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SUMMARY WITH CRITICAL APPRAISAL

Pleuroscopy for the Diagnosis of Cancer in Patients with Pleural Effusion: A Review of the Diagnostic Accuracy, Safety, Cost-Effectiveness and Guidelines

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Abbreviations

AGREE	Appraisal of Guidelines for Research & Evaluation
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
CI	Confidence Interval
LAT	Local anesthetic thoracoscopy
MT	Medical thoracoscopy
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies
VATS	Video-assisted thorascopic surgery

Context and Policy Issues

A pleural effusion is characterized by an excessive accumulation of fluid in the pleural space and the underlying cause may be benign or life threatening. The appropriate treatment of pleural effusions can be determined once the etiology is known, however, the etiology is unclear in approximately 20% of cases.[1] A pleural aspiration revealed a positive cytology diagnosis of malignancy in 60% of cases and a positive result of mesothelioma in 32% of cases.[2] The subsequent step in evaluating pleural effusions of unknown cause has been closed pleural biopsies which have been noted as affordable and accessible in clinical settings, however, this procedure has been less sensitive compared to image-guided pleural biopsy or medical thoracoscopy (MT) in the diagnosis of malignant pleural effusion.[2] The conventional closed pleural biopsy is conducted with either Abrams or Cope biopsy needles however this technique does not offer direct visualization of the pleura.[3,4] The field of diagnostic procedures have evolved to overcome the poor sensitivity associated with closed pleural biopsy in the diagnosis of pleural effusions with unknown etiology.

Pleuroscopy, also referred to as MT or local anesthetic thoracoscopy (LAT), is a minimally invasive diagnostic procedure that entails the direct visualization of the pleura followed by a biopsy of visually abnormal areas.[2,5] Medical thoracoscopy is performed by a non-surgeon in a non-operation room (e.g., endoscopy unit) under local anesthesia and moderate sedation.[6,7] Key steps undertaken during pleuroscopy include preparation and positioning of the patient, aspiration of fluids, induction of pneumothorax, local anesthesia and sedation (if applicable), introduction of the trocar, assessment of the thoracic cavity via pleuroscope using photography or video, retrieving multiple biopsy samples followed by controlling bleeding.[8] The reported sensitivity of pleuroscopy ranges from 90 to 100%.[7]

Medical thoracoscopy may be delivered via rigid or semi-rigid (flexi-rigid) instruments. The rigid instrument has been identified as the most commonly used for MT however, semi-rigid is being increasingly used.[6] Overall, the diagnostic results and tolerability of rigid and semi-rigid thoracoscopy are comparable.[6] Major complications reported with MT include prolonged air-leak, hemorrhage, empyema, and port site tumour growth. Minor complications due to MT may encompass subcutaneous emphysema, wound infection, fever, hypotension and cardiac arrhythmias.[7]

In contrast to MT, video-assisted thoracoscopic surgery is more invasive and conducted by a surgeon in an operating room under general anesthesia with single lung ventilation and involves multiple ports.[7]

While the literature suggests pleuroscopy to be safer and less invasive compared to VATS, there is variation in the use of pleurosocpy and VATS as some centres are using one technique in favor of the other.

The purpose of this review is to evaluate the diagnostic accuracy of pleuroscopy in patients with pleural effusions of unknown etiology; their adverse effects, their cost-effectiveness and evidence-based guidelines if any.

Research Questions

1. What is the diagnostic accuracy of medical thoracoscopy (pleuroscopy) for the diagnosis of cancer in patients with pleural effusion of unknown etiology?
2. What is the safety of pleuroscopy for the diagnosis of cancer in patients with pleural effusion of unknown etiology?
3. What is the cost-effectiveness of pleuroscopy for the diagnosis of cancer in patients with pleural effusion of unknown etiology?
4. What are the evidence-based guidelines regarding the use of pleuroscopy for the diagnosis of cancer in patients with pleural effusion of unknown etiology?

Key Findings

One systematic review pooled estimates for diagnostic accuracy and found that semi-rigid thoracoscopy had high sensitivity and specificity for diagnosing pleural effusions of unknown etiology. One non-randomized retrospective study observed a high sensitivity and specificity for rigid thoracoscopy for the diagnosis of tuberculous pleural effusion. Similarly, non-randomized retrospective and prospective studies found a high sensitivity and specificity for rigid or semi-rigid thoracoscopy for the diagnosis of malignant pleural effusion or malignancy. One non-randomized retrospective study reported no statistical difference in diagnostic accuracy between semi-rigid thoracoscopy compared with video-assisted thoracoscopic surgery in the assessment of pleural effusions that were malignant, suspicious for malignancy, or granulomatous inflammation combined.

An economic evaluation reported the mean procedure-related cost of semi-rigid thoracoscopy as $2,815 Canadian dollars (95% Confidence Interval $2,010 to $3,620) compared to video-assisted thoracoscopic surgery of $7,962 Canadian dollars (95% Confidence Interval $7,134 to $8,790) in patients with undiagnosed pleural effusions. Since all video-assisted thoracoscopic surgery was conducted in the hospital whereas 68% of semi-rigid thoracoscopy was performed as outpatient procedures, the longer hospital stay associated with video-assisted thoracoscopic surgery may have contributed to some of the difference in procedure cost.

Among the systematic reviews, randomized, and non-randomized retrospective and prospective studies, few significant procedural complications occurred among patients with undiagnosed pleural effusions that received medical thoracoscopy (pleuroscopy).

One evidence-based guideline suggests that medical thoracoscopy is well tolerated among patients with undiagnosed pleural effusions and exhibits a higher likelihood of diagnosis and pleurodesis in comparison to video-assisted thoracoscopic surgery as patients may have comorbidities and not tolerate general anesthesia.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were pleuroscopy/thoracoscopy and pleural effusion. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between January 1, 2010 and March 2, 2020. A supplemental search was ran on March 31, 2020 to capture additional articles published since the original search.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Any adult patient (outpatient or inpatient) with a pleural effusion of unknown etiology where open pleural biopsy is clinically warranted. (e.g., patients with suspected cancer)
Intervention	Q1-4: Pleuroscopy, also referred to as local anaesthetic thoracoscopy, and medical thoracoscopy
Comparator	Q1: Video-assisted thoracoscopic surgery (VATS) under general anesthesia with single lung ventilation performed in the operating room by a surgeon ; No treatment; Q2: VATS under general anesthesia with single lung ventilation performed in the operating room by a surgeon; No comparator; No treatment Q3: VATS under general anesthesia with single lung ventilation performed in the operating room by a surgeon Q4: Not applicable
Outcomes	Q1: Diagnostic accuracy (sensitivity, specificity, negative predictive value, positive predictive value for the diagnosis of cancer) Q2: Adverse events (empyema, hemorrhage, port site tumour growth, bronchopleural fistula, pneumothorax or air leak post-op, pneumonia, mortality) Q3: Cost-effectiveness Q4: Recommendations regarding the use of pleuroscopy for the diagnosis of cancer
Study Designs	Health technology assessments, systematic reviews/meta-analyses, randomized controlled trials (RCTs), non-randomized studies and economic evaluations

VATS= video assisted thoracoscopy surgery,

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1: Selection Criteria , they were duplicate publications, or were published prior to 2010. Articles with the following study designs were excluded: case reports and case series, narrative and review articles. Guidelines with unclear methodology, studies where results specific to patients with pleural effusions of unknown etiology could not be obtained and types of complications were not specified were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using AMSTAR II,[9] randomized controlled trials and non-randomized retrospective and prospective studies were critically appraised using Downs and Black checklist,[10] diagnostic studies were assessed using QUADAS-2,[11] economic evaluations were assessed using the Drummond checklist,[12] and guidelines were assessed using AGREE II.[13] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were narratively described

Summary of Evidence

Quantity of Research Available

A total of 654 citations were identified in the literature search. After screening titles and abstracts, 614 citations were excluded and 40 potentially relevant citations from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search. Based on the 44 potentially relevant articles from the electronic and grey literature search, 22 publications were excluded for various reasons, 22 publications met the inclusion criteria and were included in this report. These 22 publications comprised one systematic review,[14] one study that included results for both a systematic review and diagnostic accuracy study (non-randomized retrospective study),[15] three diagnostic studies,[16-18] one economic evaluation,[19] three prospective randomized controlled studies,[20-22] 11 non-randomized retrospective studies,[23-33] one non-randomized prospective study[34] and one evidence-based guideline.[2]

Based on the data collection time periods in Rozman et al.,[17,18] it was unclear if there was overlap between patients. Therefore, both studies were included. Similarly, Metintas et al.[21] and Metintas et al.[30] were both included as it is unclear if there was overlap between patients. Although Dhooria et al.[20] was included in the systematic review by Nattusamy et al.[15] only results on the safety of semi-rigid thoracoscopy were reported. Therefore, Dhooria et al.[20] was included in the report to capture the results related to the safety of rigid thoracoscopy.

Appendix 1 provides the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Study characteristics are summarized below and details are available in Appendix 2 , Tables 3 to 6.

Study Design

Two systematic reviews[14,15] were identified. One publication included a systematic review conducted in 2015 that was comprised of four studies published between 2010 to 2014. In this publication, the author also conducted a non-randomized, retrospective study that reported diagnostic test accuracy results of semi-rigid thoracoscopy.[15] A second systematic review[14] conducted in 2010 included five studies published between 1998 and 2008.

There were three additional diagnostic test accuracy studies identified. The same author conducted a randomized, prospective diagnostic test accuracy study[18] and non-randomized, prospective study.[17] One non-randomized retrospective study of diagnostic accuracy met the inclusion criteria.[16]

Three prospective randomized controlled studies met the inclusion criteria.[20-22]

Eleven non-randomized retrospective studies[23-33] published between 2011 to 2018 met the inclusion criteria. One non-randomized prospective study published in 2016 [34] met the inclusion criteria.

One retrospective study reported results of an economic evaluation and diagnostic test accuracy. The economic evaluation consisted of a cost-analysis that reflected a single-payer public health care system. Procedure-related direct and indirect costs were pre-specified at the outset of the study and based on the costing index year of 2017.[19]

One evidence-based guideline was published in 2010 by the British Thoracic Society that provides recommendations based on evidence available for the use of MT in the United Kingdom.[2] These guidelines and recommendations were developed by a working group of professionals and a lay representative with an interest in pleural disease. Through consultation with stakeholders, the appropriate population, intervention, comparison, outcomes and timeframe for study eligibility were discussed to inform a literature search strategy.

Country of Origin

One systematic review and diagnostic test accuracy study was conducted in India with all four included studies from India.[15] Another systematic review was conducted in the United Kingdom which consisted of two studies from the United Kingdom and one study each from Hong Kong, Singapore and Japan.[14] Two diagnostic test accuracy studies were conducted in Slovenia.[17,18] One diagnostic test accuracy study was conducted in Qatar.[16] One prospective, randomized controlled study was conducted in Turkey[21] and two prospective, randomized controlled studies were conducted in India.[20,22] Of the 11 non-randomized retrospective studies, one was conducted in India,[32] one was conducted in the United Kingdom,[31] three were conducted in China,[24,28,29] one was conducted in Taiwan,[23] one study was conducted in Malaysia,[27] one study was conducted in Iran,[26] one study was conducted in Denmark,[33] one study was conducted in Italy,[25] and one study was conducted in Turkey.[30] One non-randomized prospective study that met the inclusion criteria was conducted in India.[34]

One economic evaluation was conducted in Canada.[19]

One evidence-based guideline was developed for the use of MT in the United Kingdom.[2]

Patient Population

One publication included a systematic review comprised of 159 patients with undiagnosed pleural effusions that received semi-rigid thoracoscopy.[15] The patient demographics (e.g., mean age, sex) of the included studies were not reported. The same author reported diagnostic test accuracy results from a non-randomized retrospective study conducted between August 2012 to December 2013 of 48 patients with a mean age of 50.9 years and 64.58% of patients were males.[15] The second systematic review consisted of 154 patients with pleural effusion of unknown etiology that also received semi-rigid thoracoscopy.[14] The patient demographics (e.g., mean age, sex) of the included studies were not reported.

One diagnostic study with a data collection period of 2008 to 2011 included 111 consecutive patients with unilateral pleural effusions of unknown origin and/or pleural irregularities suspicious for pleural malignancy. The median age was 64 years and 71.4% were males.[18] This author also conducted a diagnostic study of 123 patients based on the

same inclusion criteria however the data collection period was between 2008 to 2012.[17] The median age of patients was similar (65 years) and a higher proportion of male patients (86.6%). Both studies took place in a single centre university clinic. One diagnostic study conducted between January 2008 to December 2015 included 407 patients in a tertiary referral center with the presence of undiagnosed exudative pleural effusions who received rigid thoracoscopy and among these patients, hematological, microbiological, and cytological analyses were inconclusive.[16] The mean age was 33.3 years and 87.7% were males.

One randomized, prospective parallel study included 124 patients from a single centre between January 2006 to January 2008 with undiagnosed pleural effusions. The mean age was 60.9 years and 53% of patients were males.[21] One randomized, prospective study included 145 patients from a single tertiary care referral centre between May 2011 to October 2012 with exudative pleural effusions where a specific diagnosis was not ascertained following two cytological and/or microbiological examinations.[20] The mean age was 51.5 years and 69% of patients were males.[20] One investigator-initiated, prospective randomized controlled study included 88 patients with undiagnosed exudative pleural effusions from a single centre between July 2016 to June 2018.[22] The mean age of patients was 50.1 years and 42.5% of patients were males.

All non-randomized, single-arm retrospective studies included patients with pleural effusions of unknown origin. Brims et al.[31] included 58 patients over a 12 month time period from a single hospital with a median age of 73.0 years and 77.2% males. Mootha et al.[32] included 35 patients between January 2007 to December 2008 from a single hospital with a mean age of 48.68 years and 71.4% were males. Gao et al.[29] included 215 consecutively recruited patients between January 2011 to February 2013 from a university and hospital. No patient demographics were reported. Willendrup et al.[33] included 69 patients between March 2009 to September 2013 from the electronic databases of two hospitals with a mean age of 70 years and male to female ratio of 4.75. Kiani et al.[26] included 300 patients between June 2013 to April 2015 from a single hospital with a mean age of 51 years and 64% were males. Lad et al.[27] included 219 patients between January 2010 to December 2011 from a single hospital with a mean age of 63 years and male to female ratio of 1.2:1. Wang et al.[28] included 833 patients between July 2005 to June 2014 from a singe hospital with a mean age of 57.8 years and 60.4% males. Colella et al.[25] included 10 patients between January 2008 to August 2016 from a single hospital with a mean age of 72.4 years and 90% males. Chen et al.[24] included 86 patients between May 2012 to November 2013 from a single hospital with a mean age of 58 years and 62.5% were males. Ooi et al.[23] included 25 patients over a 5-year time period from an intensive care unit with a mean age of 74 years and 68% males.

One non-randomized prospective study included 129 patients with undiagnosed exudative pleural effusions over 2 years that presented to a single center. The mean age was 54 years and 71.3% were males.[34]

One retrospective study included 78 patients that received semi-rigid thoracoscopy and 99 patients that received VATS. In the cost analysis, complete cost data was available for 65 patients that received semi-rigid thoracoscopy and 83 patients that received VATS. The mean age of patients that received semi-rigid thoracoscopy was 68.3 years and the mean age of patients that received VATS was 62.1 years, P = 0.004. There were 73.1% and 64.6% of males that received semi-rigid thoracoscopy and VATS (P = 0.301), respectively.[19]

The evidence-based guidelines were developed by the British Thoracic Society in 2010 intended for physicians in United Kingdom on the use of MT services. These guidelines had a boarder focus than the purposes of this report. Thus, the relevant section on safety of MT in United Kingdom among patients with undiagnosed pleural effusions is included.[2]

Interventions and Comparators

The publication that included a systematic review included patients that received semi-rigid thoracoscopy alone.[15] In the diagnostic study component of the publication, before patients received semi-rigid thoracoscopy, all patients underwent thoracentesis (i.e., cell count, protein, glucose, ADA, acid fast stain, gram stain and bacterial cultures and three cytology examinations).[15]

One diagnostic study included patients randomized to either rigid or semi-rigid thoracoscopy.[18] The same author conducted another diagnostic study however patients received semi-rigid thoracoscopy in a single arm study design with no comparator.[17] In both diagnostic studies, a final diagnosis of non-specific pleuritis was concluded after a 12 month follow-up when no other definitive diagnosis was made during that time. One diagnostic study included patients that received rigid thoracoscopy in a single arm study design with no comparator.[16] In this study where patients underwent rigid thoracoscopy to confirm the etiology of undiagnosed exudative pleural effusions, an initial hematological, microbiological and cytological analyses was inconclusive.[16]

One prospective randomized study investigated patients that received Abrams needle pleural biopsy under CT scan guidance versus rigid thoracoscopy.[21] For the purpose of this report, results relevant to rigid thoracoscopy are reported. Two prospective randomized studies investigated patients that received rigid thoracoscopy compared to semi-rigid thoracoscopy.[20,22]

Of the 11 non-randomized, single-arm retrospective studies, four studies[25,30-32] investigated rigid thoracoscopy, two studies[28,33] assessed the use of semi-rigid thoracoscopy, three studies[23,27,29] evaluated flexible rigid thoracoscopy, and in two studies[24,26] it was unclear the type of thoracoscopy administered. One non-randomized, single-arm prospective study assessed rigid thoracoscopy.[34] No comparators were present in the non-randomized, single-arm retrospective and prospective studies.

One non-randomized retrospective study conducted a cost analysis of patients with undiagnosed pleural effusions that received semi-rigid thoracoscopy compared to VATS.[19]

Outcomes

One systematic review evaluated pooled sensitivity, specificity, positive and negative likelihood ratios.[14] For diagnostic studies, outcomes assessed included diagnostic accuracy[16-18] sensitivity,[15-18] specificity,[15,16,18] positive predictive value (PPV)[15,17] and negative predictive value (NPV).[15,17] In Thomas et al.,[16] it is unclear how diagnostic accuracy was evaluated. In Rozman et al.,[18] the specimens were assessed and classified as the following: "*easily interpretable (enough tissue with all elements required for diagnosis), 'interpretable with some difficulty' (less tissue or fewer diagnostic elements, diagnosis less reliable), 'interpretable with great difficulty' (little tissue or scant diagnostic elements, low reliability of diagnosis) or 'non-interpretable' (diagnosis not possible)." pp2-3* In Rozman et al.,[17] specimens were stained and immunohistochemistry was conducted.

Two systematic reviews,[14,15] four diagnostic studies,[15-18] three randomized prospective studies,[20-22] 11 non-randomized retrospective studies,[23-33] and one non-randomized prospective study[34] assessed the safety and complications associated with MT. Specifically Metintas et al.[30] defined at the outset of the study specific types of early complications (i.e., transient attack of hypertension or hypotension, air leaking for >1 day or a prolonged air leak of over 5 days, subcutaneous emphysema or mediastinal emphysema, pain, cutaneous infection localized at the entry site, pleural infection arising <7 days, arrhythmias, hemorrhage of >20mL, an uncomfortable cough, fever, and transient attack of hypoxemia, which improves with oxygen) and late complications (i.e., local tumoral invasion through the entry site and empyema) accepted. Ooi et al.[23] defined at the outset of the study major complications as events requiring medical or surgical intervention while patients remained at the hospital and minor complications as events that warranted supervision by healthcare staff.

One retrospective study conducted a cost analysis of the mean procedure-related cost of semi-rigid thoracoscopy compared to video-assisted thoracoscopic surgery.[19] A hospital administrative database was used to provide procedure-related direct and indirect costs based on the costing index year of 2017. Direct costs were defined as *"costs related to direct patient care, and included equipment and facility costs, supplies, medications, nursing and other labor costs, ambulatory and inpatient unit costs, diagnostic and therapeutic costs (eg, laboratories, diagnostic imaging, pharmacy, and allied health services). Indirect costs were related to administrative and patient care supports, including administration (corporate, finance, human resources), information systems, materials management, housekeeping, biomedical engineering, infection control, security, and health records."*[19] *(pp. 2)* Indirect and direct costs associated with patient and caregiver loss of productivity due to the diagnosis and management were not taken into consideration in the cost analysis.[19]

One guideline reported on the safety of MT in UK among patients with undiagnosed pleural effusions.[2]

Summary of Critical Appraisal

Critical appraisal of the studies is summarized below and details are available in Appendix 3, Tables 7 to 11.

Systematic Reviews

In the publication by Nattusamy et al.[15] that included a systematic review, the study objective along with population inclusion criteria, description of the intervention and outcomes were outlined. In addition, databases searched were described. Limitations included the following: it was unclear whether stakeholders were consulted to inform the study eligibility criteria for the search strategy (e.g., inclusion and exclusion of study designs, population, intervention, outcomes, comparators and timeframe) the search, it was unclear whether two authors were involved in determining the eligibility of studies and data extraction, patient demographics of included studies was not provided, risk of bias in individual studies was not conducted and sources of funding and conflict of interest was not reported.[15] This systematic review did not perform meta-analyses and a rationale was not provided. Furthermore, heterogeneity was not discussed among the included studies.[15] Another systematic review outlined a clear search strategy and assessment of quality was described.[14] This systematic review did perform meta-analyses combining the sensitivities, specificities and likelihood ratios of individual studies (i.e., all prospective study designs).

Eligibility of studies and data extraction was performed by two authors. The rationale for the inclusion and exclusion of study designs as part of the eligibility criteria were unclear however reasons for excluded studies were reported. Moreover, risk of bias of individual studies, heterogeneity and strengths and limitations of the systematic review were transparent.

Diagnostic Studies

Nattusamy et al.[15] conducted a diagnostic study that provided a description of the index test and method of patient selection. The reference test was interpreted prior to conducting the index test and all patients received the same reference standard. It was unclear if consecutive patients were enrolled or random samples, how the reference standard was conducted, whether index test results were interpreted without knowledge of reference test results, the interval between index test and reference standard, and if all patients were included in the analysis. Among the included diagnostic studies by Rozman et al. (one randomized prospective study[18] and one non-randomized prospective study[17]), several strengths of these diagnostic studies included a description of an index test, method of patient selection, clear interval between the index test and reference standard, index test results were interpreted without knowledge of reference test results and the analysis included all patients that received either rigid or semi-rigid thoracoscopy. A12-month interval was present between the index text and reference standard, it is possible this longer gap may have allowed disease progression. In both diagnostic studies, it was unclear if there was any inappropriate exclusion of patients, if all patients received the same reference standard, and a description of how reference standard was conducted was lacking. If there was inconsistency in the reference standards used, this may contribute towards variability in the values obtained for diagnostic test accuracy. In the diagnostic study by Thomas et al.[16], while the reference standard was interpreted prior to conducting the index test, it is unclear if consecutive patients were enrolled, how the reference standard was conducted, if index test results were interpreted without knowledge of reference test results, the interval between index test and reference standard, and if all patients were included in the analysis. For all diagnostic studies included in this report, no 2x2 table was available.

Randomized Controlled Trials

Three randomized controlled trials[20-22] provided a clear purpose of the study; patient inclusion and exclusion criteria, and intervention were described. Dhooria et al.[20] specified the types of complications of interest at the outset of the study whereas Metintas et al.[21]and Bansal et al. [22] did not. The randomization process and allocation concealment were described in all three studies. In Bansal et al.,[22] patients were blinded to the instrument used during the procedure. All analyses were planned at the outset of the study and P values were stated. Metintas et al.[21] included a sample size calculation whereas Dhooria et al.[20] and Bansal et al.[22] did not. In three studies, it's unclear about the source population from which the patients were included in the study and the single site of the study may be equipped with more highly trained staff to perform thoracoscopy which may limit the generalizability of the results.

Non-Randomized Retrospective Studies

In 11 retrospective studies, the purpose of the study was outlined along with a description of the inclusion criteria, intervention and outcomes. Two studies[23,30] specified the complications of interest a priori in the study. One study[30] identified confounders that were

adjusted for in analyses in the study. Statistical analyses were outlined at the outset of the study in four studies[26,28,30,31] whereas seven studies[23-25,27,29,32,33] did not provide a statistical analysis plan. None of the studies included a sample size calculation. One retrospective study[33] was conducted in two centers whereas nine retrospective studies[23-26,28-32] were conducted in a single site which may be equipped with more highly trained staff to perform thoracoscopy thereby limiting the generalizability of the findings. In one study, the location from where patients were identified was unclear.[27]

Non-Randomized Prospective Study

Patil et al.[34] outlined the purpose of the study, and the inclusion criteria and intervention were clearly described however the exclusion criteria was unclear, confounders were not identified and investigated, sample size calculation was not performed, statistical analyses was not outlined at the outset of the study and major and minor complications of interest were not defined a priori.

Economic Evaluations

McDonald et al.[19] stated the outcome measure of the cost analysis (i.e., procedure-related cost), rationale for selecting video-assisted thoracoscopic surgery as an alternate to semi-rigid thoracoscopy and defined direct and indirect costs. The cost analysis was conducted to reflect a single-payer public health care system. While the study authors concluded that there was no statistically significant difference in the diagnostic test performance between semi-rigid thoracoscopy and VATS, a single P value was provided which makes it unclear if this P value reflects the sensitivity, specificity, positive predictive value or negative predictive values. It is important to note that characteristics such as age (years) and presence of comorbidities (i.e., diabetes mellitus, congestive heart failure and coronary artery disease) were statistically different between patients in the semi-rigid thoracoscopy and VATS group and these characteristics were not adjusted for in the cost analysis. While VATS is the more expensive procedure, the true difference in procedure-related costs associated with semi-rigid thoracoscopy compared to VATS is unknown due to the lack of robustness in how the cost-analysis was conducted. In addition, indirect and direct costs associated with patient and caregiver loss of productivity due to the diagnosis and management were not captured in the cost analysis and may be relevant for consideration. Furthermore, no details were provided of how the cost analysis was performed. It is unclear whether quantities of resource use were separated from unit costs.

Evidence-Based Guidelines

The evidence-based guidelines by Rahman et al.[2] on pleural disease were developed by a working group of professionals and a lay representative with an interest in pleural disease. Through consultations with stakeholders (e.g., medical and nursing professions, patient groups, health management, industry), the scope and purpose of the guidelines were defined, and a systematic literature search was conducted. The methodology of the guidelines followed the Appraisal of Guidelines Research and Evaluation (AGREE) tool. The guidelines provide a clear description of areas covered, aims, objectives and methodology used to inform the recommendations. Although there were no competing interests declared among the working group, the types of medical specialties/professions in the working group are unclear which may impact whether all relevant perspectives were taken into consideration during the development of the guidelines. It is unclear whether potential resource implications of applying recommendations were considered during

developing recommendations. In addition, the guidelines did not report strengths and limitations of the body of evidence.

Summary of Findings

Findings are summarized below and details are available in Appendix 4 , Tables 12-14.

What is the diagnostic accuracy of pleuroscopy for the diagnosis of cancer in patients with pleural effusion of unknown etiology?

Six studies reported results on diagnostic accuracy.[14-19] One systematic review reported the pooled sensitivity, specificity, positive likelihood ratio and negative likelihood ratio of semi-rigid thoracoscopy in patients with pleural effusions of unknown etiology as 0.97 (95% confidence interval [CI] 0.92 to 0.99), 1.00 (95% CI 0.69 to 1.00), 5.47 (95% CI 1.77 to 16.86) and 0.08 (95% CI 0.04 to 0.18) respectively.[14] One retrospective study reported the diagnostic accuracy of rigid thoracoscopy for tuberculous pleural effusion as 91% with a sensitivity and specificity of 90% and 100%, respectively.[16] One retrospective study reported the sensitivity and specificity of semi-rigid thoracoscopy for malignant pleural effusion as 97% and 100%, respectively, with a positive predictive value of 100% and negative predictive value of 67%.[15] In one randomized study and one non-randomized prospective study that assessed the diagnostic test accuracy of semi-rigid or rigid thoracoscopy in patients with pleural effusions of unknown etiology, overall diagnostic accuracy of malignancy ranged from 97% to 100%. The value of sensitivity for malignancy (semi-rigid and/or rigid thoracoscopy combined) ranged from 96% to100% and the value of specificity for malignancy (semi-rigid and/or rigid thoracoscopy combined) was100%.[17,18] Positive predictive value for malignancy was 100% and negative predictive value for malignancy was 93% for semi-rigid thoracoscopy.[17] One retrospective study reported the sensitivity, specificity, positive predictive value and negative predictive value of malignant, suspicious for malignancy and granulomatous inflammation combined for patients that received semi-rigid thoracoscopy as 85%, 100%, 100% and 79%, respectively. In the same study, sensitivity, specificity, positive predictive value and negative predictive value of malignant, suspicious for malignancy and granulomatous inflammation combined for patients that received VATS was 93%, 94%, 99% and 76%, respectively.[19] According to the study authors, the diagnostic test performance was not statistically significant between semi-rigid thoracoscopy and VATS (P value 0.591).[19] Table 2 presents the results.

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Table 2: Summary of Diagnostic Studies

Study (first author, year, country)	Procedure	Diagnostic accuracy (%)	Sensitivity (%)	Specificity (%)	Positive Likelihood Ratio	Negative Likelihood Ratio	Positive Predictive Value (%)	Negative Predictive Value (%)
McDonald,[a19] 2018, Canada	Semi-rigid thoracoscopy or VATS	Not assessed	Semi-rigid 85 VATS 93	Semi-rigid 100 VATS 94	Not assessed	Not assessed	Semi-rigid 100 VATS 99	Semi-rigid 79 VATS 76
Thomas,[b16] 2017, Qatar	Rigid thoracoscopy	91.4	90	100	Not assessed	Not assessed	Not assessed	Not assessed
Nattusamy,[c15] 2015, India	Semi-rigid thoracoscopy	Not assessed	96.77	100	Not assessed	Not assessed	100	66.67
Rozman,[d17] 2014, Slovenia	Semi-rigid thoracoscopy	97.4	96.0	Not assessed	Not assessed	Not assessed	100	93.0
Rozman,[d18] 2013, Slovenia	Semi-rigid or rigid thoracoscopy	Semi-rigid 97.6 Rigid 100	Semi-rigid 96.6 Rigid 100	Semi-rigid 100 Rigid 100	Not assessed	Not assessed	Not assessed	Not assessed
Mohan,[e14] 2010, United Kingdom	Semi-rigid thoracoscopy	Not assessed	0.97 (95% CI 0.92 to 0.99)	1.00 (95% CI 0.69 to 1.00)	5.47 (95% CI 1.77 to 16.86)	0.08 (95% CI 0.04 to 0.18)	Not assessed	Not assessed

VATS=video assisted thoracoscopic surgery, CI=confidence interval

[a] Assessment in malignant, suspicious for malignancy and granulomatous inflammation combined

[b] Assessment in tuberculous pleural effusion

[c] Assessment in malignant pleural effusion

[d] Assessment in malignancy

[e] Values represent pooled estimates

What is the safety of pleuroscopy for the diagnosis of cancer in patients with pleural effusion of unknown etiology?

Semi-Rigid Thoracoscopy

One systematic review included four studies conducted in India that reported on significant complications associated with semi-rigid thoracoscopy. Two studies found no significant complications. Results from one study showed one patient experienced prolonged air leak and one study identified one patient each with empyema and air leak, respectively, and one patient with minor hemorrhage.[15] One systematic review found no major complications and mortality after 30 days' follow-up period. Air leakage occurred in 2 patients (0.01%) and pneumothorax in 1 patient (0.01%).[14]

In a randomized prospective analysis of 111 consecutive patients, of which 41 patients received semi-rigid thoracoscopy, one major complication occurred (i.e., empyema caused by methicillin-sensitive Staphylococcus). This patient recovered following chest-tube drainage and antibiotic treatment.[18] In a randomized prospective study of 88 patients, of which 36 patients received rigid thoracoscopy and 37 patients received semi-rigid thoracoscopy, there were no serious adverse events and procedure-related mortality.[22]

In a non-randomized prospective analysis conducted by the same author that included 123 patients that received semi-rigid thoracoscopy, serious adverse events occurred among 3 patients. One patient experienced empyema caused by methicillin-sensitive Staphylococcus aureus (MSSA). Following chest tube drainage and antibiotic treatment, the patient recovered. Among two patients, pleural infection occurred which resulted in trapped lung, subsequent bronchopleural fistula, and prolonged chest drainage which lasted a duration of up to 22 days.[17]

In a non-randomized retrospective study that included 48 patients that underwent semi-rigid thoracoscopy, results found that procedure-related complications were classified as minor and morality did not occur.[15] In a non-randomized retrospective study of 833 patients that received semi-rigid thoracoscopy, 3 patients (0.4%, 95% CI -0.03 to 0.8) experienced empyema. Minor bleeding occurred in 38 patients (4.6%, 95 CI 3.2 to 6.0). No major bleeding occurred in patients.[28] In a retrospective study that compared semi-rigid thoracoscopy with VATS, there were no patients that experienced death within 30 days in the semi-rigid thoracoscopy group compared to 2 patients (2%) in the VATS group (P = 0.504). There were no patients that experienced hemorrhage in the semi-rigid thoracoscopy group compared to 2 patients (2%) in the VATS group (P = 0.504). One patient (1.3%) experienced alveolar-pleural fistula in the semi-rigid thoracoscopy group compared to no patients in the VATS group (P = 0.441).[19]

In a non-randomized retrospective study of 215 patients that received flexible rigid thoracoscopy, results showed minimal to moderate hemorrhage observed at the site of biopsy however no special treatment was required and the proportion of cases is unclear.[29] In a non-randomized retrospective study of 219 patients that received flexi-rigid thoracoscopy, no serious complications were encountered.[27] In a non-randomized retrospective study that included 60 patients of which 25 patients underwent flexible rigid thoracoscopy, major complications defined as bleeding and death (procedure related) did not occur in any patients. Minor complications occurred in 11 patients (44%) of which zero patients experienced pneumonia/empyema.[23]

Rigid Thoracoscopy

In a randomized prospective analysis of 111 consecutive patients, of which 38 patients received rigid thoracoscopy, a major complication of severe bleeding occurred in one patient due to an aberrant blood vessel after pleural biopsy. The patient recovered from the hemorrhage without sequelae.[18] In a randomized prospective study of 145 patients with exudative pleural effusions, a total of 16 major and minor complications occurred among the 45 patients that received rigid thoracoscopy. Three cases each of empyema occurred and persistent air leak (> 3days). No major hemorrhage occurred.[20]

In a non-randomized prospective study that involved 129 patients that received rigid thoracoscopy, no major complications were reported. Minor complications such as air leak (4.6%) and empyema (2.3%) occurred in patients. No patients experienced mortality related to the procedure.[34] In one retrospective study that included 35 patients with undiagnosed pleural effusions that received rigid thoracoscopy, two cases developed empyema (5.2%). There were no instances of haemorrhage, shock or subcutaneous emphysema.[32] Similarly, in a retrospective analysis of 57 patients with complete data that underwent rigid thoracoscopy, empyema occurred in 2 patients (3.5%) and pneumonia occurred in 4 patients (7.0%). There was no death (as a result of the procedure) and bleeding (minor/major) reported.[31] In a retrospective study of 355 patients that received rigid thoracoscopy, there were 208/355 patients (58.6%) with no complications. Hemorrhage occurred in 3 patients (1.7%), prolonged air leak ≤ 5 days in 4 patients (2.3%), prolonged air leak > 5 days in 4 patients (2.3%) and empyema in 1 patient (0.6%). [30] In a retrospective study that involved 10 patients that underwent rigid thoracoscopy, results showed no complications due to the procedure occurred. [25]

Unclear type of thoracoscopy

In a non-randomized retrospective study comprised of 300 patients that received thoracoscopy, 11 patients reported minor complications. Of these 11 patients, 4 patients experienced minor bleeding.[26] In a non-randomized retrospective study of 86 patients that received medical thoracoscopy pleural hemorrhage occurred in 8 cases (9.3%). No mortality was present.[24]

What is the cost effectiveness of pleuroscopy for the diagnosis of cancer in patients with pleural effusion of unknown etiology?

In a retrospective study that conducted a cost analysis of semi-rigid thoracoscopy compared to VATS, the mean procedure-related cost was based on complete cost data for 65 patients that received semi-rigid thoracoscopy and 83 patients that received VATS. The mean procedure-related cost of semi-rigid thoracoscopy was reported as $2,815 Canadian dollars (95% CI $2,010 to $3,620) compared to VATS of $7,962 Canadian dollars (95% CI $7,134 to $8,790) P < 0.001. The cost analysis results demonstrated significantly lower costs in patients that received semi-rigid thoracoscopy and a difference in mean per-procedure cost of greater than $5,000 Canadian dollars between the semi-rigid thoracoscopy and VATS group.

What are the evidence-based guidelines regarding the use of pleuroscopy for the diagnosis of cancer in patients with pleural effusion of unknown etiology?

One evidence-based guideline developed by the British Thoracic Society on pleural disease was identified. These evidence-based guidelines address the safety of MT.[2]

The guidelines state that patients with undiagnosed pleural effusions are not appropriate candidates for therapeutic procedures (e.g., VATS) for reasons such as comorbidities, poor survival and not tolerating general anesthesia. In these circumstances, MT under sedation is a well tolerated procedure and offers these patients a higher likelihood of diagnosis and pleurodesis.[2]

Limitations

As five diagnostic studies[14-18] were conducted in countries outside Canada, there may be variation in how MT was performed (e.g., length of time of procedure, quality of instrument used etc.). In addition, the patient demographics (e.g., mean age, presence of comorbidities) in these diagnostic studies may not represent the profile of patients with undiagnosed pleural effusions in Canada. Thus, the diagnostic accuracy and safety results may not be generalizable to the Canadian context.

One retrospective study that reported cost analysis results was conducted in a leading tertiary thoracic surgery hospital in Ontario.[19] Thus, there may be variation in the direct and indirect costs that contributed towards the per-procedure related cost in this hospital compared to other community hospital settings. Therefore, the cost analysis results may not be generalizable across all clinical settings and jurisdictions in Canada.

Where multiple studies were conducted by the same group, it is unclear whether there was overlap in the study population. Therefore these studies may not represent unique experiences.

The included evidence-based guidelines and recommendations were intended for MT service in UK and addressed MT in the context of malignant disease. For the purpose of this report, guidelines relevant to patients with pleural effusions of unknown etiology were extracted.

Conclusions and Implications for Decision or Policy Making

This report was comprised of one study that included results for both a systematic review and non-randomized retrospective diagnostic study,[15] one systematic review,[14] three diagnostic studies,[16-18] three prospective randomized controlled studies,[20-22] 11 non-randomized retrospective studies,[23-33] one non-randomized prospective study[34] one retrospective study that conducted a cost analysis of semi-rigid thoracoscopy compared to VATS[19] and one evidence-based guideline.[2]

One high quality systematic review reported that the pooled negative likelihood ratio was less than 0.1 which suggests the usefulness of MT in ruling out a diagnosis among patients with pleural effusions of unknown etiology.[14]

Among the included systematic reviews, diagnostic studies, randomized and non-randomized studies that reported on adverse events associated with MT, few major procedural complications occurred.

An economic evaluation reported the mean procedure-related cost of semi-rigid thoracoscopy as $2,815 Canadian dollars (95% CI $2,010 to $3,620) compared to VATS of $7,962 Canadian dollars (95% CI $7,134 to $8,790) P value <0.001 in patients with undiagnosed pleural effusions. Since all VATS was conducted in the hospital whereas 68% of semi-rigid thoracoscopy was performed as outpatient procedures, the longer hospital stay associated with VATS may have contributed to some of the difference in procedure

cost. It is important to note that the characteristics such as age (years) and presence of comorbidities (i.e., diabetes mellitus, congestive heart failure and coronary artery disease) were statistically different between patients in the semi-rigid thoracoscopy and VATS group. While VATS is the more expensive procedure, the true difference in procedure-related costs associated with semi-rigid thoracoscopy compared to VATS is unknown due to the lack of robustness in how the cost-analysis was conducted.[19]

The limitations of the included diagnostic studies (e.g., no description of how reference standard was conducted, unclear if inappropriate exclusion of patients) economic evaluation (e.g., no details of how statistical analysis was performed and indirect and direct costs associated with patient and caregiver loss of productivity due to the diagnosis and management were not captured in the cost analysis and may be relevant for consideration) and non-randomized studies (e.g., missing statistical analysis plan, sample size calculation, singe site of study) should be considered when interpreting the results. Further research on the comparison of pleuroscopy with VATS and the cost-effectiveness would support decision-makers on which therapeutic procedure to approve.

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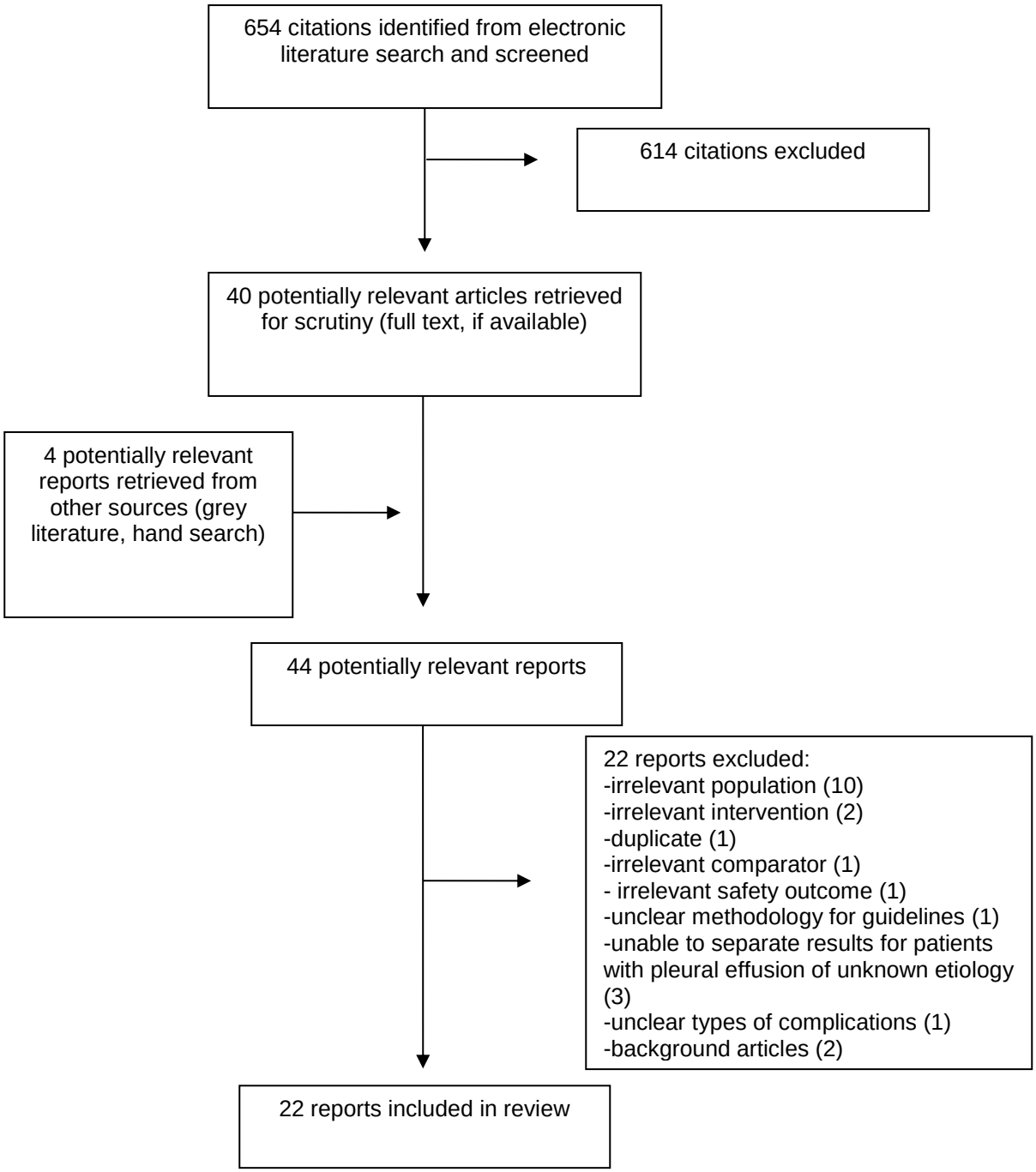
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 3: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes of interest for this review
Nattusamy,[15] 2015, India	Systematic review included four studies (n=159 patients) that reported on the utility of semi-rigid thoracoscopy in India. Study designs of included studies not reported. Unclear time period of literature search conducted in PubMed and EMBASE databases Two studies published in 2010, one study published in 2012 and one study published in 2014. Aim: to report the diagnostic efficacy of semi-rigid thoracoscopy in Indian studies. Excluded case reports and case series with <10 patients.	No information available on patient demographics of included studies. Studies conducted in India hat investigated the diagnostic efficacy of semi-rigid thoracoscopy were included. The following study designs were excluded: case reports and series with <10 patients.	Semi-rigid thoracoscopy	Procedural complications
Mohan,[14] 2010, United Kingdom	Systematic review included five studies (n=154 patients) that reported on the utility of semi rigid thoracoscopy. Study designs of included studies not reported. Studies were published between 1998 and 2008 (2 studies reported from the United Kingdom and 1 each from Hong Kong, Singapore, and Japan) Aim: To determine the diagnostic accuracy of	No information available on patient demographics (e.g., age, sex etc.) of included studies. Prospective studies (based on original research available in English) that enrolled consecutive patients with pleural effusions of unknown etiology that received semi-rigid thoracoscopy were included.	Semi-rigid thoracoscopy	Pooled sensitivity, pooled specificity, pooled positive likelihood ratio, pooled negative likelihood ratio

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes of interest for this review
	the relatively new technique of semirigid thoracoscopy in patients with pleural effusion of unknown etiology through this systematic review			

Table 4: Characteristics of Included Diagnostic Studies, Randomized Controlled Trials and Non-Randomized Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes of interest for this review
Diagnostic Studies				
Thomas,[16] 2017, Qatar	Retrospective-descriptive study Time period: January, 2008 till December, 2015 Setting: only tertiary referral center performing MT in the State of Qatar	Patients that received MT to confirm the etiology of undiagnosed exudative pleural effusions and in whom initial hematological, microbiological, and cytological analyses were inconclusive N=407 Age mean +/- SD: 33.3 years +/- 12.1 % Males: 87.7	Intervention: Rigid thoracoscope Reference standard: Patients had an initial hematological, microbiological and cytological analyses that was inconclusive.	Sensitivity, specificity, diagnostic accuracy
Nattusamy,[15] 2015, India	Non randomized retrospective study Time period: patients between August 2012 and December 2013 Setting: Patients that received pleuroscopy	Patients with undiagnosed pleural effusion that received semi-rigid thoracoscopy N=48 % males: 64.5	Intervention: Semi rigid thoracoscopy Reference standard: All patients underwent thoracentesis (i.e., cell count, protein, glucose, ADA, acid fast stain, gram stain and bacterial cultures	Sensitivity, specificity, positive and negative predictive value, safety

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes of interest for this review
	in a tertiary care teaching and referral center	Age mean +/- SD: 50.9 +/- 4.1	and three cytology examinations).	
Rozman,[17] 2014, Slovenia	Prospective study Time period: between 2008 to 2012 Setting: single center university clinic	Patients with unilateral pleural effusion of unknown origin and/or pleural irregularities suspicious for pleural malignancy referred for semi rigid thoracoscopy N=123 Median age (range) years: 65.0 (28-86) %Males: 86.6	Intervention: Semi-rigid thoracoscopy Reference standard: A final diagnosis of non-specific pleuritis was concluded after a 12 month follow-up when no other definitive diagnosis was made during that time.	Diagnostic accuracy, sensitivity, positive and negative predictive value, safety
Rozman,[18] 2013, Slovenia	Prospective randomized study Time period: patients 2008 to 2011 Setting: single center university clinic	Patients with unilateral pleural effusion of unknown origin and/or pleural irregularities suspicious for pleural malignancy referred for thoracoscopy (semi rigid or rigid) N=111 Median age (range): 64 years (41-78) % Males: 71.4	Intervention: Semi-rigid or rigid thoracoscopy Reference standard: A final diagnosis of non-specific pleuritis was concluded after a 12-month follow-up when no other definitive diagnosis was made during that time.	Diagnostic accuracy, sensitivity, specificity, safety
Randomized Controlled Trials				
Dhooria,[20] 2014, India	Prospective, randomized study Time period: between May 2011 and October 2012	Patients with exudative pleural effusions where a specific diagnosis was not obtained after 2 cytological and/or	Intervention: Rigid thoracoscopy or semi rigid thoracoscopy Comparator: none	Complications

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes of interest for this review
	Setting: tertiary care referral center	microbiological examinations N= 145 Age mean /- SD: 51.5 +/- 14.3 years % Males: 68.9%		
Metintas,[21] 2010, Turkey	Prospective, randomized, parallel study Time period: patients between January 2006 to January 2008 Setting: Department of the Medical Faculty of Eskisehir Osmangazi University	Patients with the presence of exudative pleural effusions which a diagnosis could not be determined based on cytologic examination N=124 Age mean +/- SD: 60.9 years +/- 13.5 years % Males: 53%received MT and 63% received CT-ABPB	Patients were randomized to either Abrams needle pleural biopsy under CT scan guidance (CT-ANPB) or MT	Complications
Non-Randomized Studies				
Chen, [24]2018, China	Non-randomized retrospective study Time period: May 2012 to November 2013 Setting: clinical data from a single hospital	Patients with undiagnosed pleural effusions in which the cause of disease could not be identified through routine examination of pleural fluid, biochemical tests, bacteriology, exfoliative cytology as well as closed pleural biopsy examination. N=86 Age mean +/- SD: 58.0 years +/- 15.0	Intervention: MT Comparator: none	Safety

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes of interest for this review
		% Males: 58%		
Ooi,[23] 2018, Taiwan	Non-randomized retrospective study Time period: 5 years (date of data collection not reported) Setting: intensive care unit	Patients with recurrent. undiagnosed exudative pleural effusions that received bedside pleuroscopy N=25 Age (mean +/- SD): 74 years +/- 3 years % Males: 68	Intervention: Flexible rigid thoracoscope under local anesthesia Comparator: none	Complications
Colella,[25] 2017, Italy	Retrospective study Time period: between January 2008 and August 2016 Setting: clinical consultations at Pulmonary Unit, “C. & G. Mazzoni” Hospital	Patients with chronic kidney disease who had unexplained PE that received rigid or semi rigid thoracoscopy N=10 Age mean years (range): 72.4 (62 to 82 years) %Males: 90	Intervention rigid or semi rigid thoracoscopy Comparator: none	Complications
Patil,[34] 2016, India	Prospective, non-randomized, interventional study Time period: 2 years (date of data collection is not reported) Setting: Patients presenting to the center	Patients with undiagnosed exudative pleural effusions that received thoracoscopy under local anesthesia N=129 Age mean +/- SD” 54 years +/- 20.6 years % Males: 71.3	Intervention Rigid thoracoscopy Comparator: none	Complications

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes of interest for this review
Kiani,[26] 2015, Iran	Retrospective study Time period: between June 2013 to April 2015 Setting; Patients referred to Daneshvari Hospital	Patients with undiagnosed pleural effusions that received pleuroscopy N=300 Age mean +/- SD: 51 +/- 14.7 years % males: 64	Intervention: pleuroscopy under local anesthesia Comparator: none	Complications
Lad,[27] 2015, Malaysia	Retrospective study Time period: patients between January 1, 2010 to December 31, 2011 Setting: Hospital	Patients with undiagnosed exudative pleural effusions that received pleuroscopic biopsy samples N=219 Mean age: 63 years Male: female ratio: 1.2:1	Intervention: flexi-rigid fiber-optic pleuroscope under local anesthesia Comparator: none	Complications
Wang,[28] 2015, China	Non-randomized retrospective study Time period: between July 2005 and June 2014 Setting: hospital	patients with undiagnosed pleural effusions who received at least one MT N=833 Age mean +/- SD: 57.8 years +/- 14.5 years % Male: 60.4	Intervention: semi-rigid under local anesthesia Comparator: none	Complications of MT
Gao,[29] 2014, China	Retrospective study Time period: consecutively recruited patients between January 2011 and February 2013	Patients with undiagnosed exudative pleural effusions that received flexi-rigid thoracoscope N=215	Intervention: flexi-rigid thoracoscope Comparator: none	Complications

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes of interest for this review
	Setting: First College of Clinical Medical Science of China Three Gorges University and Yichang Central People's Hospital,	Patient demographics not provided		
Willendrup,[33] 2014, Denmark	Non-randomized retrospective study Time period: between March 1, 2009 to September 1, 2013 Setting: patients that received MT were included from hospitals' electronic databases in 2 departments	Patients with unexplained exudative pleural effusions for the indication of MT N=69 Age median (range) = 70 years (46-85 years) Males/Females ratio: 4.75	Intervention: A semi-rigid thoracoscope was used with local anesthesia Comparator: none	Safety
Metintas,[30] 2013, Turkey	Retrospective study Time period: January 2002 to January 2009 Setting: Eskisehir Osmangazi University Medical Faculty	Consecutive patients with evidence of exudative pleural effusion which a specific diagnosis could not be determined by cytologic, microbiological, or clinical examinations N=355 Age mean +/- SD: 61.3 years +/- 12.5 years % Males: 58.9%	Intervention: rigid thoracoscopy Comparator: none	Complications
Brims,[31] 2012, United Kingdom	Non-randomized retrospective analysis Time period: 12 months	Patients with unexplained exudative pleural effusions that received thoracoscopy	Intervention: Rigid thoracoscope under local anesthesia Comparator: none	Complications

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes of interest for this review
	Setting: Portsmouth National Health Service (NHS) Trust Hospitals	N=58 (data was available for 57 patients) Age median (IQR) years: 73.0 (66.5-79.0)		
Mootha,[32] 2011, India	Non-randomized retrospective study Time period: January 2007 to December 2008 Setting: patients in the department of pulmonary medicine	Patients with undiagnosed pleural effusions that received rigid video thoracoscope between January 2007 to December 2008 N=35 Age mean +/- SD: 48.68 years +/-14 years % Males: 71.4	Intervention: rigid video thoracoscope Comparator: none	Safety

MT=medical thoracoscopy, DTA=diagnostic test accuracy

Table 5: Characteristics of Included Economic Evaluation

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
McDonald,[19] 2018, Canada	Cost analysis was performed to reflect a single-payer public health care system.	To identify whether semi-rigid thoracoscopy can reduce the overall cost associated with the diagnosis and management of pleural effusions	Patients with undiagnosed pleural effusions N=78 patients received semi-rigid thoracoscopy and 99 patients received VATS Age (mean 95% CI) for semi-rigid thoracoscopy	Semi-rigid thoracoscopy and VATS	No model was conducted	Procedure-related direct and indirect costs were retrieved from the hospital administrative database for 2017 as the costing index year. Direct costs reflected "*direct*	Not reported

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
			68.3 years (95% CI 65.2-71.4) Age (mean 95% CI) for VATS 62.1 years (95% CI 59.2-65) Cost data were evaluated based on complete data for 65 patients that received semi-rigid thoracoscopy and 83 patients that received VATS. 13 patients with semi-rigid thoracoscopy and 2 patients with VATS had incomplete data. 14 patients with VATS were excluded from the cost analysis based on hospital admission that exceeded 2 days prior to the procedure date.			*patient care, and included equipment and facility costs, supplies, medications, nursing and other labor costs, ambulatory and inpatient unit costs, diagnostic and therapeutic costs (eg, laboratories, diagnostic imaging pharmacy, and allied health services).”*[19] *(pp2)* Indirect costs encompassed “*administrative and patient care supports, including administration (corporate, finance, human resources), information systems, materials management, housekeeping, biomedical engineering, infection control, security, and health records.”*[19]*(pp2)*	

VATS=video-assisted thoracoscopic surgery

Table 6: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Rahman, 2010[2]						
Intended users: UK physicians Target population: patients with unilateral pleural effusion in adults, spontaneous pneumothorax, malignant pleural effusion, pleural infection in adults	LAT in UK clinical practice	LAT service in the UK. Evidence for conducting LAT as a diagnostic and therapeutic tool. The conditions and patients in whom LAT could be considered. Levels of competence in LAT. Practical aspects of performing the procedure.	• A working group was assembled that encompassed professionals and a lay representative who expressed interest in pleural disease • Questions relating the population, intervention, outcomes and Time format were identified to inform the literature search strategy	• Methodology followed criteria outlined in Appraisal of Guidelines Research and Evaluation (AGREE) • Critical appraisal was performed by at least 2 guidelines reviewers who applied the Scottish Intercollegiate Guidelines Network (SIGN) critical appraisal checklist. Evidence was graded according to the SIGN levels of evidence	"Local anesthetic thoracoscopy under intravenous sedation offers these patients a reasonably high likelihood of diagnosis and pleurodesis in a single procedure that is well tolerated. Overall, local anesthetic thoracoscopy is a safe procedure."(*ppii56*)	The final guidelines are endorsed by 13 Royal Colleges and societies

LAT=local anesthetic thoracoscopy; UK=United Kingdom

Appendix 3: Critical Appraisal of Included Publications

Table 7: Strengths and Limitations of Systematic Reviews using AMSTAR II [9]

Strengths	Limitations
Nattusamy,[15] 2015	
• The objective along with population, intervention and outcomes were outlined • Study designs excluded were stated • Databases searched included PubMed and EMBASE	• Unclear methods used to inform search strategy • Unclear rationale for inclusion and exclusion of study designs • Unclear whether two review authors determined eligibility of studies • Unclear whether data extraction was performed in duplicate • A list of excluded studies was not provided • Risk of bias in individual studies was not conducted • Unclear rationale for why there was no meta-analysis • Heterogeneity was not discussed • Sources of funding for included studies is unclear • Unclear about potential sources of conflict for the SR authors
Mohan,[14] 2010	
• The objective along with population, intervention and outcomes were outlined • Clear description of search strategy • Databases searched included PubMed and EMBASE • A flow chart of study selection was provided • Appropriate statistical methods used in analysis • Two review authors determined eligibility of studies • Data extraction was performed in duplicate • Risk of bias in individual studies was conducted • Meta-analyses were conducted pooling the sensitivities, specificities and likelihood ratios of individual studies • Heterogeneity across included studies was discussed • Review authors stated that they had no conflicts of interest related to this review	• Unclear rationale for study design eligibility criteria • A list of excluded studies was not provided • Sources of funding for included studies is unclear

SR = systematic review

Table 8: Strengths and Limitations of Randomized and Non-Randomized Clinical Studies using Downs and Black checklist [10]

Strengths	Limitations
Randomized Controlled Trials	
Bansal,[22] 2019	
• Purpose of the study is described • Patient inclusion and exclusion criteria and intervention were described • Reasons for patients excluded were stated • Primary and secondary outcomes were stated	• Unclear about the source population from which the patients were included in the study. • The single center where the study was conducted may be equipped with more highly trained staff to perform thoracoscopy

Strengths	Limitations
• Randomization was computer-generated and allocation concealment was observed • Patients were blinded to the instrument used during the procedure • Patients were blinded to the instrument used during medical thoracoscopy • P values were stated • Statistical analyses planned at outset of study	• Major and minor complications were not defined at outset of study • Sample size calculation was not performed
Dhooria,[20] 2014	
• Purpose of the study is described • Patient inclusion and exclusion criteria, intervention and outcomes were described • Major and minor complications due to rigid or semirigid thoracoscopy were reported • All analyses were planned at the outset of the study • Randomization was computer-generated and allocation concealment was observed • P values were stated	• Unclear about the source population from which the patients were included in the study. • The single site of the study (i.e., tertiary care referral center) may be equipped with more highly trained staff to perform thoracoscopy • Health care staff were not blinded during randomization • Sample size calculation was not performed
Metintas,[21] 2010	
• Purpose of the study is described • Patient inclusion and exclusion criteria, intervention and outcomes were described • Randomization process and allocation concealment was described • All analyses were planned at the outset of the study (i.e., primary endpoint was stated) • P values were stated • Sample size was calculated	• Unclear about the source population from which the patients were included in the study. • The single site of the study may be equipped with more highly trained staff to perform thoracoscopy • disproportionately more males included in the study than females
Non-Randomized Observational Studies	
Chen,[24] 2018	
• Patient inclusion criteria and intervention was clearly described • Potential complications associated with medical thoracoscopy were reported	• Purpose of study not stated upfront • Unclear exclusion criteria and outcomes to be assessed apriori • Unclear about the source population from which the patients were included in the study. • The single site of the may be equipped with more highly trained staff to perform thoracoscopy • Sample size calculation was not performed • Confounders were not identified and investigated • Statistical analyses was not outlined at outset of study
Ooi,[23] 2018	
• Purpose of the study was provided • Inclusion criteria, intervention and outcomes of interest (i.e., major and minor complications) were defined upfront • No conflicts of interest	• Exclusion criteria is unclear • Unclear about the source population from which the patients were included in the study. • Since patients included in the study were those admitted to the ICU, these patients may be more high risk and therefore likely to experience complications

Strengths	Limitations
	• Sample size calculation was not performed • Confounders were not identified and investigated • Statistical analyses was not outlined at outset of study
Colella,[25] 2017	
• Purpose of the study is described • Patient inclusion criteria and intervention was clearly described	• Unclear exclusion criteria and what outcomes were defined under 'usefulness' in the study's aim • Unclear about the source population from which the patients were included in the study. • The single site of the may be equipped with more highly trained staff to perform thoracoscopy • Unclear what was defined as immediate complications • Sample size calculation was not performed • Confounders were not identified and investigated • Statistical analyses was not outlined at outset of study
Patil,[34] 2016	
• Purpose of the study is described • Patient inclusion criteria and intervention was clearly described	• Unclear about exclusion criteria • Confounders were not identified and investigated • Sample size calculation was not performed • Statistical analyses was not outlined at outset of study • Major and minor complications were not defined apriori
Wang,[28] 2015	
• Purpose of the study is outlined • Inclusion criteria, intervention and outcomes were stated upfront • Statistical analysis was outlined at the outset of the study	• Unclear about exclusion criteria • The single site of the may be equipped with more highly trained staff to perform thoracoscopy • Unclear if all possible complications were assessed. For example, mortality was not reported • Confounders were not identified and investigated • Sample size calculation was not performed
Lad,[27] 2015	
• Purpose of the study is described • Patient inclusion and exclusion criteria and intervention was clearly described	• Unclear about location of the study and whether cases were identified from a database • Unclear how serious complications were defined and not all possible adverse events associated with flexi-rigid thoracoscopy were identified • Sample size calculation was not performed • Confounders were not identified and investigated • Statistical analyses was not outlined at outset of study
Kiani,[26] 2015	
• Purpose of the study is described • Patient inclusion and exclusion criteria, as well as outcomes were described • Statistical analyses outlined at outset of study • Complications associated with thoracoscopy were reported • Authors declared no conflict of interest.	• Unclear about the source population from which the patients were included in the study. • The location of the study (i.e., tertiary referral centre) is where all tuberculosis and complicated lung disease patients are referred which may contribute to more adverse events reported • Confounders were not identified and investigated

Strengths	Limitations
	• Sample size calculation was not performed • Unequal distribution of males and females in sample • Unclear whether rigid or semi rigid thoracoscopy was performed •
Willendrup,[33] 2014	
• Purpose of the study is described • Inclusion criteria and intervention were described • Time period of study is stated • Study was conducted in two hospital centers increasing the generalizability of the results	• Exclusion criteria is unclear • Unclear about the source population from which the patients were included in the study. • Outcomes not clearly defined a priori (e.g., types of adverse events of interest) • Sample size calculation was not performed • Statistical analyses not outlined at outset of study • Confounders were not identified and investigated • Study not reported to the Research Ethics Committee
Gao,[29] 2014	
• Purpose of the study is described • Patient inclusion and exclusion criteria, intervention and outcomes were described • Complications due to flexible rigid thoracoscopy were reported • Time period of study is stated	• The single site may be equipped with more highly trained staff to perform thoracoscopy • Sample size calculation was not performed • Statistical analyses not outlined at outset of study • Confounders were not identified and investigated • Portion of patients that experienced minimal to moderate hemorrhage is unclear
Metintas,[30] 2013	
• Purpose of the study is described • Patient inclusion and exclusion criteria, intervention and outcomes (e.g., complications of interest) were described at the outset of the study • Time period of retrospective study was stated • Ethics committee approval was obtained • Statistical analyses were outlined at the outset of the study • Confounders were adjusted • P values were stated	• Unclear about the source population from which the patients were included in the study. • The single site of the may be equipped with more highly trained staff to perform thoracoscopy • Sample size calculation was not performed
Brims,[31] 2012	
• Purpose of the study is described • Patient inclusion criteria, intervention and outcomes were described • Statistical analyses outlined at outset of study • None of the authors have any conflicts of interest, no financial or other potential conflicts of interest • Complications due to rigid thoracoscopy were reported	• Unclear about the starting year and completion of the 12 month study period • Ethics committee approval was not considered necessary • unclear exclusion criteria • Sample size calculation was not performed • The single site of the may be equipped with more highly trained staff to perform thoracoscopy • Confounders were not identified and investigated
Mootha,[32] 2011	
• Purpose of the study is described • Patient inclusion and exclusion criteria, intervention and outcomes were described • Time period of retrospective study was stated	• Unclear about the source population from which the patients were included in the study. • The single site may be equipped with more highly trained staff to perform thoracoscopy

Strengths	Limitations
• Complications due to rigid thoracoscopy were reported	• Unclear how patients were recruited and enrolled in study • Sample size calculation was not performed • Statistical analyses not outlined at outset of study • Confounders were not identified and investigated

Table 9: Strengths and Limitations of Diagnostic Studies using QUADAS 2[11]

Strengths	Limitations
Thomas,[16] 2017	
• The reference test was interpreted prior to conducting the index test	• Unclear if consecutive patients enrolled or random sample • Description of how reference standard was conducted is unclear • Unclear if index test results were interpreted without knowledge of reference test results • Unclear the interval between index test and reference standard • Unclear if all patients were included in the analysis • No 2x2 table available
Nattusamy,[15] 2015	
• Method of patient selection described • Description of index test provided • The reference test was interpreted prior to conducting the index test • All patients received the same reference standard	• Unclear if consecutive patients enrolled • Description of how reference standard was conducted is unclear • Unclear if there was any inappropriate exclusion • Unclear if index test results were interpreted without knowledge of reference test results • Unclear the interval between index test and reference standard • No 2x2 table available
Rozman,[17] 2014	
• Description of index test provided • Method of patient selection is outlined • The interval between the index test and reference standard is clear • Index test results were interpreted without knowledge of reference test results • Analysis included all patients that received either rigid or semi rigid thoracoscopy	• Unclear if consecutive patients enrolled • Unclear if there was any inappropriate exclusion • Description of how reference standard was conducted is unclear • No 2x2 table available • Unclear if all patients received the same reference standard
Rozman,[18] 2013	
• Consecutive patients were enrolled • Method of patient selection is provided • Description of index test is provided • The interval between the index test and reference standard is clear • Index test results were interpreted without knowledge of reference test results • Analysis included all patients that received either rigid or semi rigid thoracoscopy	• Description of how the reference standard was conducted is unclear • Unclear if there was any inappropriate exclusion and reasons why 27 patients declined to participate • No 2x2 table is available • Unclear if all patients received the same reference standard

Table 10: Strengths and Limitations of Economic Studies using the Drummond Checklist[12]

Strengths	Limitations
McDonald,[19] 2018	
• Cost analysis was conducted to reflect a single-payer public health care system • The secondary aim is stated and outcome measure (i.e., procedure-related cost) • The rationale for choosing video-assisted thoracoscopic surgery as an alternative technique is stated and described • Direct and indirect costs were defined and retrieved from the hospital administrative database • Cost data were adjusted for inflation to Canadian dollars according to the price level of May 2017 • Shorter hospital length of stay associated with semi-rigid thoracoscopy performed in an outpatient setting is noted when presenting the results of cost per procedure for semi-rigid thoracoscopy compared to video-assisted thoracoscopic surgery	• Characteristics such as age (years) and presence of comorbidities (i.e., diabetes mellitus, congestive heart failure and coronary artery disease) were statistically different between patients in the semi-rigid thoracoscopy and VATS group and these characteristics were not adjusted for in the cost analysis • The study authors concluded that there was no statistically significant difference in the diagnostic test performance between semi-rigid thoracoscopy and VATS, however a single P value was provided which makes it unclear if this P value reflects the sensitivity, specificity, positive predictive value or negative predictive values • No details of how the cost analysis (e.g., how cost data were synthesized and analyzed) was provided • Unclear whether quantities of resource use were separated from unit costs • Indirect and direct costs associated with patient and caregiver loss of productivity due to the diagnosis and management were not captured in the cost analysis No sensitivity analysis and incremental analysis is reported

Table 11: Strengths and Limitations of Guidelines using AGREE II[13]

Item	Guideline
	Rahman et al., 2010[2]
Domain 1: Scope and Purpose	
1. The overall objective(s) of the guideline is (are) specifically described.	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Unclear
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes
Domain 2: Stakeholder Involvement	
4. The guideline development group includes individuals from all relevant professional groups.	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes
6. The target users of the guideline are clearly defined.	Yes
Domain 3: Rigour of Development	
7. Systematic methods were used to search for evidence.	Yes
8. The criteria for selecting the evidence are clearly described.	Yes

Item	Guideline
	Rahman et al., 2010[2]
9. The strengths and limitations of the body of evidence are clearly described.	No
10. The methods for formulating the recommendations are clearly described.	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Yes
14. A procedure for updating the guideline is provided.	No
Domain 4: Clarity of Presentation	
15. The recommendations are specific and unambiguous.	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes
17. Key recommendations are easily identifiable.	Yes
Domain 5: Applicability	
18. The guideline describes facilitators and barriers to its application.	Yes
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes
20. The potential resource implications of applying the recommendations have been considered.	No
21. The guideline presents monitoring and/or auditing criteria.	Yes
22. The views of the funding body have not influenced the content of the guideline.	No
23. Competing interests of guideline development group members have been recorded and addressed.	Yes

Appendix 4: Main Study Findings and Authors' Conclusions

Table 12: Summary of Findings of Included Systematic Reviews

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Nattusamy,[15] 2015</td></tr>
<tr><td>Four studies met the inclusion criteria for patients with undiagnosed pleural effusions that received semi-rigid thoracoscopy in India. Two studies reported no significant procedural complications. One study reported subcutaneous emphysema (n=3) and prolonged air leak (n=1). One study reported the following significant major procedural complications: empyema (n=1), air leak (>3 days) (n=1), re-expansion pulmonary edema (n=1). Minor complications included the following: subcutaneous emphysema (n=3), operative site infection (n=1), minor hemorrhage (n=1), non-infective fever (n=1)</td><td>According to the author, "Medical thoracoscopy should be considered in all patients with undiagnosed exudative pleural effusions. Semi-rigid thoracoscopy is a safe procedure with high diagnostic yield in undiagnosed pleural effusion."[15] (pp8)</td></tr>
<tr><td colspan="2">Mohan,[14] 2010</td></tr>
<tr><td>Five studies (n=154 patients) met the inclusion criteria for patients with pleural effusion of undetermined etiology.

<table><tr><td>Pooled sensitivity (95% CI)</td><td>Pooled specificity (95% CI)</td><td>positive likelihood ratio (95% CI)</td><td>negative likelihood ratio (95%CI)</td></tr><tr><td>0.97 (0.92 to 0.99)</td><td>1.00 (0.69 to 1.00)</td><td>5.47 (1.77 to 16.86)</td><td>0.08 (0.04 to 0.18)</td></tr></table>
No major complications and mortality occurred after 30 days' follow-up period. Air leakage occurred in 2 patients (0.01%) and pneumothorax in 1 patient (0.01%).</td><td>The authors concluded that, "MT is a highly specific test to determine etiology in PEUE with diagnostic odd ratio of over 96. A negative LR less than 0.1 is generally considered clinically useful.[17] Three of the included studies had negative LRs of less than 0.1 and the pooled negative LR is less than 0.1, thereby further enhancing the usefulness of MT in the diagnosis of PEUE. All the patients tolerated MT well with no major complication and 30-day mortality rate of 0%." [14] (pp6)</td></tr>
</table>

Table 13: Summary of Findings of Included Randomized and Non-Randomized Studies

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Randomized Controlled Studies</td></tr>
<tr><td colspan="2">Dhooria,[20] 2014</td></tr>
<tr><td>Among the 45 patients that received rigid thoracoscopy, 16 major and minor complications occurred. Three cases each of empyema occurred and persistent air leak (> 3days). No major hemorrhage occurred</td><td>The author concluded, "complication rate was similar in the 2 arms. More subjects in the rigid arm had persistent air leak and/or empyema, which was attributed to extensive adhesiolysis."[20]. (pp8)</td></tr>
<tr><td colspan="2">Rozman,[18] 2013</td></tr>
<tr><td><table><tr><td>Procedure</td><td>Diagnostic accuracy (%)</td><td>Sensitivity for malignancy (%)</td><td>Specificity for malignancy (%)</td><td>NPV for malignancy (%)</td></tr><tr><td>Semi rigid thoracoscopy</td><td>97.6</td><td>96.6</td><td>100</td><td>92.3</td></tr></table></td><td>The author concluded, "semi-rigid thoracoscopy is not only safe but is also a highly accurate diagnostic method for evaluating pleural effusion of unknown aetiology and pleural irregularities suspicious for pleural malignancy."[18] (pp6)</td></tr>
</table>

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td>
<table>
<tr><td>Rigid thoracoscopy</td><td>100</td><td>100</td><td>100</td><td>100</td></tr>
</table>
For rigid thoracoscopy, a major complication of severe bleeding occurred in one patient due to an aberrant blood vessel after pleural biopsy. The patient recovered from the hemorrhage without sequelae. For semi rigid thoracoscopy, one major complication occurred (i.e., empyema caused by methicillin-sensitive Staphylococcus). This patient recovered following chest-tube drainage and antibiotic treatment
</td><td></td></tr>
<tr><td colspan="2">Metintas,[21] 2010</td></tr>
<tr><td>Among 62 patients that received Thoracoscopy, 10 patients experienced percutaneous emphysema, 2 patients with extended air leakage and 0 patients had pneumothorax</td><td>According to the authors, "When the two methods were compared in terms of complications, both were observed to be safe."[21] (pp6)</td></tr>
<tr><td colspan="2">Non-Randomized Studies</td></tr>
<tr><td colspan="2">Bansal,[22] 2019</td></tr>
<tr><td>There were no procedure-related death.</td><td>According to the authors, "there were no serious adverse events or procedure-related mortality."(pp1)</td></tr>
<tr><td colspan="2">Chen,[24] 2018</td></tr>
<tr><td>Complications associated with MT was assessed in 86 patients. Pleural hemorrhage occurred in 8 cases (9.3%)</td><td>The authors concluded that medical thoracoscopy "has the advantages of visual inspection, easy procedure, high safety and few complications."[24] (pp5)</td></tr>
<tr><td colspan="2">McDonald,[19]2018</td></tr>
<tr><td>
<table>
<tr><th>Procedure</th><th>Sensitivity (%)</th><th>Specificity (%)</th><th>PPV (%)</th><th>NPV (%)</th></tr>
<tr><td>Semi rigid thoracoscopy*</td><td>85</td><td>100</td><td>100</td><td>79</td></tr>
<tr><td>VATS*</td><td>93</td><td>94</td><td>99</td><td>76</td></tr>
</table>
*assessment of malignant, suspicious for malignancy, and granulomatous inflammation

There were no patients that experienced death within 30 days in the semi-rigid thoracoscopy group compared to 2 patients (2%) in the VATS group (P value 0.504). There were no patients that experienced hemorrhage in the semi-rigid thoracoscopy group compared to 2 patients (2%) in the VATS group (P value 0.504). One patient (1.3%) experienced alveolar-pleural fistula in the semi-rigid thoracoscopy group compared to no patients in the VATS group (P value 0.441).

The mean procedure-related cost in Canadian dollars for patients that received semi-rigid thoracoscopy was $2,815 (95% CI 2,010 to 3,620) compared to $7,962 (95% CI 7,134 to 8,790) for patients that received VATS (P value <0.001).
</td><td>According to the authors, "semi-rigid thoracoscopy and VATS have a similar diagnostic yield and safety profile in the assessment of undiagnosed exudative pleural effusions. In this patient population, semi-rigid thoracoscopy is associated with a shorter hospital stay and a lower average per-procedure cost."[19](pp7)</td></tr>
</table>

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Ooi,[23] 2018</td></tr>
<tr><td>Complications associated with MT was assessed in 86 patients. Pleural hemorrhage occurred in 8 cases (9.3%)</td><td>The authors concluded that medical thoracoscopy "has the advantages of visual inspection, easy procedure, high safety and few complications."[24] (pp5)</td></tr>
<tr><td colspan="2">Thomas,[16] 2017</td></tr>
<tr><td>The diagnostic accuracy of MT for tuberculous pleural effusion was 91.4%. In addition, the sensitivity was 90% and specificity was 100%.</td><td>The authors stated the "safety and value of MT as a diagnostic modality for undiagnosed exudative pleural effusions."[16] (pp4)</td></tr>
<tr><td colspan="2">Colella,[25] 2017</td></tr>
<tr><td>Complications associated with rigid thoracoscopy was assessed in 10 patients. Results showed no immediate complications related to the procedure were recorded</td><td>The authors concluded "the safety and the effectiveness of MT in patients with CKD." [25] (pp5)</td></tr>
<tr><td colspan="2">Patil,[34] 2016</td></tr>
<tr><td>Complications associated with rigid thoracoscopy was evaluated. No major complications occurred. Air leak occurred in 4.6% of patients and empyema (2.3%). There was no procedure related mortality.</td><td>The authors concluded that "pleuroscopy is a safe, well-tolerated procedure with minimal risk." [34] (pp5)</td></tr>
<tr><td colspan="2">Kiani,[26] 2015</td></tr>
<tr><td>11 patients experienced minor complications of which 4 patients reported minor bleeding.</td><td>The author stated that "pleuroscopy is a safe procedure when performed by a skilled and experienced practitioner; it has a high diagnostic yield and results in only minor complications." [26] (pp4)</td></tr>
<tr><td colspan="2">Lad,[27] 2015</td></tr>
<tr><td>No serious complications were reported while the procedure was performed.</td><td>The author stated that "flex-rigid pleuroscopic biopsies provided a definitive diagnosis in 70.5% cases of exudative pleural effusion of unknown origin where other less invasive procedures like pleural fluid cytology and sputum examination were inconclusive." [27] (pp7) No conclusions were made on the safety of flex-rigid thoracoscopy.</td></tr>
<tr><td colspan="2">Nattusamy,[15] 2015</td></tr>
<tr><td>The following results are presented for semi rigid thoracoscopy.

<table>
<tr><th>Sensitivity for malignant pleural effusion (%)</th><th>Specificity for malignancy (%)</th><th>PPV for malignant pleural effusion (%)</th><th>NPV for malignant pleural effusion (%)</th></tr>
<tr><td>96.77</td><td>100</td><td>100</td><td>66.77</td></tr>
</table>

Minor bleeding occurred in 2 patients and there was no procedure-related mortality.</td><td>The authors concluded that, "Medical thoracoscopy should be considered in all patients with undiagnosed exudative pleural effusions and semi-rigid thoracoscopy is a safe procedure."[15] (pp8)</td></tr>
<tr><td colspan="2">Wang,[28] 2015</td></tr>
<tr><td>Complications of semi rigid thoracoscopy were assessed among 833 patients. Three patients (0.4%, 95% CI -0.03 to 0.8) experienced empyema. Minor bleeding occurred in 38 patients (4.6%, 95 CI 3.2 to 6.0). Major bleeding did not occur.</td><td>The authors concluded that "MT is an efficacious procedure in the diagnosis of undiagnosed exudative pleural effusions with excellent safety." [28] (pp4)</td></tr>
</table>

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Willendrup,[33] 2014</td></tr>
<tr><td>A pro-longed air leak of >48 hours along with an additional chest tube placement occurred on 2 patients. No mortality was present as a result of MT.</td><td>The author stated that "MT performed under local anesthesia with a semirigid scope is a simple and safe procedure." [33] (pp5)</td></tr>
<tr><td colspan="2">Rozman,[17] 2014</td></tr>
<tr><td>The following results are presented for semi rigid thoracoscopy.

<table><tr><td>Diagnostic accuracy (%)</td><td>Sensitivity for malignancy (%)</td><td>PPV for malignancy (%)</td><td>NPV for malignancy (%)</td></tr><tr><td>97.4</td><td>96.0</td><td>100</td><td>93</td></tr></table>
In two patients, pleural infection occurred which resulted in trapped lung, subsequent bronchopleural fistula, and prolonged chest drainage which lasted a duration of up to 22 days.</td><td>The author stated "Semirigid thoracoscopy is an effective and safe method for diagnosing and to some extent treating pleural disorders. " [17] (pp5)</td></tr>
<tr><td colspan="2">Gao,[29] 2014</td></tr>
<tr><td>The proportion of patients that experienced minimal to moderate hemorrhage at the biopsy site is unclear however no special treatment was required.</td><td>The author concluded that "flexi-rigid thoracoscopy, with the guidance role for primary disease, has the higher diagnosis rate in differentiating exudative pleural effusion of unknown
etiology, and it is worthy to wider clinical use because of its
satisfactory effectiveness and safety."[29] (pp5)</td></tr>
<tr><td colspan="2">Metintas,[30] 2013</td></tr>
<tr><td>There were 208/355 patients (58.6%) with no complications. Hemorrhage occurred in 3 patients (1.7%), prolonged air leak ≤ 5 days in 4 patients (2.3%), prolonged air leak > 5 days in 4 patients (2.3%) and empyema in 1 patient (0.6%).</td><td>The author stated that "MT under local anesthesia and mild sedation was a safe method for the diagnosis of patients with pleural effusions." [30] (pp8)</td></tr>
<tr><td colspan="2">Brims,[31] 2012</td></tr>
<tr><td>Among 57 patients with complete data that received rigid thoracoscopy, empyema occurred in 2 patients (3.5%) and pneumonia occurred in 4 patients (7.0%). There was no death (as a result of the procedure) and bleeding (minor/major) reported.</td><td>The author concluded that "serious complications after conducting rigid thoracoscopy are rare." [31] (pp1)</td></tr>
<tr><td colspan="2">Mootha,[32] 2011</td></tr>
<tr><td>Based on 35 thoracoscopic procedures performed, empyema occurred in 2 patients (5.2%). Hemorrhage did not occur.</td><td>The authors stated that "medical thoracoscopy is a safe procedure."[32] (pp1) The authors suggest that "medical thoracoscopy should be considered in patients with undiagnosed pleural effusions, particularly those lymphocytic exudative effusions where TB and malignant pleural effusion are clinical possibilities and initial pleural fluid analysis is inconclusive." [32] (pp4)</td></tr>
</table>

MT = medical thoracoscopy, VATS= video-assisted thoracoscopic surgery, CI=confidence interval

Table 14: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
British Thoracic Society pleural disease guideline, 2010[2]	
Safety of local anesthetic thoracoscopy The authors stated, *"Many patients with undiagnosed pleural effusion are unsuitable for surgical diagnostic and therapeutic strategies such as VATS procedures due to comorbidity, limited survival and inability to tolerate general anaesthetic. Local anaesthetic thoracoscopy under intravenous sedation offers these patients a reasonably high likelihood of diagnosis and pleurodesis in a single procedure that is well tolerated."*[2] (pp3)	These recommendations were developed by a working party comprised of professionals and a lay representative whom consulted with stakeholders (e.g., nursing professions, patient groups, health management and industry) to inform the clinical questions, population, intervention, comparator and outcome. A literature search was developed.

VATS = video-assisted thoracoscopic surgery,