hours. Antiemetics were administered at the patient's wishes or at the time of vomiting by the judgments of medical staff.

Comment 2:

Impact of PONV on postoperative outcomes? Which ones? Mobilization alone seems a bit slim on its own. Time to discharge? I think stating an effect on “clnical outcomes” is a bit of a stretch.

Reply:

We have modified our text as advised (see Page 9, line 145-147).

We evaluated the impact of PONV on postoperative mobilization within 4 hours after surgery, and postoperative hospitalization**.**

Comment 3:

Anesthesia protocol is unclear to me. Fentanyl ok, but premedication? Propofol or gas? Preoperative antiemetic prophylaxis (when was it administered? Beforehand? With the information present, I cannot really relate to what was done when). If there is no protocol/standard for antiemetic prophylaxis, I find the statement (p.11 “none of the antiemetic prohypaxis administered was significantly associated effective in preventing PONV”) problematic. Maybe only those with a higher risk received one or more antiemetics?

Reply:

We described our text as advised (see Page 8, line 124-128).

However, there was no uniform protocol for the interval of added fentanyl, use of inhalation anesthesia, steroid, antiemetic drugs, or intraoperative infusion, and this was determined according to the anesthesiologist’s preference. Sevoflurane was used for inhalation anesthesia, propofol was used for intravenous anesthesia. Premedication was not performed in all patients.

We have modified our text as advised (see Page 16, line 261-263).

Risk assessment for PONV and use of antiemetics were varied on each anesthesiologist, which may make it difficult to accurately determine the effectiveness of antiemetics.

Comment 4:

Was this study preregistered somewhere (e.g. clinicaltrials.gov?). Were the analyses predefined or just ad hoc?

Reply:

We have described our text as advised (see Page 16, line 257-258).

First, this investigation was a retrospective observation in a single facility, and the generalizability of the findings is limited.

Comment 5:

Discussion: no strengths and limitations. This is an interesting study, but one with quite a few limitations. This is fine, but these limitations whould be addressed for the reader.

Reply:

We have modified our text as advised (see Page 16, line 257-267).

This study has several limitations. First, this investigation was a retrospective observation in a single facility, and the generalizability of the findings is limited. We could not obtain information about alcohol. Second, there was no protocol for anesthesia, and anesthetic management was varied compared with a well-planned prospective study. Risk assessment for PONV and use of antiemetics were varied on each anesthesiologist, which may make it difficult to accurately determine the effectiveness of antiemetics. It is therefore possible that the inevitable bias associated with the study design may have affected our analysis. Third, because our facility is a cancer hospital and benign diseases are minor, we analyzed without benign diseases in this study. Further prospective studies with more accurate data are necessary to confirm our findings.

Comment 6:

Statistics: median, std. dev. Probably does not make too much sense. I would just present median and IQR. Univariate analysis: generally, one would expect an OR and not just a p-value in a table (table 2).

Reply:

After univariate analysis, selected risk factors ($p<0.1$) were cleared by showing OR and CI95% in multivariate analysis (Table 3).

Comment 7:

Text p. 8 states “female sex, non-smokers, and lower plasma creatinine levels tended to be associated with PONV (0.075 [n.s.!], and 0.055 [n.s.], respectively” If $p<0.05$ then it is not associated with PONV according to your predefined characteristics and the 3rd p

value is missing.

Reply:

We have modified our text as advised (see Page 11, line 182- Page 12, line 184).

Although female non-smokers, and lower plasma creatinine levels were not statistical risk factors of PONV, they tended to be associated with PONV (p=0.075 and 0.055, respectively).

Additionally, we changed 'Female sex and non-smoker' to 'Female non-smoker' as a variable in our text and table 1. We added Female non-smoker in multivariate analysis.

Comment 8:

Fig 2: ROC Curve: 95% CI, 45° line, and optimum should be marked.

Reply:

We have modified Fig 2 as advised.

Comment 9:

Table 1 unnecessary with table 2 present. Blood loss 0-100ml? Paper must be written by surgeons =). Also not sure spiroergometry data useful here.

Reply:

We modified the tables as advised (see Table 1, 2).

We have modified our text as advised (see Page 6, line 96-98).

To our knowledge, this investigation is the first literature to evaluate multiple risk factors for PONV after TPWR.

Comment 10:

Univariate analysis should be with an OR and 95% CI. Maybe fentanyl should also be presented linearly (e.g. per 25mcg fenta opr whatever) rather than just as a own data driven cut-0ff.

Reply:

After univariate analysis, risk factors were cleared by showing OR and CI95% in multivariate analysis (Table 3).

In this paper, the dose of fentanyl was evaluated as a risk factor in consideration of body weight and operation time. The evaluation of every 25 ug of fentanyl was judged to be inappropriate because it would not be possible to incorporate weight and time factors.

Reviewer C

Comment 1:

First, concerning definition, what the authors name Thoracoscopic partial resection seems to be identified as thoracoscopic wedge resection, ie non-anatomical resection, which is not the standard of care for lung carcinoma. Moreover, you do not mention node harvest. So it is an issue to focus on a non-standard technique. Can you be clearer on this aspect and explain why you do not mention node harvest. Also, the surgical technique chapter is not enough detailed for a surgical journal.

Reply:

We have modified our text as advised (see Page 8, line 119-120).

Surgeons used staplers in TPWR. Lymph node dissections were not performed in all patients.

Additionally, we changed ‘thoracoscopic partial resection’ to ‘thoracoscopic pulmonary wedge resection’ in all text.

Comment 2:

Second, the authors excluded from their analyse benign lesion and pneumothoraces, this must be justified as the technical aspect of the procedure seems to be the subject of analyse, not the pathology especially if no node harvest was done. Maybe you put them back in the analyze.

Reply:

We have modified our text as advised (see Page 16, line 264-267).

Third, because our facility is a cancer hospital and benign diseases are minor, we analyzed without benign diseases in this study. Further prospective studies with more accurate data are necessary to confirm our findings.

Comment 3:

Third, the authors mention the lack of anaesthetic protocole which is a major biais in this retrospective study.

The term "experience of chemotherapy" is not accurate, replace by "history of chemotherapy"

Reply:

We have modified our text as advised (see Page 16, line 259-264).

Second, there was no protocol for anesthesia, and anesthetic management was varied compared with a well-planned prospective study. Risk assessment for PONV and use of antiemetics were varied on each anesthesiologist, which may make it difficult to

accurately determine the effectiveness of antiemetics. It is therefore possible that the inevitable bias associated with the study design may have affected our analysis.

Reply:

We replaced `experience` with `history` in all text and tables.

Comment 4:

Fourth, line 158 it is mentioned that patients with severe comorbidities were excluded. How can you justify this and how many of those patients were in this group. They shall not be excluded from analyze.

Reply:

We have modified our text as advised (see Page 11, line 171-173).

In this study, there was no patient with severe comorbidities, such as chronic heart failure, chronic kidney disease requiring dialysis, or liver cirrhosis of Child–Pugh Class B or higher.

Comment 5:

The discussion is well written. The message concerning the lack of anaesthetic protocol is clearly mentioned but the conclusion is tricky. We know that anaesthetic and surgeon need to work as a team, the way you present it could suggest a local difficulty your encounter in your department so this could be counterproductive, may be you could soften this message.

Reply:

We have modified our text as advised (see Page 15, line 243-244).

Thus, it is important to avoid the inadvertent administration of intraoperative opioids.

Reply:

We have modified our text as advised (see Page 5, line 75-76).

It is important to avoid the inadvertent administration of intraoperative fentanyl.

Reply:

We have modified our text as advised (see Page 17, line 270-272).

Conclusions:

An increased dose of fentanyl/kg/h was the strongest risk factor for PONV during TPWR. The optimal cut-off value for PONV was 3.58 μg/kg/hr. It is important to avoid the inadvertent administration of intraoperative fentanyl.