

## 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  $30 \pm 2$  (95% CI, 26–35) and  $32 \pm 7$  (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.<sup>50</sup> The incidence of chronic pain after thoracotomy or video-assisted thoracoscopy (VATS) is reported to be between 20% and 80%.<sup>12,13,21,40,48</sup> 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.<sup>39,58</sup> In general, however, attempts to prevent the development of postthoracotomy pain syndrome have yielded inconsistent results.<sup>58</sup> 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

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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 ( $\geq 19$  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<sup>33</sup> ( $n = 7$ , VATS) and 2 studies at 6 months ( $n = 7$ , VATS<sup>33</sup> and  $n = 49$ , VATS<sup>17</sup>) 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.<sup>34</sup>

### 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.<sup>58</sup> 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<sup>9</sup> 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,<sup>52</sup> random effects models and associated 95% CIs for the incidences with the Freeman-Tukey double arcsine variance-stabilizing transformation<sup>10</sup> 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.<sup>18</sup> 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,  $I^2$  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.<sup>36</sup>  $I^2$  is reported on a scale between 0 and 100%.<sup>18</sup>  $I^2$  of 25%, 50%, and 75% can be interpreted as low, moderate, and high heterogeneity, respectively.<sup>19</sup>  $I^2$  of near 100% implies that most of the observed variance is real.<sup>2</sup> For data with high heterogeneity ( $I^2 > 75$ ), 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

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