Critical Review

Incidence and Severity of Chronic Pain at 3 and 6 Months After Thoracotomy: Meta-Analysis

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Abstract: This systematic review was performed to determine the incidence and the severity of chronic pain at 3 and 6 months after thoracotomy based on meta-analyses. We conducted MEDLINE, Web of Science, and Google Scholar searches of databases and references for English articles; 858 articles were reviewed. Meta-regression analysis based on the publication year was used to examine if the chronic pain rates changed over time. Event rates and confidence intervals with random effect models and Freeman-Tukey double arcsine variance-stabilizing transformation were obtained separately for the incidence of chronic pain based on 1,439 patients from 17 studies at 3 months and 1,354 patients from 15 studies at 6 months. The incidences of chronic pain at 3 and 6 months after thoracotomy were 57% (95% confidence interval [CI], 51–64%) and 47% (95% CI, 39–56%), respectively. The average severity of pain ratings on a 0 to 100 scale at these times were 30 ± 2 (95% CI, 26–35) and 32 ± 7 (95% CI, 17–46), respectively. Reported chronic pain rates have been largely stable at both 3 and 6 months from the 1990s to the present.

Perspective: This systematic review’s findings suggest that reported chronic pain rates are approximately 50% at 3 and 6 months and have been largely stable from the 1990s to the present. The severity of this pain is not consistently reported. Chronic pain after thoracotomy continues to be a significant problem despite advancing perioperative care.

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Key words: Chronic pain, thoracotomy, thoracic surgery, meta-analysis, incidence.

In the United States, more than 40,000 thoracic surgeries are performed per year. The incidence of chronic pain after thoracotomy or video-assisted thoracoscopy (VATS) is reported to be between 20% and 80%. The wide range of estimates for chronic pain after thoracic surgery is likely due to differences in definitions and the time of postoperative follow-up. Results are also possibly deviated by recall bias, as most analyses are based on retrospective studies.

For more than 20 years, investigators have reported the incidence of postthoracotomy pain syndrome in both observational studies and trials in order to prevent its development. In general, however, attempts to prevent the development of postthoracotomy pain syndrome have yielded inconsistent results. In this systematic review, separate meta-analyses were performed on prospective studies to find incidences of chronic pain at 3 and 6 months after thoracotomy. We explored whether the incidence of chronic postthoracotomy pain syndrome has or has not changed greatly over time. In addition, the severity of pain at 3 and 6 months after thoracotomy is systematically reviewed and summarized. The primary outcomes of the study are incidence of pain at 3 and 6 months after thoracotomy. Secondary outcomes included changes over time and the severity of pain.

Methods

Literature Review

To estimate the population incidence of chronic pain and to estimate the severity of the pain at 3 and 6 months after thoracic surgery among those patients with pain, 2 separate systematic reviews were performed after a...
single literature search. A MEDLINE (PubMed) search was performed on September 13, 2012, and on February 19, 2014, the MEDLINE search was updated for new references and the Web of Science and Google Scholar searches were performed. The exact search terms used were “(thoracotomy OR video-assisted thoracoscopic surgery)” AND “(postoperative pain OR pain measurement)” in All Fields, and “limits” (under “publication types”) were used to exclude review articles, meta-analyses, case reports, commentaries, editorials, letter to the editor, and systematic reviews for MEDLINE search. Limits were also used to select English articles on human-only studies and adults (≥19 years). The title and abstract were reviewed, and, if needed, the whole article was reviewed by both authors independently. To prevent recall bias of patients’ pain rating, only studies with prospective pain assessments at 3 and/or 6 months were included. Those studies regarding thoracic surgery that was not for lung cancer (eg, open heart surgery) were excluded. Finally, studies that considered only acute pain and studies that did not provide the incidence or severity of chronic pain specifically at either 3 or 6 months were excluded.

Our initial interest was to examine the incidence and severity of chronic pain for both thoracotomy and VATS. However, data for only 1 study at 3 months (n = 7, VATS) and 2 studies at 6 months (n = 7, VATS and n = 49, VATS) fit our inclusion criteria and reported results for VATS for the initial MEDLINE search. Therefore, results for patients only undergoing thoracotomy are provided.

**Data Extraction and Outcomes**

Both authors independently extracted the information regarding the sample size at baseline and at the time of follow-up assessment for pain (3 or 6 months). For the incidence of pain, only those studies that examined the presence of pain (yes/no) were included, and the number of subjects with chronic pain was recorded. For the severity of pain, those studies that provided the mean or median pain severity were included whether the severity was reported using the numerical rating scale (NRS, 0–10 or 0–100), the visual analog scale (0–10 or 0–100), the verbal rating scale, the Brief Pain Inventory, or the pain subscale of SF-36 (the short-form health survey with 36 questions). It was also noted whether the authors reported current, average, or worst pain. For those severity assessments that used a 0 to 10 scale, results were converted to a 0 to 100 scale, where 0 indicates no pain and 100 indicates the worst pain imaginable. We recorded whether severity assessment was from those patients with or without pain or if this information was not provided. The authors of the included studies were contacted to clarify in the event any of this information was not clear or was not reported but available.

The primary endpoints were 1) having thoracotomy-related pain (yes/no) and 2) the severity of pain (0–100) at 3 or 6 months after thoracotomy. The incidence and severity of pain were calculated by combining results from all intervention groups from each study, when applicable. This systematic review is conducted and reported according to the PRISMA Checklist 2009.34

**Statistical Methods for Incidence of Pain**

It was assumed that one patient's chance of developing chronic pain is independent of another patient's chance. The majority of papers in the literature were derived from clinical trials aimed to prevent chronic postthoracotomy pain syndrome; however, no pre- or intraoperative treatment has consistently demonstrated that any therapeutic treatment reduces the incidence of chronic postthoracotomy pain syndrome.58 Therefore, it was assumed that out of those patients who underwent thoracotomy, the observed number of patients who develop chronic postthoracotomy pain has a binomial distribution.

The pooled incidence assessments were analyzed using the DerSimonian and Laird method of moments assuming random effects and binomial rate. Two-sided 95% confidence intervals (CIs) are provided for random effects models. As a sensitivity analysis, as recommended by Trinquart,52 random effects models and associated 95% CIs for the incidences with the Freeman-Tukey double arcsine variance-stabilizing transformation10 are also provided. The 95% CI excluding zero indicates a statistically significant overall result. Forest plots for actual and back-transformed incidence rates are presented. Q-test statistics were used to test whether the incidence rate at 3 months after thoracotomy is different from the incidence rate at 6 months.

Systematic reviews of the literature using meta-analysis address a common question with different designs, patient groups, and interventions.18 Such variation in outcomes among studies is called heterogeneity. The presence of heterogeneity was tested formally by the Cochran's Q statistic, which is a measure of squared deviances. In addition, I² values are provided to quantify the degree of heterogeneity for both actual incidence rates and the Freeman-Tukey transformed incidence rates as described by Naguib.36 I² is reported on a scale between 0 and 100%.18 I² of 25%, 50%, and 75% can be interpreted as low, moderate, and high heterogeneity, respectively.18 I² of near 100% implies that most of the observed variance is real.2 For data with high heterogeneity (I² > 75), random effects model results are presented.

To examine if the chronic pain rates were changed over time, random effects model meta-regression analyses were performed using the publication year as a predictor of the incidence of chronic pain. Regression coefficients and P values associated with the year of publication were provided as statistical tests for meta-regression analyses. Meta-regression plots were also provided. When random effects models were used, because of the high heterogeneity among studies, study weights become close to equal weighting.

Some of the reviewed articles were from interventional trials to prevent the development of chronic pain after thoracotomy, and some others were observational studies reporting the incidence rates. Although most trials have not reduced postthoracotomy pain syndrome, it was possible that an intervention reduced the incidence of chronic postthoracotomy pain...
and influenced the incidence we report. Therefore, analyses were repeated only in observational studies and in the placebo or control groups.

The upper 95% confidence bound for the binomial proportion was calculated based on the Clopper-Pearson interval, which uses an exact method and is conservative.

**Statistical Analysis for the Severity of Pain**

In addition to the incidence, it is also important to know the severity of pain after surgery, which is recommended by both the IMMPACT group and VanDenKerkhof et al as one of the core outcome measures in chronic pain studies. For this reason, same articles were systematically reviewed to determine if the severity of pain at 3 and/or 6 months was provided.

The pooled average of severity (0–100) of postthoracotomy pain were analyzed using the DerSimonian and Laird method of moments assuming random effects, effect measure of mean, and unequal within-study variance. Upper and lower 95% confidence limits were provided for random effects models. Forest plots of means were presented.

Statistical analyses were performed using Comprehensive Meta-Analysis (version 2.2.050; Biostat, Engelwood, NJ). Freeman-Tukey double-arcsine transformation was implemented using “metafor” package in R version 2.15.2. Forest plots were obtained from Meta-Analyst (Beta 3.13) software. Meta-regression plots were created using SigmaPlot (version 12.5; Systat Software, San Jose, CA).

### Results

The MEDLINE, Web of Science, and Google Scholar searches provided a total of 858 articles. Queries on 4 of 858 articles to be included on the final list of studies were resolved by discussions between the 2 authors. References of included articles were also searched, but no other study satisfied our inclusion criteria for incidence.

#### Incidence of Chronic Pain at 3 and 6 Months After Thoracotomy

We retrieved 858 reports to assess the incidence, and 836 of those were excluded for various reasons (Supplementary Fig 1), including duplicate data presentation and pain assessments not specifically at 3 or 6 months (Supplementary Table 1). As a result, 22 studies were used for the incidence of chronic pain at 3 and/or 6 months after thoracotomy (Supplementary Table 2). Ten of these studies reported incidences at both 3 and 6 months, whereas 7 studies were used only for 3-month pain, and 5 studies were used only for 6-month pain.

#### Incidence of Chronic Pain at 3 Months After Thoracotomy

The incidence of chronic pain at 3 months after thoracotomy ranges between 31% and 96% (Table 1). Based on 1,439 patients from 17 studies, the overall incidence of chronic pain with the random effects model at 3 months after thoracotomy is 57%.

### Table 1. Patient and Outcome Data for Incidence of Chronic Pain at 3 and 6 Months After Thoracotomy

<table>
<thead>
<tr>
<th>Source, Year</th>
<th>Patients Followed Up (n)</th>
<th>Patients With Chronic Pain (n)</th>
<th>Incidence Rate</th>
<th>Patients Followed Up (n)</th>
<th>Patients With Chronic Pain (n)</th>
<th>Incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miguel, 1993</td>
<td>33</td>
<td>16</td>
<td>48%</td>
<td>75</td>
<td>56</td>
<td>75%</td>
</tr>
<tr>
<td>Perttunen, 1999</td>
<td>84</td>
<td>67</td>
<td>80%</td>
<td>58</td>
<td>29</td>
<td>50%</td>
</tr>
<tr>
<td>Obata, 1999</td>
<td>58</td>
<td>37</td>
<td>64%</td>
<td>69</td>
<td>43</td>
<td>62%</td>
</tr>
<tr>
<td>Sennuk, 2002</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Tiippana, 2003</td>
<td>87</td>
<td>52</td>
<td>60%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Giwak, 2004</td>
<td>50</td>
<td>32</td>
<td>64%</td>
<td>50</td>
<td>18</td>
<td>36%</td>
</tr>
<tr>
<td>Yang, 2004</td>
<td>80</td>
<td>36</td>
<td>45%</td>
<td>80</td>
<td>28</td>
<td>35%</td>
</tr>
<tr>
<td>Maguire, 2006</td>
<td>31</td>
<td>16</td>
<td>52%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Suzuki, 2006</td>
<td>44</td>
<td>21</td>
<td>48%</td>
<td>44</td>
<td>17</td>
<td>39%</td>
</tr>
<tr>
<td>Gottschalk, 2008</td>
<td>112</td>
<td>51</td>
<td>46%</td>
<td>103</td>
<td>36</td>
<td>35%</td>
</tr>
<tr>
<td>Ju, 2008</td>
<td>98</td>
<td>64</td>
<td>65%</td>
<td>91</td>
<td>57</td>
<td>63%</td>
</tr>
<tr>
<td>Katz, 2009</td>
<td>47</td>
<td>32</td>
<td>68%</td>
<td>47</td>
<td>38</td>
<td>81%</td>
</tr>
<tr>
<td>Handy, 2010</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>192</td>
<td>56</td>
<td>29%</td>
</tr>
<tr>
<td>Salengros, 2010</td>
<td>38</td>
<td>20</td>
<td>53%</td>
<td>38</td>
<td>21</td>
<td>55%</td>
</tr>
<tr>
<td>Guastella, 2011</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>47</td>
<td>38</td>
<td>81%</td>
</tr>
<tr>
<td>Ryu, 2011</td>
<td>133</td>
<td>62</td>
<td>47%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Miyazaki, 2011</td>
<td>25</td>
<td>17</td>
<td>68%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Song, 2012</td>
<td>343</td>
<td>162</td>
<td>47%</td>
<td>343</td>
<td>144</td>
<td>42%</td>
</tr>
<tr>
<td>Mendola, 2012</td>
<td>61</td>
<td>19</td>
<td>31%</td>
<td>57</td>
<td>13</td>
<td>23%</td>
</tr>
<tr>
<td>Kinney, 2012</td>
<td>110</td>
<td>75</td>
<td>68%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Kampe, 2013</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>60</td>
<td>14</td>
<td>23%</td>
</tr>
<tr>
<td>Pu, 2013</td>
<td>52</td>
<td>50</td>
<td>96%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
There is evidence of large heterogeneity among the studies (I² is 82%, Q = 86.8 [df = 16], P value < .001). When the Freeman-Tukey double arcsine transformation is used before combining the proportions and back-transformed to the original scale after fitting the model, results are almost identical: incidence 58% (95% CI: 50–67%), I² = 89%, Q = 132.6 (df = 16), P < .0001. The forest plot of the actual incidences (Fig 1) is almost identical to the forest plot of the back-transformed incidences.

Incidence of Chronic Pain at 3 Months After Thoracotomy, No Intervention Groups

When analyses were repeated on those 707 patients from 11 studies who did not receive any intervention, the incidence of chronic pain is 58% (95% CI, 45–70%) at 3 months after thoracotomy based on the random effects model. Heterogeneities remain high, I² = 85%, Q = 65.1 (df = 10), P < .0001.

Incidence of Chronic Pain at 6 Months After Thoracotomy

Fifteen studies reported data from 1,354 patients, which we used to assess the incidence of chronic pain at 6 months after thoracotomy; incidences vary between 23%31 and 81%14 (Table 1). The overall incidence of chronic pain at 6 months after thoracotomy is 47% (95% CI: 39–56%) based on the random effects model (Fig 2) and 47% (95% CI: 38–57%) based on the Freeman-Tukey transformed proportions. Both Q statistics (Q = 123.7, Q = 142.8 [df = 14], P < .0001) and I² (89% and 92%) indicate large heterogeneity among studies for random effects models and the transformed incidences, respectively.

Incidence of Chronic Pain at 6 Months After Thoracotomy, No Intervention Groups

Data from 817 patients in 9 studies were considered cases with no preventative intervention. The incidence of chronic pain at 6 months after thoracotomy is 49% (95% CI, 34–64%) (Q = 97.9 [df = 8], P < .0001). An I² of 92% indicates high heterogeneity in this subgroup.

The overall incidence of pain at 3 months after thoracotomy is not statistically different from the incidence at 6 months according to both random effects models (Q = 3.11 [df = 1], P = .08) and transformed incidences (Q = 2.85, P = .09). When only those 10 studies that assessed the incidence of pain at both 3 and 6 months were included for the comparison, the conclusions did not change (Q = 2.2 [df = 1], P = .14) according to the random effects model.

For the incidence of pain at both 3 and 6 months after thoracotomy, heterogeneity is high as indicated by I². However, within-study dispersions are negligible compared to the variance of the true effect sizes among studies. Because the overall incidences of chronic pain are high, further research is necessary to identify effective preventative interventions.

### Incidence at 3 Months: 95% Confidence Interval

<table>
<thead>
<tr>
<th>Study Name</th>
<th>N</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miguel 1993 (32)</td>
<td>33</td>
<td>0.485 (0.322, 0.651)</td>
</tr>
<tr>
<td>Pertunen 1999 (40)</td>
<td>84</td>
<td>0.798 (0.698, 0.870)</td>
</tr>
<tr>
<td>Obata 1999 (37)</td>
<td>58</td>
<td>0.638 (0.508, 0.751)</td>
</tr>
<tr>
<td>Tiippa 2003 (51)</td>
<td>87</td>
<td>0.598 (0.492, 0.695)</td>
</tr>
<tr>
<td>Owak 2004 (15)</td>
<td>50</td>
<td>0.640 (0.499, 0.760)</td>
</tr>
<tr>
<td>Yang 2004 (59)</td>
<td>80</td>
<td>0.450 (0.345, 0.560)</td>
</tr>
<tr>
<td>Maguire 2006 (29)</td>
<td>31</td>
<td>0.516 (0.345, 0.683)</td>
</tr>
<tr>
<td>Suzuki 2006 (49)</td>
<td>44</td>
<td>0.477 (0.336, 0.623)</td>
</tr>
<tr>
<td>Gottschalk 2008 (13)</td>
<td>112</td>
<td>0.455 (0.366, 0.548)</td>
</tr>
<tr>
<td>Ju 2008 (20)</td>
<td>98</td>
<td>0.653 (0.554, 0.740)</td>
</tr>
<tr>
<td>Salengros 2010 (44)</td>
<td>38</td>
<td>0.526 (0.370, 0.677)</td>
</tr>
<tr>
<td>Ryu 2011 (43)</td>
<td>133</td>
<td>0.466 (0.393, 0.551)</td>
</tr>
<tr>
<td>Miyazaki 2012 (33)</td>
<td>25</td>
<td>0.680 (0.478, 0.831)</td>
</tr>
<tr>
<td>Song 2012 (46)</td>
<td>343</td>
<td>0.472 (0.420, 0.526)</td>
</tr>
<tr>
<td>Mendola 2012 (31)</td>
<td>61</td>
<td>0.311 (0.208, 0.437)</td>
</tr>
<tr>
<td>Kinney 2012 (26)</td>
<td>110</td>
<td>0.682 (0.589, 0.762)</td>
</tr>
<tr>
<td>Pu 2013 (42)</td>
<td>52</td>
<td>0.962 (0.859, 0.990)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.573 (0.508, 0.637)</td>
</tr>
</tbody>
</table>

Figure 1. Forest plot for the incidence of pain at 3 months after thoracotomy.
estimates are close to 50%, the shape of the binomial distribution is close to a normal distribution. When studies with the lowest and highest incidence rates are discarded and analyses were repeated, as recommended by Spiegelhalter,47 I2 remains high (82% to 75% at 3 months and 89% to 87% at 6 months), but the estimate of the overall incidence at both 3 and 6 months did not change. Therefore, we conclude that most of the observed variance is real and can be estimated precisely.2 For this reason, regardless of using the binomial assumption with the DerSimonian and Laird9 method or using the Freeman-Tukey variance stabilizing transformation,10 we reached the same conclusion. In summary, the incidence of persistent postthoracotomy pain is 57% and 47% at 3 and 6 months, respectively. Excluding patients who did not undergo interventions did not change the incidence, heterogeneity among studies reporting incidence is high, and including studies that reported incidence at both 3 and 6 months did not change the conclusions.

**Incidences of Chronic Pain in Time by the Publication Year**

Because of overall improvements in perioperative medicine,41 we examined whether the incidence of chronic pain after thoracotomy was reduced from the 1990s to present. Random effect meta-regression analyses were used to assess the incidence rates over time when the predictor is the publication year.

**Chronic Pain at 3 Months After Thoracotomy by Publication Year**

For the incidence of chronic pain at 3 months after thoracotomy, there are 3 studies published before 2000 and more studies published recently (Fig 3A). When the publication year is entered as a predictor in the model to estimate the incidence at 3 months, the year effect is not significant (β = –.01, standard error [β] = .003, P = .68).

**Chronic Pain at 6 Months After Thoracotomy by Publication Year**

Similar to pain at 3 months, more studies were observed in recent years compared to studies published in the 1990s (Fig 3B). Even if the overall trend seems to be that the incidence of chronic pain at 6 months after thoracotomy is reducing, this effect is not statistically significant (β = –.06, standard error [β] = .004, P = .13).

**Severity of Chronic Pain After Thoracotomy**

The same 858 articles were systematically reviewed to determine if the severity of pain at 3 and/or 6 months was provided. One study that was not found by the search strategy that was identified from the reference list was added. Exclusion criteria for the severity assessments were similar to the reasons for exclusion from the incidence of chronic pain analyses (Supplementary Fig 2). Thirty-one studies that provided the severity of pain at 3 and/or 6 months after thoracotomy were
those 31 studies that reported severity of chronic pain were individually summarized in Supplementary Table 4 to show the heterogeneities in reporting. Out of 31 studies reporting the severity of pain, there were no more than 2 studies using the same severity measurements at the same assessment time. The upper 95% 1-sided Clopper-Pearson CI for this probability (2/31) is 19%. Because of these heterogeneities, an estimate of severity of pain using meta-analysis is provided from 4 of 31 studies at 3 or 6 months.

Severity of Average Pain at 3 Months After Thoracotomy

Two studies\(^{26,46}\) presented the severity of chronic pain at 3 months in terms of the average NRS scores for those patients with pain graded higher than 0, and 1 study\(^ {38}\) presented the severity of chronic pain for all patients and also provided the incidence of pain (Table 2). Thus, it was possible to estimate the mean and the standard deviation for patients with pain graded higher than 0. The severity of average pain in terms of the NRS (0–100) at 3 months after thoracotomy for those 282 patients with pain graded higher than 0 is 30 ± 2 from 3 studies\(^{26,38,46}\) (95% CI: 26–35, \(P < .0001\)) (Fig 4).

Severity of Average Pain at 6 Months After Thoracotomy

The severity of average pain at 6 months after thoracotomy is obtained from 3 studies\(^ {23,38,46}\) (Table 2) in 212 patients with pain graded higher than 0. The severity was 32 ± 7 (95% CI: 17–46, \(P < .0001\), Supplementary Fig 3) on a 0 to 100 scale.

In addition to the average severity of pain, it may be helpful to present the severity as mild, moderate, and severe for those patients with pain. However, this information was not available from most of the studies.

Pain at 12 Months After Thoracotomy

Data for the 12-month time point were derived from 5 studies: 3 studies\(^ {13,20,23}\) that measured the incidence of chronic pain at 3 and/or 6 and 12 months after thoracotomy, and 2 studies\(^ {12,35}\) that did not report pain at 3 or 6 months but reported the incidence of chronic pain at 12 months (Supplementary Fig 1). Data from these 5 studies based on 348 patients were used to assess the incidence of chronic pain at 12 months after thoracotomy (Supplementary Table 5). The overall incidence of chronic pain at 12 months after thoracotomy is 43% (95% CI:

Table 2. Severity of Average Pain, NRS (0–100), for Those Patients With Pain Graded Higher Than 0, at 3 and 6 Months After Thoracotomy

<table>
<thead>
<tr>
<th>Source, Year</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ochroch, 2002(^ {38})</td>
<td>33</td>
<td>20</td>
<td>51</td>
</tr>
<tr>
<td>Kinney, 2012(^ {26})</td>
<td>26</td>
<td>13</td>
<td>69</td>
</tr>
<tr>
<td>Song, 2012(^ {46})</td>
<td>32</td>
<td>11</td>
<td>162</td>
</tr>
<tr>
<td>6 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ochroch, 2002(^ {38})</td>
<td>37</td>
<td>20</td>
<td>36</td>
</tr>
<tr>
<td>Katz, 2009(^ {23})</td>
<td>39</td>
<td>20</td>
<td>32</td>
</tr>
<tr>
<td>Song, 2012(^ {46})</td>
<td>20</td>
<td>9</td>
<td>144</td>
</tr>
</tbody>
</table>
31–56%) based on the random effects model, and 43% (95% CI: 30–57%) based on the Freeman-Tukey transformed proportions, Q statistics (Q = 21.64, Q = 64.67 [df = 4], P < .001). As was noted for the incidences at 3 and 6 months, I² indicates large heterogeneity among studies for both random effects models (82%) and the transformed incidences (84%).

The severity of average pain at 12 months after thoracotomy is obtained from 3 studies23,35,38 (Supplementary Table 6) from 71 patients with pain graded higher than 0 and is 26 ± 9 (95% CI: 9–45, P < .0001).

Discussion

From this meta-analysis of prospective studies, we identified for the first time that at 3 and 6 months after thoracotomy, 57% and 47% of patients, respectively, have thoracotomy-related pain. The incidence of chronic pain has been stable from studies published over 3 decades. There are large heterogeneities among studies in terms of measuring and reporting chronic pain. The inconsistencies in reporting of severity of pain caused us to conduct the meta-analyses for severity from only a few studies. Severity of average pain for those patients with pain graded higher than 0 is approximately 30 (out of 100) at 3 and 6 months after thoracotomy. Few studies report chronic pain after VATS.

There are previous systematic and nonsystematic reviews regarding chronic pain after thoracotomy. Perkins et al22,24,28 systematically reviewed chronic pain after thoracotomy, in addition to other surgeries, from studies published between 1992 and 1999 based on both prospective and retrospective studies with follow-up times of 3 to 33 months. Wildgaard et al68 systematically reviewed risk factors for developing chronic postthoracotomy pain from both retrospective and prospective studies published between 1991 and 2008, with follow-up times of 3 months to 7 years. This is the first study quantifying the incidence of chronic postthoracotomy pain at specific time points from prospective studies.

Incidence of Pain by Year of Publication

As reported by most single-center studies, the incidence of chronic pain at 3 months after thoracotomy is slightly higher than the incidence at 6 months, but this reduction is not significant. It is generally thought that the use of regional analgesia, nonopioid adjuncts, and early physiotherapy have improved acute pain–related outcomes for thoracotomy patients. It was surprising that we could not identify eligible studies on the incidence of chronic pain after thoracotomy before 1993, a time after most of these therapies had been utilized. Any advances in perioperative care since 1993 do not appear to have reduced the incidence of chronic pain either 3 or 6 months after thoracotomy.

Attempts to Reduce Chronic Pain

Despite earlier studies that explored chronic postthoracotomy pain,21,24,28 the problem has gained more recognition after Crombie et al8 and Perkins et al39 reviewed the role of surgery and trauma on chronic postsurgical pain. Most studies used various treatments to attempt to reduce the incidence of chronic pain after thoracotomy. There is no reduction in the incidence over time despite these attempts. Our analysis thus assumes that these treatments have limited influence.
on the development of chronic pain graded higher than 0 after thoracotomy. A recent Cochran database review suggested a modest reduction in the incidence of chronic pain after surgery with perioperative ketamine administration. However, the sample size for thoracic surgery patients (n = 44) is limited and we think precludes us from making meaningful conclusions. Similarly, another Cochran review using 250 patients concluded that regional anesthesia may reduce the chronic pain rates at 6 months. Twenty-two studies were included for the incidence of pain in our meta-analysis; 14 of these studies are randomized clinical trials and the other 8 are observational studies. Even when only the control groups from clinical trials were analyzed, the incidence of chronic pain at both 3 and 6 months after thoracotomy did not change. This was similar to the observational data, thus demonstrating our presumption of a limited influence on the incidence of chronic postthoracotomy pain despite a variety of treatment strategies.

The incidence of chronic pain after thoracotomy from 3 to 6 months is stable. From a limited number of patients, the severity of pain from 3 to 6 months is also stable. At 1 year after thoracotomy, 43% of patients still have pain graded higher than 0. The data indicate that few patients move to pain graded 0 from 6 to 12 months.

Severity of Pain

It is possible that since the 1990s, improvements in perioperative care have decreased the severity but not the incidence of chronic pain graded higher than 0 after thoracotomy; however, we could not analyze trends for severity of pain. Even if the NRS is the most popular method used to report the severity of pain, there are inconsistencies for the scales for intensity and the condition of measurement. It was shown that less than 20% of the reviewed studies measured the severity of chronic pain in a homogeneous way.

Eight of the 31 studies that provided severity of pain did not specify if they provided severity for all the patients or only for those patients with pain. These data could not be included. Given that the chronic pain rates after thoracotomy are 57% and 47% at 3 and 6 months, respectively, utilizing data for average pain of all the patients would underestimate the severity of pain.

A consensus is needed both on the scale of pain intensity and on the condition of measurement. The IMMPACT group recommends using an NRS (0–10) to measure pain intensity as a core outcome coupled with the instructions on clearly defining the conditions under which the scoring is based—for example, the average pain report during the last 24 hours, the average pain report over the last week, or the worst pain episode over the last week. Investigators should report the incidence of and number of patients with pain and then report the severity of pain only for those patients with pain. Given that this is a long-term pain assessment, the most appropriate measure appears to be the average pain during the last week.

To capture the multidimensional nature of pain, not only the presence and the severity of pain but also the information regarding the disability, workability, and psychosocial status should be collected. The Brief Pain Inventory–Short Form is a short (9 items) questionnaire that collects information in these domains as well as pain (worst, least, average, and present NRS). Using the Brief Pain Inventory–Short Form for future studies on chronic pain may help to have more homogeneity across studies.

High Heterogeneity Among Studies

Meta-analyses are commonly used to integrate findings comparing 2 treatments. When included studies are homogeneous, fixed effects models can be used to obtain overall estimates. In the case of heterogeneous studies, random effects models are recommended. Gavanaghan et al showed by simulation that most homogeneity tests have limited power and recommended using fixed effects models only when studies are clinically homogeneous. In our analyses, there are no comparisons between groups, and meta-analyses were used to create weighted summary incidence from individual studies. Therefore, it was expected to observe large heterogeneities, as quantified by the I² statistic, among studies in terms of the reported incidence rates after thoracotomy. Heterogeneities remained high (I² ≥ 85%) when the data are analyzed in no-intervention and control groups. Because of high heterogeneities, we pooled the incidence rates to produce a more stable overall incidence estimate than any estimate from individual studies, based on the random effects model.

Need for Comprehensive Studies

There are several studies that have evaluated predictors of chronic pain after surgery; most of these analyses vary by discipline. For example, surgical studies measured incision size and duration of surgery, whereas anesthesia-related studies focused on postoperative analgesia use and relations of acute postoperative pain to chronic pain. However, pain is a multidimensional problem with interactions among biological, surgical, and psychological factors. Preoperative psychological factors have not been extensively studied for thoracotomy patients; however, studies after other surgeries have shown that pain-related fear and anxiety may be associated with the development of chronic pain and functional disability. To address individual and joint associations among diverse groups of predictors, we need large comprehensive prospective studies.

Thoracotomy Versus VATS

Our initial MEDLINE search included both thoracotomy and VATS patients with the idea to present the incidence and the severity of chronic pain for each procedure separately, in addition to presenting combined results for all thoracic surgery patients. However, there are only a few studies with patients undergoing VATS that satisfied our inclusion criteria. Therefore,
only thoracotomy results are presented, and we cannot make any inferences regarding the differences in incidences of chronic pain after thoracotomy versus VATS.

Limitations

Our analyses have some limitations, most of which are found in any meta-analysis. First, we assumed that we captured all the studies with our MEDLINE, Web of Science, and Google Scholar searches. We did not include non-English articles in our search. It is doubtful that exclusion of non-English articles affected our conclusions. Second, we only included those studies that examined chronic pain at 3, 6, and 12 months after thoracotomy. Therefore, we were unable to capture those studies that examined chronic pain at different follow-up times such as 2 or 9 months. Third, to examine if the incidence of pain changed over time, timing of publication was considered as the time of the study. This does not take into account delays from study completion to publication. Fourth, surgical technique (that is, a posterolateral versus anterior approach) may vary among studies; however, the importance of surgical approach for the incidence and severity of chronic pain is not clear. Other data suggest that technique for surgical closure may also influence chronic pain. Fifth, even if we were aiming to provide meta-analysis results for the severity of pain after thoracotomy, as explained previously, we were unable to make statistical inferences for the severity of pain assessment from all included studies. Regardless, we were able to quantify the variability for the severity measurements and provide meta-analysis results from 4 studies. Sixth, we did not exclude those patients with preexisting chronic pain condition.

Conclusions

Chronic pain is a significant problem affecting 57% and 47% of patients at 3 and 6 months after thoracotomy, respectively. Despite improvements in perioperative care, the incidence of chronic pain after thoracotomy did not change much from 1990s to the present and from 3 months to 6 months after thoracotomy. There is room for improvement not only for reducing the incidence but also for consistently reporting the severity of chronic pain after thoracotomy. Despite the recent popularity of video-assisted procedures, not many chronic pain studies using this approach that fit the inclusion criteria are available, so chronic pain after thoracic surgery reports is mostly from open thoracotomy procedures.

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Supplementary Data

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