Letter to the Editor

Response to "VATS *vs.* thoracotomy regarding postoperative chronic pain"

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The first point made by the commentary was related with "The definition of the primary endpoint (chronic pain after 6 months in relation to what?)". The International Association for the Study of Pain (1) defines chronic postsurgical pain as pain persisting at least 3 months after surgery. The primary outcome variable of our study was chronic pain related to thoracic surgery (yes/no) at 6 months after surgery, based on the following question: "Do you currently have pain related to your thoracic surgery?" Those patients with chronic pain related to thoracic surgery at 6 months after surgery were compared to those patients without such pain at that time.

The second comment was the operative procedures and the indication for the operations not being well defined. Type of surgery (thoracotomy *vs.* VATS) and procedure types [lobectomy, wedge resection, pneumonectomy, biopsy/resection of lung nodule(s) or infiltrate or other] were presented on Table 3 (2).

We agree that the underlying disease may have an influence on the acute pain. The reference (3) the commentary included measured pain on the second post-operative day, not chronic pain. The literature is mixed for the chronic pain rates after thoracotomy *vs.* VATS. Data for the chronic pain rates for VATS patients is small. Thus far, the data indicate that VATS and thoracotomy have similar rates of chronic pain (1,4-8).

The comment of "11 out of 30 patients in the thoracotomy group were converted from initially scheduled VATS operations. A high rate of VATS conversion could be an extra limitation of the study depicting unexpected tumor burden or inadequate experience with VATS techniques for major anatomical lung resections" is not correctly interpreting our study. We stated in our publication that "Eleven VATS patients had a thoracic epidural catheter placed. The surgeons requested epidural analgesia preoperatively for these 11 VATS patients anticipating a significant likelihood of progressing to open thoracotomy."

Incision size for thoracotomy patients was already provided in Table 3. VATS resections were usually completed with 2–3 incisions including a small access incision (4 cm). For VATS resections, a rib retractor was not used. Since we wanted our results to be generalizable to all thoracic surgery patients, we did not exclude any patient because of different techniques or approaches. Surgeons performed their usual care. Again, different approaches for thoracic surgery may be associated with acute postoperative pain, but we are not aware of their effect of chronic pain.

We agree with the point that in an ideal situation, to compare the chronic pain rates after thoracotomy *vs.* VATS, a large number of thoracic surgery patients should be randomized to thoracotomy *vs.* VATS regardless of the underlying disease. However, based on the patient and disease characteristics, some thoracotomy patients cannot be a candidate for VATS and, similarly, some patients

can be operated minimally with VATS, instead of open thoracotomy. Therefore, a randomized clinical trial of thoracotomy *vs.* VATS may not be possible or ethical for all patients undergoing thoracic surgery. As the very first item of our Study Limitations, we already indicated that this is an observational study, not a randomized clinical trial with equal number of patients in each of the surgery types. Bendixen *et al.*'s study is a very good study and its limitation is generalizability. We have noted our limitations in the paper (2) as has this correspondence.

For the point on the sample size of the study; the primary outcome variable of our study was pre-determined at the time of our grant submission (NIH, NINDS, NS080110-01A1) as the presence of chronic pain (yes/no) at 6 months after thoracic surgery. Based on our results, 33% of the 30 patients had chronic pain at 6 months after thoracotomy compared to 25% of the 69 VATS patients. We agree with authors that the power of our study is low to compare these two incidence rates. We do not think 33% *vs.* 25% incidence is a clinically meaningful difference yet. To compare 33% *vs.* 25% incidence rate at 6 months with 90% power where 70% of the patients had VATS, we need to enroll 1,104 VATS patients and 480 thoracotomy patients. If we could enroll an equal number of thoracotomy *vs.* VATS patients, then 1,350 patients would need to be enrolled and assessed at 6 months to reach 90% power. We do not believe that such study is easily attainable.

Finally, we are not suggesting that the chronic pain rates after thoracotomy and VATS are different. We are presenting the results from our data based on 99 patients that the observed incidences of chronic pain at 3 and 6 months were not statistically different. Altogether, the overall result of our study was that preoperative psychosocial factors were not predictive of developing chronic pain 6 months after thoracic surgery. The comparison of chronic pain rates between VATS and thoracotomy was not our primary result.

A statement was made that the numerical rating scale (NRS) was used for the preoperative pain assessment and cited the Rothaug *et al.* (9) study. Rothaug *et al.* (9) compared measuring post-operative pain with a binary response (yes/no) *vs.* with a NRS (0–10) after abdominal, orthopedic/trauma and oromaxillofacial surgery. Rothaug *et al.* concluded that measuring postoperative pain with the binary items had similar test-retest reliability, validity and lower internal consistency compared to NRS scale. They did not show that the binary response is better than the NRS scale. Therefore, we do not see any problem measuring the preoperative pain with the NRS scale in our study. We searched the Rothaug *et al.*'s methodological study for a statement regarding the inclusion of chronic pain patients in an observational chronic pain study, and could not find such statement. We are not sure why their study was referenced with such statement.

We disagree with the comment regarding the exclusion of patients with chronic pain in the chest area and including chronic pain in other body locations since those patients with pre-existing pain in other body locations may be an at risk group. The IMMPACT group recommended excluding pre-existing chronic pain patients with the similar chronic pain conditions (excluding those patients with back pain for a study on chronic pain after back pain surgery); however, including patients with burning pain in the feet from DPN to be included for a study assessing chronic pain after thoracic surgery (10). Therefore, excluding those patients with chronic pain in the chest area and including other pre-existing pain conditions is in line with the IMMPACT group's recommendation.

Bendixen *et al.* randomized lobectomy patients to thoracotomy *vs.* VATS and followed them up until 52 weeks after surgery (11). Results regarding patients with *moderate to severe post-operative pain* during 52 weeks follow-up were presented in their Figure 2. Bendixen *et al.* provided the p-value for the longitudinal assessment of pain from day 1 to week 52. In fact, when only results from 6 month (26 weeks) were assessed based on data from their Figure 2, the results of our study have some consistencies with Bendixen *et al.*'s findings. Based on their results, 7.5% (6 out of 80) of VATS patients developed moderate to severe (NRS ≥3) chronic pain at 6 months, compared to 11% (8 out of 74) of anterolateral thoracotomy patients (P value: 0.58). There are two major differences. First, given their strict inclusion criteria, the study from Bendixen *et al.* may not be generalizable to all thoracic surgery patients, but only to those patients eligible for anterolateral thoracotomy. Second, their pain assessment of moderate to severe post-operative pain (*NRS ≥3*) at 26 weeks *vs.* our assessment of *any pain* make it difficult to compare our group of patients and results to Bendixen. In addition, our result of not finding difference on chronic pain rates after thoracotomy *vs.* VATS is in line with the other previous publications (4-7).

We agree with the commentary regarding different postoperative pain management for thoracotomy *vs.* VATS patients. We have already indicated this as our second limitation (2). However, this is our usual care. Furthermore, it should be speculative to assume mode of acute pain

management affects the development of chronic pain.

In our study (2), to measure the severity of acute pain, patients were specifically asked to rate their pain during the previous 24 hours using NRS (0–10). Bendixen *et al.* (11) asked patients to rate their pain 6 times a day during the hospitalization. It is not clear how they used this data. It is implied that they used *current pain vs.* we assessed *average pain during the last 24 hours*. In addition, Bendixen *et al.* presented results for moderate to severe acute pain in their Figure 2 *vs.* we presented severity of pain on the continuous scale (NRS, 0–10). These differences preclude directly comparing results. Rizk *et al.* (7) used brief pain index on the 1 to 7 scale. According to their Figure 2, pain scores on days 2, 3, and 4 are around 5.5, 5.2, and 5.0 out of 7, respectively. Therefore, our acute postoperative pain scores are consistent with Rizk *et al.*'s results. All our study patients had access to opioids in addition to the regional technique.

The reason we conducted the study was to assess for any patient undergoing thoracic surgery, whether preoperative evaluations could predict those patients with high likelihood of developing chronic pain. The answer based on our 99 patients followed for 6 months is no. Preoperative biopsychosocial factors and quantitative sensory testing were not predictive.

There is little data to support that treatment of acute pain influences the development of chronic pain; rather, the literature agrees of higher acute pain being associated with the development of chronic pain. The correspondence assumes acute treatment influencing the development of chronic pain. However, high acute pain may be a marker for chronic pain.

See our answer above regarding the well powered randomized trial. The patient population candidate for either thoracotomy or VATS with equipoise is quite limited.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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