Peer review file
Article information: http://dx.doi.org/10.21037/jtd-20-2122

Reviewer A

A further analysis of the anesthetic technique is required and comparison with other previous studies:
Comment 1:
The anaesthetic technique used based on sedation with dexmetomidine should be compared with other published techniques based on propofol and remifentanil if a gold standard of anaesthetic technique is to be obtained.

Reply 1:
The aim of our study was not to develop a new gold standard. One of the main differences to previous studies is the absence of invasive monitoring and adjuncts such as bladder catheterisation. Previous studies showed that different anaesthetic approaches are feasible (Lai et al., Liu et al., Hung et al.).
From an anaesthesiological point of view, the sedatives used do not seem to generate any relevant difference. Data published from other centres showed essentially similar conversion rates and similar frequencies of the need for mild catecholamine therapy. Apnoeas forcing conversion are rare with both propofol and dexmedetomidine (Chen et al., Gonzales-Rivas et al., Wang et al.).
A direct comparison of the regimes seems difficult, as most of the original papers and most of the reviews give little information on the regimes and exact dosages of sedatives used (Hung et al.). Therefore, the only thing we can do is to put the frequency of side effects into focus.

Lai HC, Huang TW, Tseng WC, Lin WL, Chang H, Wu ZF. Sevoflurane is an effective adjuvant to propofol-based total intravenous anaesthesia for attenuating cough reflex in nonintubated video-assisted thoracoscopic surgery. Medicine (Baltimore). 2018;97(42):e12927. doi:10.1097/MD.0000000000012927

Liu J, Cui F, Li S, et al. Nonintubated video-assisted thoracoscopic surgery under epidural anaesthesia compared with conventional anaesthetic option: a randomized control study. Surg Innov. 2015;22(2):123-130. doi:10.1177/1553350614531662

Hung MH, Hsu HH, Chan KC, et al. Non-intubated thoracoscopic surgery using internal intercostal nerve block, vagal block and targeted sedation. Eur J Cardiothorac Surg. 2014;46(4):620-625. doi:10.1093/ejcts/ezu054

Gonzalez-Rivas D, Bonome C, Fieira E, et al. Non-intubated video-assisted thoracoscopic lung resections: the future of thoracic surgery? Eur J Cardiothorac Surg 2016;49(3):721-31.

Chen KC, Cheng YJ, Hung MH, et al. Nonintubated thoracoscopic surgery using regional anesthesia and vagal block and targeted sedation. J Thorac Dis 2014;6(1):31-6.

Wang ML, Galvez C, Chen JS, et al. Non-intubated single-incision video-assisted thoracic surgery: a two-center cohort of 188 patients. J Thorac Dis. 2017;9(8):2587-2598. doi:10.21037/jtd.2017.08.96

Hung MH, Hsu HH, Cheng YJ, Chen JS. Nonintubated thoracoscopic surgery: state of the art

and future directions. J Thorac Dis. 2014;6(1):2-9. doi:10.3978/j.issn.2072-1439.2014.01.16

We add the following paragraph to the revised manuscript (see below).

Changes in the text: (see Page 17, line 11)

[…] A gold standard of anaesthetic technique should not be obtained. Previous studies showed that different anaesthetic approaches are feasible (Lai et al., Liu et al., Hung et al.). However, a direct comparison of the approaches seems difficult, as most of the original papers and most of the reviews give little information on the regimes and exact dosages of sedatives used (Hung et al.). Furthermore, our anaesthetic technique based on sedation with dexmedetomidine could not be directly compared with other published techniques based on propofol and remifentanil, midazolam and/or sevoflurane due to statistical flaws (lack of control group).

The sedatives used do not seem to generate any relevant differences in clinical practice. Data published from other centres show essentially similar conversion rates and similar frequencies of the need for mild catecholamine therapy. Apnoeas forcing conversion are rare with both propofol and dexmedetomidine (Chen et al., Gonzales-Rivas et al., Wang et al.). Nevertheless, incorrect dosing of sedatives and opioids may lead to respiratory depression and sedation. Drugs with less effect on respiration and consciousness are preferred.

Comment 2:

The combination of dexmetomidine and spinal anesthesia produces hypotension and therefore in this group of patients the use of catecholamines and fluids is greater.

Dexmetomidine alone for sedation in uniportal vats is usually insufficient and more sedatives or opioids are required, in my opinion it can influence the rate of conversion to general anaesthesia.

Reply 2:

Regarding to comment 1 we want to focus on dexmedetomidine and the combination of (neuraxial) analgesia in the revised manuscript. Therefore, we like to refer to our reply on comment 1. We used a loading dose of dexmedetomidine (2-3µg*kg^{-1}*h^{-1} over 10 minutes) followed by continuous infusion of dexemedetomidine (0.5-1µg*kg^{-1}*h^{-1}) in order to avoid excessive sedation that could lead to airway problems or haemodynamic impairments. In our opinion, dexmedetomine is a suitable sedative for non-intubated VATS. We suggest performing sedation with dexmedetomidine in combination with regional anaesthetic approaches which is in concordance with other approaches (Iwata et al.).

In our patients we performed non-intubated VATS using dexmedetomidine and TEA/PVB or ESPB. We achieved sufficient sedation and analgesia in majority of cases.

If analgesia/sedation was insufficient small boli of sufentanil and propofol could be administered (see methods section, Table 2). The average amount of the used opioid (sufentanil) used was only 15.2µg. In fact, we saw more use of catecholamines using thoracic epidural anaesthesia (TEA) especially in major surgery group ($p<0.001$, Table 2). However, dosage was very low and the administration of catecholamines was stopped at the end of surgery. Due to significant longer operative times ($p<0.001$) in major surgery group, fluid administration was significantly higher ($p<0.001$) accordingly but without any clinical impact (Table 2). None of the conversions occurred due to poor haemodynamics or overdosage of additive sedatives or opioids (please see discussion section).

The total conversion rate of 6.8% is in the range reported by other centres, especially at the beginning of the use of non-intubated VATS (Hung et al).

Iwata Y, Hamai Y, Koyama T. Anesthetic management of nonintubated video-assisted thoracoscopic surgery using epidural anesthesia and dexmedetomidine in three patients with severe respiratory dysfunction. J Anesth. 2016;30(2):324-327. doi:10.1007/s00540-015-2122-9

Hung MH, Hsu HH, Cheng YJ, Chen JS. Nonintubated thoracoscopic surgery: state of the art and future directions. J Thorac Dis. 2014;6(1):2-9. doi:10.3978/j.issn.2072-1439.2014.01.16

We will highlight this issue in the revised discussion (see below).

Changes in the text: (see page 16, line 25)

We used a loading dose of dexmedetomidine followed by continuous infusion of dexmedetomidine in order to avoid excessive sedation that could lead to airway problems or haemodynamic impairments. In our opinion, dexmedetomine is a suitable sedative for non-intubated VATS. We suggest performing sedation with dexmedetomidine in combination with regional anaesthetic approaches which is in concordance with other approaches (Iwata et al.).
In our patients we performed non-intubated VATS using dexmedetomidine and TEA/PVB or ESPB. We achieved sufficient sedation and analgesia in majority of cases.
If analgesia/sedation was insufficient small boli of sufentanil and propofol could be administered (Table 2). The average amount of the used opioid (Sufentanil) used was only 15.2µg. None of the conversions occurred due to poor haemodynamics or overdosage of additive sedatives or opioids.

Reviewer B

The authors need to be congratulated for attempting to extend minimally invasive non intubated thoracic surgery outside of select centres such as those from Taiwan (10.3978/j.issn.2072-1439.2014.01.01) and from Spain where the uniportal addendum was envisioned. It is also clear from summative data that most of the centres attempting this pathway have largely focused on minor non lung resectional procedures https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0224737 and reference11).

Comment 3:

All of this notwithstanding, I would urge the authors to consider the aphorism "The best is the enemy of the good" contentiously attributed to Voltaire but with echoes from Confucius to Shakespeare!

What is the primary focus of the care pathway? It seems as if it is a. to reduce complications b. to make a distressing procedure such as a surgical operation as close to normal as feasible without compromising assertion a. The authors need to make a more cogent case for their approach based on this basic truth. To cite an example it cannot be anybody's case that chest tube durations exceeded conventional VATS even as the authors admit they wish to improve this metric. Also is a 20% air leak at 5 days acceptable for lung resection? I would urge more clarity in the discussion on these metrics in arguing for wider acceptance of this pathway vs. describing it as a niche pathway that does have a learning curve when successful.

Reply 3:

We thank the reviewer for this encouraging comment on the “basic truth” of our approach. We agree with his philosophical point of view and take the liberty of quoting Hannah

Arendt:**”[…] The law of progress holds that everything now must be better than what was there before. Don’t you see if you want something better, and better, and better, you lose the good. The good is no longer even being measured.”** We apologize in detail if it was unclear what the “basic truth” of our approach was and thank you for this eye-opening comment.
As to Voltaire, we do agree that the best is the enemy of the good. Unfortunately, we did not consider our previous clinical pathway as being anywhere close to ”good”, and wanted to become as “minimally invasive” as possible by tweaking an established but distressing anaesthetic procedure (e.g. invasive monitoring, mechanical ventilation, bladder catheterization). Due to the fact that we present a retrospective data collection and observational study design, a robust comparison between our (new) pathway and other (conventional) approaches would not even be possible.
Minimally invasive surgery such as *uniportal* VATS has seen significant advances in recent years. Hence, there is a paradigm shift in anaesthesia towards more minimally invasive approaches to improve the risk/benefit profile of analgesic and sedative techniques. In our opinion, the move towards “minimally invasive anaesthesia”, e.g. *non-intubated* VATS, parallels similar endeavours in uniportal VATS. The primary focus of our pathway, and thus the “basic truth”, is to avoid mechanical ventilation, invasive blood pressure measurements, central venous lines, monitoring in intensive care units etc. and to implement modern analgesic-sedative concepts like the use of dexmedetomidine combined with (ultrasound-guided) regional anaesthesia. In the long term (of course after completion of the learning curve), the focus is on faster recovery after surgery and less side-effects attributed to general anaesthesia and mechanical ventilation/one-lung ventilation. Two recent meta-analyses by Deng et al. and Tacconi et al. in 2016 suggested that non-intubated VATS procedures can reduce operative morbidity and hospital stay when compared to equivalent procedures performed under general anaesthesia with intubation and one-lung positive pressure ventilation (Deng et al., Tacconi et al. Liu et al.). The non-intubated VATS procedures in these articles utilize sedation or regional anaesthesia to perform these procedures with the avoidance of general anaesthesia.
The aim of our study was to describe our first experience with the presented anaesthetic approach performing non-intubated uniportal VATS in minor and major surgery patients. Moreover, we want to argue for wider acceptance of our analgesic and sedative regime based on dexmedetomidine and regional anaesthesia.

Our comparatively long chest tube duration and the ratio of examined air leaks might be related to the fact that our major resection group included several anatomical resections in lung volume reduction procedures. These are known to be associated with longer chest tube duration and are technically challenging. This notwithstanding, we would like to emphasise the retrospective nature of our collected data. In order to create transparency and for the sake of clarity we will revise the discussion on these metrics in arguing for wider acceptance of this pathway (see above). Conventional VATS under general anaesthesia may have deleterious effects in some patients: need for intubation, diaphragm relaxation, side effects of mechanical ventilation i.e. barotrauma, volutrauma, atelectrauma and proinflammatory mediator release, increasing morbidity and mortality. These facts lead to an initial push in both the surgical and anaesthesiologic community, encouraging non-intubated VATS primarly in minor thoracic procedures. In our study we focus on the anaesthetic pathway and how it affects overall invasiveness in minor but also in major surgery (s. comment/reply 6). We could conclude that the approach is safe and feasible. Nevertheless, there is still room for anaesthetic and surgical improvement. Furthermore, there is a high need for a larger number of prospective randomized studies that specifically compare the non-intubated VATS approach with conventional VATS for surgical treatment of different thoracic diseases.

Generally speaking surgical technique does not differ from uniportal VATS procedures under general anaesthesia, but certainly requires a higher degree of surgical skills (mediastinal movement, diaphragmatic motion, initial cough reflex etc.) and an increased awareness of the patient with "conscious sedation". We believe that upon completion of an initial learning curve, associated metrics like air leaks and chest tube duration will improve. Furthermore, in non-intubated VATS residual air leak is harder to detect than under mechanical ventilation.

Tacconi F, Pompeo E. Non-intubated video-assisted thoracic surgery: where does evidence stand? J Thorac Dis 2016;8:S364-75.

Deng HY, Zhu ZJ, Wang YC, et al. Non-intubated video-assisted thoracoscopic surgery under loco-regional anaesthesia for thoracic surgery: a meta-analysis. Interact Cardiovasc Thorac Surg 2016;23:31-40.

Liu J, Cui F, Pompeo E, et al. The impact of non-intubated versus intubated anaesthesia on early outcomes of video-assisted thoracoscopic anatomical resection in non-small-cell lung cancer: a propensity score matching analysis. Eur J Cardiothorac Surg 2016;50:920-5.

Please find the improvements based on your comments in the revised discussion section.

Changes in the text: (see page 14, line 14)

Minimally invasive surgery such as *uniportal* VATS has seen significant advances in recent years. Hence, there is a paradigm shift in anaesthesia towards more minimally invasive approaches to improve the risk/benefit profile of analgesic and sedative techniques. In our opinion, the move towards "minimally invasive anaesthesia", e.g. *non-intubated* VATS, parallels similar endeavours in uniportal VATS. The primary focus of our pathway is to avoid mechanical ventilation, invasive blood pressure measurements, central venous lines, monitoring in intensive care units etc. and to implement modern analgesic-sedative concepts like the use of dexmedetomidine combined with (ultrasound-guided) regional anaesthesia. In the long term (of course after completion of the learning curve), the focus is on faster recovery after surgery and less side-effects attributed to general anaesthesia and mechanical ventilation/one-lung ventilation. Unfortunately, we wanted to become as "minimally invasive" as possible by tweaking an established but distressing anaesthetic procedure (e.g. invasive monitoring, mechanical ventilation, bladder catheterization). Due to the fact that we present a retrospective data collection and observational study design, a robust comparison between our (new) pathway and other (conventional) approaches would not even be possible.

(see page 15, line 15)

Our comparatively long chest tube duration and the ratio of examined air leaks might be related to the fact that our major resection group included several anatomical resections in lung volume reduction procedures. These are known to be associated with longer chest tube duration and are technically challenging.

Basically, surgical technique does not differ from uniportal VATS procedures under general anaesthesia, but certainly requires a higher degree of surgical skills (mediastinal movement, diaphragmatic motion, initial cough reflex etc.) and an increased awareness of the patient with "conscious sedation". We believe that upon completion of an initial learning curve, associated metrics like air leaks and chest tube duration will improve. Furthermore, in non-intubated VATS residual air leak is harder to detect than under mechanical ventilation.

Comment 4:
I do not agree with the risk categorisation the authors have chosen based on the ARISCAT score or for that matter the LASVEGAS score (which was in part inspired by the former). It is important to point out that the ARISCAT derivation cohort had only 1.4% of its patients undergoing thoracic surgery (Canet et al Anesthesiology 2010; 113:1338 –50). It would not be unreasonable to suggest that a PPC predictor in non thoracic surgery would lend itself comparable to one predicting these for those undergoing thoracic surgery. A priori- the mechanistic components are sufficiently different to suggest this is not so (components of pain, loss of lung volume, pleural space violation etc) and therefore use of either of these metrics seems incorrect. Most perioperative medicine practitioners would make a case for describing postoperative predictive FEV1 and when indicated the PPO DLCO in some patients.

Reply 4:
The overall incidence of PPCs following thoracic surgery varies primarily due to the type of pulmonary complications, the clinical criteria used for PPC definition and the type of surgery (major/minor surgery). Although risk prediction equations for postoperative complications derived from ARSICAT and LASVEGAS score permit general estimates of risk in patients undergoing a variety of surgical procedures, they do not include data from the physical examination or pulmonary function tests, which are also employed by clinicians to assist in risk prediction before thoracic surgery. Furthermore, the ARISCAT/LASVEGAS derivation cohort had only 1.4% / 2.8% of its patients undergoing thoracic surgery. This underrepresented sample can be seen as a limitation using these scores.
However, producing a risk prediction formula for thoracic surgery seems to be difficult. Lung resection procedures and lung manipulations or iatrogenic pneumothorax result in physiology deficit. This deficit is variable according to the extent and duration of the surgical procedure and of course the pre-existing lung function.

We fully agree that the predicted postoperative FEV1 (or even DLCO) would be better for preoperative evaluation and clinical risk assessment, but retrospective data are limited. Predicting postoperative complications in thoracic surgery remains an arduous task, current AACP and ERS/ ESTS guidelines were formulated several years ago and may definitely benefit from an update. Our real-life experience in dealing with high-risk patients in a tertiary setting confronts us daily with people having limited exercise tolerance/ lung volumes and borderline predicted lung function. They present as a very heterogeneous thoracic-surgical population, diverging severity of underlying and secondary diseases, often requiring complex procedures, with an outcome often hard to predict. When we decided to use the present scores, we tried to take into account the results of other, more specific previous studies, combining pulmonary function associated parameters with items such as age, ASA status, BMI, SpO_2, COPD, smoking history, preoperative activity, congestive heart failure, surgery duration, etc., as they are related to occurrence of postoperative pulmonary complications (Smetana et al., Kaufmann et al., Agostini et al.). In addition, definitions of PPC are often not explicit and differ among studies. Thus, we felt compelled to use scores which represent the lowest common denominator for our patient cohort. In our opinion, our risk assessment for minor and major surgery patients based on a score like ARISCAT and LASVEGAS reflects a standardized estimation of the predicted postoperative risk, which can be interpreted by trend. Of course, these scores cannot predict which individual thoracic patient may develop complications.
As mentioned in a detailed review by *Andrew Lumb:"Postoperative pulmonary complications are common, and although many scoring systems exist to quantify PPC risk, there is no*

consensus on the best one to use, and they remain too complex to use clinically. […]" (Miskovic and Lumb).
An alternative and certainly good solution would be the European Society Objective Score (ESOS) applied by *Brunelli*. However, this was tested especially for lobectomy and pneumectomy in neoplasia (Brunelli et al.).

Smetana GW, Lawrence VA, Cornell JE; American College of Physicians. Preoperative pulmonary risk stratification for noncardiothoracic surgery: systematic review for the American College of Physicians. Ann Intern Med. 2006;144(8):581-595. doi:10.7326/0003-4819-144-8-200604180-00009

Kaufmann KB, Loop T, Heinrich S; Working Group of the German Thorax Registry. Risk factors for post-operative pulmonary complications in lung cancer patients after video-assisted thoracoscopic lung resection: Results of the German Thorax Registry. Acta Anaesthesiol Scand. 2019;63(8):1009-1018. doi:10.1111/aas.13388

Agostini P, Cieslik H, Rathinam S, et al. Postoperative pulmonary complications following thoracic surgery: are there any modifiable risk factors?. Thorax. 2010;65(9):815-818. doi:10.1136/thx.2009.123083

Miskovic A, Lumb AB. Postoperative pulmonary complications. Br J Anaesth. 2017;118(3):317-334. doi:10.1093/bja/aex002

Brunelli A, Varela G, Van Schil P, et al. Multicentric analysis of performance after major lung resections by using the European Society Objective Score (ESOS). Eur J Cardiothorac Surg. 2008;33(2):284-288. doi:10.1016/j.ejcts.2007.10.027

We would suggest pointing out critically the assessment of PPCs based on ARISCAT and LASVEAGS in the revised discussion section. Furthermore, we will delete LASVEGAS in part from the revised manuscript. Nevertheless, we thank the reviewer for this debate on risk assessment and hope that we could satisfy the reviewer.

Changes in the text: (see page 18, line 11)
The overall incidence of PPCs following thoracic surgery varies primarily due to the type of pulmonary complications, the clinical criteria used for PPC definition and the type of surgery (major/minor surgery).

(see page 19, line 5)
Although risk prediction equations for postoperative postoperative complications derived from ARSICAT and LASVEGAS score permit general estimates of risk in patients undergoing a variety of surgical procedures, they do not include data from the physical examination or pulmonary function tests, which are also employed by clinicians to assist in risk prediction before thoracic surgery. Furthermore, the ARISCAT/LASVEGAS derivation cohort had only 1.4% / 2.8% of its patients undergoing thoracic surgery. This underrepresented sample can be seen as a limitation using these scores.
However, producing a risk prediction formula for thoracic surgeries seems to be difficult. Lung resection procedures and lung manipulations or iatrogenic pneumothorax result in physiology deficit. This deficit is variable according to the extent and duration of the surgical procedure and of course the pre-existing lung function.

Predicted postoperative FEV1 (or even DLCO) would be better for preoperative evaluation and clinical risk assessment, but retrospective data are limited. Predicting postoperative complications in thoracic surgery remains an arduous task. Examined patients presented as a very heterogeneous thoracic-surgical population, diverging severity of underlying and secondary diseases, often requiring complex procedures, with an outcome often hard to predict. When we decided to use the present scores, we tried to take into account the results of other, more specific previous studies, combining pulmonary function associated parameters with items such as age, ASA status, BMI, SpO_2, COPD, smoking history, preoperative activity, congestive heart failure, surgery duration, etc., as they are related to occurrence of postoperative pulmonary complications (Smetana et al., Kaufmann et al., Agostini et al.). In addition, definitions of PPC are often not explicit and differ among studies. Thus, we felt compelled to use scores which represent the lowest common denominator for our patient cohort. In our opinion, our risk assessment for minor and major surgery patients based on a score like ARISCAT and LASVEGAS reflects a standardized estimation of the predicted postoperative risk, which can be interpreted by trend. Of course, these scores cannot predict which individual thoracic patient may develop complications.
As there is no consensus on the best PPC score to use, an alternative and certainly good solution would be the European Society Objective Score (ESOS) applied by *Brunelli*. However, this was tested especially for lobectomy and pneumectomy in neoplasia (Brunelli et al.).

Smetana GW, Lawrence VA, Cornell JE; American College of Physicians. Preoperative pulmonary risk stratification for noncardiothoracic surgery: systematic review for the American College of Physicians. Ann Intern Med. 2006;144(8):581-595. doi:10.7326/0003-4819-144-8-200604180-00009

Kaufmann KB, Loop T, Heinrich S; Working Group of the German Thorax Registry. Risk factors for post-operative pulmonary complications in lung cancer patients after video-assisted thoracoscopic lung resection: Results of the German Thorax Registry. Acta Anaesthesiol Scand. 2019;63(8):1009-1018. doi:10.1111/aas.13388

Agostini P, Cieslik H, Rathinam S, et al. Postoperative pulmonary complications following thoracic surgery: are there any modifiable risk factors?. Thorax. 2010;65(9):815-818. doi:10.1136/thx.2009.123083

Miskovic A, Lumb AB. Postoperative pulmonary complications. Br J Anaesth. 2017;118(3):317-334. doi:10.1093/bja/aex002

Brunelli A, Varela G, Van Schil P, et al. Multicentric analysis of performance after major lung resections by using the European Society Objective Score (ESOS). Eur J Cardiothorac Surg. 2008;33(2):284-288. doi:10.1016/j.ejcts.2007.10.027

Comment 5:
(a) At first sight, the absolute numbers in this patient cohort suggest these patients to be low risk for postoperative complications if one casts aside the use of the ARISCAT/ LASVEGAS paradigm that I would suggest is needed.
(b) If they were indeed such low risk then I don't think the research methods of the paper adequately show that others in the larger world need to adapt this clinical care pathway for this risk cohort- I think this needs to be clearly fleshed out in the discussion in the limitations section

Reply 5:
(a) We thank the reviewer for this comment and would like to refer to reply 4 (see above). We have made appropriate changes in the revised manuscript. Indeed, this can be seen as a limitation (see reply 8).
(b) Nevertheless, irrespective of patients risk classification, previous data supported important clinical advantages to the patients. A small number of randomized controlled trials (Pompeo et al. Liu et al.) and two recent meta-analyses (Tacconi et al., Deng et al.) have shown that niVATS can be associated with some advantages over an intubated technique and may be a beneficial alternative. In particular, these meta-analyses show a reduction in operating room time, a reduction in hospital length of stay and a decrease in perioperative complications (Tacconi et al., Deng et al.). In the largest RCT to date by Liu et al., postoperative morbidity was lower in the non-intubated group at 6.7% vs. 16.7% in the intubated group (P=0.004). In particular, respiratory complications were reduced from 10% to 4.2% (P=0.039) (Liu et al.). Other benefits have been shown including shortened recovery (Pompeo et al.) and faster return to oral intake (Liu et al.). Moreover, studies have also reported improved patient satisfaction with a non-intubated VATS approach (Pompeo et al.).
In our opinion, it cannot be deemed appropriate to make these advantages available to all patients. So, we would argue for wider acceptance of niVATS approaches and adoption of our/any analgesic-sedative approach (see above).

Pompeo E, Mineo D, Rogliani P, et al. Feasibility and Results of Awake Thoracoscopic Resection of Solitary Pulmonary Nodules. Ann Thorac Surg 2004;78:1761-8.

Pompeo E, Tacconi F, Mineo D, et al. The role of awake video-assisted thoracoscopic surgery in spontaneous pneumothorax. J Thorac Cardiovasc Surg 2007;133:786-90.

Pompeo E, Rogliani P, Tacconi F, et al. Randomized comparison of awake nonresectional versus nonawake resectional lung volume reduction surgery. J Thorac Cardiovasc Surg 2012;143:47-54.

Pompeo E, Dauri M. Awake Thoracic Surgery Research Group. Is there any benefit in using awake anesthesia with thoracic epidural in thoracoscopic talc pleurodesis? J Thorac Cardiovasc Surg 2013;146:495-7.

Liu J, Cui F, Li S, et al. Nonintubated Video-Assisted Thoracoscopic Surgery Under Epidural Anesthesia Compared With Conventional Anesthetic Option: A Randomized Control Study. Surg Innov 2015;22:123-30.

Tacconi F, Pompeo E. Non-intubated video-assisted thoracic surgery: where does evidence stand? J Thorac Dis 2016;8:S364-75.

Deng HY, Zhu ZJ, Wang YC, et al. Non-intubated video-assisted thoracoscopic surgery under loco-regional anaesthesia for thoracic surgery: a meta-analysis. Interact Cardiovasc Thorac Surg 2016;23:31-40.

We thank the reviewer for this comment and would like to refer to reply 3 and 4 (see above). We have made appropriate changes in the revised manuscript.

Changes in the text: (see page 20, line 18)

Irrespective of patients risk classification previous data supported important clinical advantages to the patients. A small number of randomized controlled trials (Pompeo et al. Liu et al.) and two recent meta-analyses (Tacconi et al., Deng et al.) have shown that niVATS can be associated with some advantages over an intubated technique and may be a beneficial alternative. In particular, these meta-analyses show a reduction in operating room time, a reduction in hospital length of stay and a decrease in perioperative complications (Tacconi et al., Deng et al.). In the largest RCT to date by Liu et al., postoperative morbidity was significantly lower in the non-intubated group (p=0.004). In particular, respiratory complications were reduced from 10% to 4.2% (p=0.039) (Liu et al.). Other benefits have been shown including shortened recovery (Pompeo et al.) and faster return to oral intake (Liu et al.). Moreover, studies have also reported improved patient satisfaction with a non-intubated VATS approach (Pompeo et al.).

In our opinion, it cannot be deemed appropriate to make these advantages available to all patients. So, we would argue for wider acceptance of niVATS approaches and adoption of our/any analgesic-sedative approach.

Comment 6:

I would suggest the comparison between minor and major procedures infructuous- most practitioners would agree that the real dynamic in complications in thoracic surgery correlate to the presence and extent of lung resection playing on baseline respiratory status. I would therefore recommend separate descriptions of these two distinct groups without an attempt to compare them as I believe they are essentially incomparable and add no value to the authors' description of this pathway, in any case. This of course, extends to comparisons beyond outcomes to metrics such as fluid administration (intrinsically linked to duration and extent of procedure) and catecholamine use.

Reply 6:

We fully agree with you that these two groups are very difficult to compare due to heterogeneous patient cohorts with both different underlying diseases and pathologies and surgical procedures (minor/major surgery). Perhaps we can convince you, or at least explain to you why we would like to try anyway:

(1) The application of our departmental anaesthetic pathway represents one “intervention”. The surgical procedure, i.e. minor or major thoracic surgery represents a main characteristic allowing the reader to differentiate between two surgical groups. Of course, numerous metrics (e.g. fluid administration etc) differed between groups because they are intrinsically linked to duration and extent of the procedure (see Table 2-4). We lack for a real control group, but already emphasised that this is a retrospective observational study (see limitation section). Thus, the comparison focuses on the feasibility and practicability of our anaesthetic approach in terms of two different surgical procedures.

(2) You made mention of the fact that non-intubated VATS is often only used for minor surgery (see introduction of your review:*[...] that most of the centres attempting this pathway have largely focused on minor non lung resectional procedures. […]”*). This is absolutely true, and only a very limited amount of publications report larger cohorts of major resections, most of them stemming from Jin-Shing Chen´s group. While minor niVATS procedures can nowadays be considered standard of care in dedicated units, the same is not true for major resections. These facts prompted us to present our personal experience in a European tertiary care centre.

In our study we focus on the anaesthetic pathway and its transformation to non-invasiveness in minor but also in major surgery (s. comment/reply 6). We would like to describe that this anaesthetic pathway, using a standardised protocol, is equally suitable for major surgery. We concluded that the approach is safe and feasible both in minor and major surgery.
Nevertheless, there is still room for anaesthetic and surgical improvement. Furthermore, there is a high need for a larger number of prospective randomized studies that specifically compare the non-intubated VATS approach with conventional VATS for the surgical treatment of different thoracic diseases.

In the revised manuscript we will point out this issue (see revised discussion section/limitation).

Changes in the text: (see page 21, line 8)
These two groups are very difficult to compare due to heterogeneous patient cohort with both different underlying diseases and pathologies and surgical procedures (minor/major surgery). The application of our departmental anaesthetic pathway represents one "intervention". The surgical procedure, i.e. minor or major thoracic surgery represents a main characteristic allowing the reader to differentiate between two surgical groups. Of course, numerous metrics (e.g. fluid administration etc) differed between groups because they are intrinsically linked to duration and extent of the procedure. Thus, the comparison focuses on the feasibility and practicability of our anaesthetic approach in terms of two different surgical procedures.
Furthermore, in previous studies most of the centres attempting this pathway have largely focused on minor non lung resectional procedures. Only a very limited amount of publications report larger cohorts of major resections, most of them stemming from Jin-Shing Chen´s group. While minor niVATS procedures can nowadays be considered standard of care in dedicated units, the same is not true for major resections. These facts prompted us to present our personal experience in a European tertiary care centre.
Conventional VATS under general anaesthesia may have deleterious effects in some patients: side-effects of analgesics, need for intubation, diaphragm relaxation, side effects of mechanical ventilation i.e. barotrauma, volutrauma, atelectrauma and proinflammatory mediator release, increasing morbidity and mortality. These facts lead to an initial push in both the surgical and anaesthesiologic community, encouraging non-intubated VATS primarly in minor thoracic procedures. In our study we focus on the anaesthetic pathway and its transformation to non-invasiveness in minor but also in major surgery. We would like to describe that this anaesthetic pathway, using a standardised protocol, is equally suitable for major surgery. We concluded that the approach is safe and feasible both in minor and major surgery.
Nevertheless, there is still room for anaesthetic and surgical improvement. Furthermore, there is a high need for a larger number of prospective randomized studies that specifically compare the non-intubated VATS approach with conventional VATS for the surgical treatment of different thoracic diseases.

Comment 7:
Were other parameters causing switch to intubated VATS such as excessive mediastinal movement (Chen et al J Thorac Dis 2014 ;4:347) less in this experience? I think a comparison of the authors' experience to those from Taiwan and from Spain expressed graphically in terms of outcomes would greatly add to this paper and make the larger case for adoption easier to assess for others.

Reply 7:
We have included the exact reasons with their respective numbers in the discussion and also made a comparison with previous data from Spain and Taiwan.

Changes in the text: (see page 13, line 25)
Our overall conversion rate to orotracheal intubation was 6.8% and did not differ significantly between both groups, which is in line with data published by other groups who reported conversion rates between 2-10% depending on the experience of the centre and the extent of the intervention (minor vs. major surgery) (Gonzales-Rivas et al.). Reasons for conversion were excessive breathing excursions (n=3), exceedingly long operating time (n=2) and intraoperative seizure (n=1), which mirrors previously published data (Gonzales-Rivas et al., Chen et al., Wang et al.).

Gonzalez-Rivas D, Bonome C, Fieira E, et al. Non-intubated video-assisted thoracoscopic lung resections: the future of thoracic surgery? Eur J Cardiothorac Surg 2016;49(3):721-31.

Chen KC, Cheng YJ, Hung MH, et al. Nonintubated thoracoscopic surgery using regional anesthesia and vagal block and targeted sedation. J Thorac Dis 2014;6(1):31-6.

Wang ML, Galvez C, Chen JS, et al. Non-intubated single-incision video-assisted thoracic surgery: a two-center cohort of 188 patients. J Thorac Dis. 2017;9(8):2587-2598. doi:10.21037/jtd.2017.08.96

Comment 8:
Lastly, I would argue for a clear disclaimer that this was a low risk cohort and a real comparison with well conducted intubated VATS in the form of a trial alone can address the question as to whether other operating groups should strive to adopt non intubated VATS.

Reply 8:

Please see reply on comment 4.
As described above, we will adjust the risk classifications, and we will now explicitly point out in the discussion which limitations result from the observational design. In addition, we will mention again that a large proportion of patients do not belong to the high-risk group.
Finally, we would like to point out once again that we were not interested in employing our algorithm in place of other algorithms that already work. Rather, we want to underline that this procedure can be used for minor as well as major surgery. This is even true when this approach lacks invasive forms of monitoring and intensive care monitoring. Of course, it is our firm conviction that other approaches work at least as well with other analgesia and sedation concepts.

Changes in the text: (see page 22, line 18)
Even though the PPC prediction scores predicted moderate to high risk of pulmonary complications after surgery in some patients, a large proportion of patients do not belong to the high-risk group from a clinical point of view.

(see page 23, line 10)
[…] Randomised controlled trials comparing the presented approach with conventional approaches focusing on patient-centred outcome parameters are necessary in future.