Indwelling Pleural Catheters versus Chemical Pleurodesis for Managing Malignant Pleural Effusions: A Population-based Study and Real-World Economic Evaluation Protocol

Chanel Kwok

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Faculty of Medicine

University of Ottawa

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Preface

This thesis is composed of two related components presented in manuscript format: an analysis of indwelling pleural catheter and chemical pleurodesis post-procedure mortality and trends of use in Ontario, Canada and a comparison of post-procedure health service utilization and costs; as well as a protocol for a cost-effectiveness analysis comparing these two interventions for malignant pleural effusions.

The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act (PHIPA), which does not require review by a Research Ethics Board.

For both manuscript components, Dr. Chanel Kwok was involved in the design of the study along with Dr. Tetyana Kendzerska, Dr. Kednapa Thavorn, Dr. Kayvan Amjadi and Dr. Shawn Aaron. De-identified health administrative data from ICES (formerly the Institute for Clinical Evaluative Sciences) was used. Dr. Kwok performed all the data analyses within ICES. She also wrote the manuscripts with feedback and approval obtained from all co-authors prior to submission. For the economic evaluation protocol, Dr. Kwok contributed to the study design with Dr. Thavorn. The thesis manuscript was written by Dr. Kwok with guidance from her thesis advisory committee (Dr. Thavorn, Dr. Kendzerska, Dr. Amjadi and Dr. Aaron).

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information provided by Cancer Care Ontario (CCO). The opinions, results, view, and conclusions reported in this paper are those of the authors and do not necessarily reflect those of CCO. No endorsement by CCO is intended or should be inferred. Parts of this material are based on data and/or information compiled and provided by Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions and statements expressed in the material are those of the author(s), and not necessarily those of CIHI.

Abstract

There is limited data on mortality, health service use and costs following treatment of malignant pleural effusions (MPE) in the real-world setting.

We performed a retrospective population-based study using health administrative data of adults with indwelling pleural catheter (IPC) insertion (n=4,574) or pleurodesis (n=1,235) for MPE between 2015 to 2019. Inverse probability of treatment weighting using the propensity score was performed to adjust for baseline characteristic imbalances.

After weighting to balance on baseline characteristics, there was no significant difference in post-procedure mortality between individuals receiving IPCs and pleurodesis, with IPCs inserted significantly later after an initial cancer diagnosis. IPCs with home nursing drainage were associated with reduced subsequent health resource use and healthcare costs compared to pleurodesis. A protocol was developed for a future economic evaluation to compare the cost-effectiveness of the procedures. This thesis provides the foundation for further research to help optimize the treatment of individuals with MPEs.

Acknowledgments

I wish like to thank my supervisors Dr. Kednapa Thavorn and Dr. Tetyana Kendzerska for their incredible support and guidance throughout this thesis, as well as the other members of my thesis advisory committee Dr. Kayvan Amjadi and Dr. Shawn Aaron for sharing their time and expertise. It has been a privilege to learn from such a knowledgeable group of individuals. I also wish to thank Meltem Tuna, Anan Eddeen, and Roshanak Mahdavi for their assistance with using ICES data. I am very grateful for the financial support of The Ottawa Hospital Department of Medicine Academic Scholarship and the TOHAMO Innovation Fund grant, which helped to make completion of this thesis possible.

Finally, I wish to thank my family (which grew by one during the course of this Masters) for their support through this journey during these unpredictable times.

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List of abbreviations

ADG = Aggregated Diagnosis Groups
ATE = Average treatment effect
ATT = Average treatment effect among the treated population
CADTH = Canadian Agency for Drugs and Technologies in Health
CCI = Canadian Classification of Health Interventions
CCO = Cancer Care Ontario
CHF = Congestive heart failure
CI = Confidence interval
CIHI = Canadian Institute for Health Information
COPD = Chronic obstructive pulmonary disease
CUA = Cost utility analysis
DAD = Discharge Abstract Database
ED = Emergency department
HR = Hazard ratio
HSU = Health service utilization
ICER = Incremental cost-effectiveness ratio
IPC = Indwelling pleural catheters
IPTW = Inverse probability of treatment weighting
IQR = Interquartile range
LOS = Length of stay
MPE = Malignant pleural effusion
OHIP = Ontario Health Insurance Plan
PS = Propensity score
QALY= Quality-adjusted life year
RCT = Randomized control trial
SD = Standard deviation
SDS = Same Day Surgery Database
SHR = Subdistribution hazard

Chapter 1. Introduction

1.1 Overview of malignant pleural effusions

Malignant pleural effusions (MPE) are a manifestation of advanced stage cancer, developing most commonly in patients with lung cancer, mesothelioma and breast cancer.(1) They are typically defined by definitive histocytological proof of malignancy on pleural biopsy or pleural fluid cytology, or clinically in the presence of a (exudative) pleural effusion with (histocytological) evidence of malignancy outside the pleura. MPEs develop when fluid accumulates in the pleural space due to an underlying malignancy. It is thought this is due to a combination of increased fluid production from leaky pleural vessels and impaired fluid absorption at the levels of parietal pleural lymphatic stomata to hilar and mediastinal lymph nodes.(2)

1.1.1 Epidemiology of malignant pleural effusions

Although epidemiologic data is quite sparce, with no data available for Canadian patients, in the United States the annual incidence of MPE is estimated to be greater than 150,000 cases.(3) Older studies have found 15% of cancer patients who had autopsies performed had malignant effusions.(4) In patients with mesothelioma the incidence can be as high as 90%. For lung cancer, up to 15% of patients will have a MPE at time of presentation, up to 50% will develop one over the duration of their disease.(5–7) It has also been reported that up to 65% of breast cancer patients with disseminated disease will develop a MPE.(3) As lung cancer is the most commonly diagnosed cancer in Canada with an estimated 29,800 new cases diagnosed in 2020, and breast cancer is the most common cancer among Canadian women, accounting for 1 in 4 new cancer diagnoses, MPEs are likely to affect a significant number of Canadians.(8)

1.1.2 Natural history of malignant pleural effusions

Although nearly every kind of malignancy has been reported to cause MPEs, their natural history is highly variable. Some patients may be asymptomatic, while others will develop dyspnea, cough and chest discomfort, leading to reduced quality of life.(9–12) In lung cancer, approximately half of effusions are asymptomatic and too small to attempt drainage.(7, 13) Over 80% of the remaining patients will require one or more palliative interventions for symptomatic relief.(7) In patients over 65 years, 55% required a second pleural drainage after an initial thoracentesis for a MPE.(11) Over half of these repeat procedures occurred within 2 weeks, suggesting a rapid re-accumulation.

1.2 Current evidence on interventions for malignant pleural effusions

International guidelines have been developed for the management of MPEs.(14, 15) They recommend management with either indwelling pleural catheter (IPC) insertion or chemical pleurodesis, for which talc is the agent with the highest reported effectiveness and can be administered as a slurry through a chest tube.(14, 15)

1.2.1 Indwelling pleural catheters

An IPC is a tunneled catheter that can be placed during an outpatient procedure and remain in situ for months to years. IPCs allow access to the pleural space for intermittent drainage which is ideal for MPEs which often continue to reaccumulate. Intermittent drainage can be performed in the patient’s residence and internationally is typically performed by patients themselves or their relatives with the frequency guided by symptoms. In Canada, drainage is performed by home nursing services funded by the public health care system, and the frequency of drainage is per physician orders. There is no standardized drainage frequency regimen, however one randomized control trial (RCT) demonstrated that patients who had daily drainage had a shorter time to pleurodesis than drainage every other day.(16)

IPCs are typically removed when ‘pleurodesis’ has been achieved and there is minimal to no further pleural fluid drainage. Once the catheter has been removed, home nursing services are only required for an additional 1 to 2 weeks. The most common complications include skin and pleural infections, pleural fluid loculations and catheter dislodgement.(12) Complication rates reported in Canadian studies are lower than those reported in international studies, which could be partially due to the differences in drain management.(17–19)

1.2.2 Chemical pleurodesis

Chemical pleurodesis requires the patient to be admitted to a hospital for administration of a sclerosing agent into the pleural space. Pleurodesis with talc has demonstrated reduced pleural effusion recurrence compared to other sclerosing agents such as bleomycin and tetracycline.(15) Pleurodesis can either be performed thoracoscopically with talc poudrage (via surgical video-assisted thoracoscopic surgery or medical thoracoscopy) or at the bedside with talc slurry. Large-particle (graded) talc is recommended, but there has been no clear benefit of one form of administration over the other.(14, 15)

Bedside pleurodesis requires insertion of a small-bore intercostal chest tube for drainage of the pleural space.[3,11](20) If the lung is able to re-expand such that it appears the two pleural surfaces (parietal and visceral) are sufficiently apposed on chest radiograph, a sclerosing agent can then be instilled through the chest tube into the pleural space. The tube is typically clamped for 1 to 2 hours before being opened to drain. Pleural fluid output is subsequently monitored to ensure minimal drainage before the chest tube can be removed 24 to 48 hours after the procedure. Pleurodesis is typically associated with pain and can also result in pleural infection (lower rates compared to IPCs), loculations and rarely airspace disease/interstitial lung disease and death.(17, 21–25)

1.2.3 Choosing interventions

Guidelines do not currently recommend one therapy over the other as IPCs are associated with reduced hospital days and additional ipsilateral interventions due to failed pleurodesis, but increased infectious complications compared to pleurodesis.(12, 14, 15, 17, 21, 22) Either therapy may be initially unsuccessful or the patient may have recurrence of their effusion at a later date after initially achieving pleurodesis.

1.3 Importance of malignant pleural effusions - morbidity, mortality, and resource use

MPEs are associated with significant morbidity, mortality, and resource use.(11, 14, 15) MPEs account for more than 125,000 hospital admissions per year with pleural procedures being performed during 57% of those hospitalizations.(26, 27) A study of US health administrative data found that 25% of patients were readmitted within 30 days of index hospitalizations for MPEs with a 17.3% mortality rate during the repeat admission.(28) Protective factors for readmission were chest tube placement, pleurodesis or pleuroscopy. Due to the nature of the data, the authors were unable to determine which type of chest tube was placed (i.e. IPC versus pigtail chest tube).

Survival with a MPE depends on the underlying cancer type and patient factors, but ranges between 1 to 12 months.(7, 29) The LENT prognostic score for patients with MPE, which includes pleural lactate dehydrogenase levels, Eastern Cooperative Oncology Group performance score, serum neutrophil-to-lymphocyte ratio and tumor type has previously been developed.(29) Participants in the validation cohort with a high risk score had a median survival of 51 days.

Patients with MPE and mesothelioma or breast cancer typically have a much better prognosis than those with lung cancer, where median survival is between 2 to 5 months. Additionally, among lung cancer patients with distant metastases, the presence of a MPE is associated with reduced survival.(6) Only two randomized studies have previously looked at survival as a (secondary) outcome, after IPC insertion and pleurodesis.(17, 30) A network meta-analysis did not find any significant difference in post-procedure survival between IPCs or talc slurry pleurodesis, although there was a low degree of certainty about the findings due to wide credible intervals and variable times of follow-up in the included studies.(12)

No studies have assessed health service utilization (HSU) other than hospital days following IPC insertion or pleurodesis, such as Emergency Department (ED), outpatient or home nursing visits. The latter of which is especially important given the care delivery model following IPC insertion in Canada. Patients with advanced malignancy may require home nursing care for symptom management or other complications related to their disease and/or its treatments. It is not known how much additional home nursing care is required for patients with an IPC.

1.4 Economic evaluation of IPC insertion versus chemical pleurodesis

IPC insertion and pleurodesis provide two very different approaches to care, with the same aim to reduce symptoms. The goal of IPC insertion is to minimize hospital days required to perform the procedure and instead provide effusion-related care at home where the IPC can be intermittently accessed. The goal of pleurodesis is to perform a single procedure that following hospital discharge, does not require ongoing home nursing care. Given the rising healthcare costs and high HSU by patients with MPE, it is important to determine how best to effectively manage them.

1.4.1 Procedure costs

The cost for IPCs include the cost of the initial insertion and ongoing costs after insertion due to the need for home nursing drainage and drainage supplies. Costs for pleurodesis relate to costs of inserting a pigtail catheter at the bedside with administration of a sclerosing agent through the tube, or performing a video-assisted thoracoscopic surgery under anesthesia with instillation of the sclerosing agent and placement of a chest tube. Additional costs relate to the hospital admission days required for both pleurodesis procedures for post-operative recovery and/or cessation of drainage from the chest tube. The only study to directly compare post-procedure costs between these procedures was based on a RCT population, which limits the applicability to the real-world setting, and assumed home care hours and costs.(31)

1.4.2 Importance of economic evaluations

Economic evaluations measure both cost and outcomes in order to assess trade-offs between interventions.(32, 33) They are especially useful when one of the interventions is not dominant (i.e. the most effective option is not also the cheapest option or vice versa). The results of an economic analysis can then detail how much must be paid for the improved outcome. Due to the limitations on healthcare funding this is an important metric, as funding for one program will remove resources from another area, so called opportunity cost.(33) Cost utility analysis (CUA) is a type of economic evaluation that allows comparison between interventions to determine the incremental cost of one intervention over another, per quality-adjusted life year (QALY) gained, the incremental cost-effectiveness ratio (ICER). These results can provide decision makers with the information to guide funding and support initiatives to improve patient care.

1.4.3 Previous economic evaluations of IPC insertion versus pleurodesis

Only a few studies have previously looked at the cost-effectiveness of IPC insertion compared to pleurodesis. Two such studies were performed before the main RCTs were published, and are therefore based on limited and outdated efficacy and complication data.(34, 35) A more recent cost-effectiveness analysis was based on a small RCT (n=106).(31) It found that IPCs were more cost-effective compared to talc pleurodesis, with an ICER of $US10,870 per QALY gained. This result was associated with significant uncertainty due to the small sample size resulting in the 1000 bootstrapped ICER point estimates subsiding in all four quadrants of the cost-effectiveness plane. Additionally, home nursing requirements and time data were based on an assumption due to a paucity of data. The impact of these variables on the cost-effectiveness of IPC requires further exploration. More importantly, it remains unknown whether IPC is cost-effective for the Canadian context.

1.5 Thesis overview and objectives

This thesis consists of two components presented as manuscript 1 and manuscript 2, as well as an economic evaluation protocol. Both manuscripts will be submitted for publication. Overall, this thesis had the following objectives:

1. To compare post-procedure mortality of patients receiving IPC insertion to those receiving pleurodesis.
2. To describe and compare baseline characteristics (patient-, physician-, and hospital-level) of individuals receiving IPC insertion to those receiving chemical pleurodesis.

3. To compare annual and regional trends in IPC insertions and pleurodesis procedures.
4. To compare post-procedure HSU including hospital admissions, length of stay, ED, and home care visits among individuals with MPE in Ontario who were treated with IPC insertion or pleurodesis.
5. To calculate and compare health system costs from the time of the procedure (IPC insertion or pleurodesis) until death, 12-months or end of follow-up, whichever occurs first.
6. To outline a protocol for conducting a cost-utility analysis comparing IPC insertion to pleurodesis.

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Chapter 2. Mortality after treatment of malignant pleural effusions with indwelling pleural catheters versus pleurodesis: A population-based study (Manuscript 1)

Chanel Kwok[1,2,3], Kednapa Thavorn[2,3,4], Kayvan Amjadi[1,4], Shawn D. Aaron[1,3,4], Tetyana Kendzerska[1,2,3,4]

[1]Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada; [2]ICES Ottawa;
[3]School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada;
[4]Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

Corresponding author:
Chanel Kwok, MD
The Ottawa Hospital, Division of Respirology
501 Smyth Road, Box 211
Ottawa, ON K1H 8L6
Phone: 613-737-8899 Ext. 79679
Fax: 613-737-6993
chkwok@toh.ca

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2.1 Abstract

Rationale: Little is known about patient outcomes following treatment of malignant pleural effusions (MPE) in the real-world setting.

Objectives: We aimed to compare post-procedure all-cause mortality between individuals who received indwelling pleural catheter (IPC) insertion versus pleurodesis for managing MPEs.

Methods: We performed a retrospective population-based study using provincial health administrative data (Ontario, Canada) of adults with a MPE who underwent IPC insertion or pleurodesis between 2015 to 2019. Individuals were followed until death or March 31, 2021. Difference in post-procedure mortality was calculated using inverse probability of treatment weighting-adjusted Cox proportional hazard regression analysis to balance potential confounders.

Measurements and Main Results: We identified 4,790 (77.3%) individuals who received an IPC and 1,407 (22.7%) who had pleurodesis for MPE. The majority of IPCs were inserted in outpatients (61%), by pulmonologists (64.2%) and at sites with higher annual IPC volume. Median time from initial cancer diagnosis to intervention was significantly longer in the IPC group (244 days, interquartile range [IQR]:33-903) compared to pleurodesis group (81 days, IQR:10-737; p<0.0001). Median time from index procedure to death was significantly longer in the pleurodesis group (165[IQR:48-457] days vs 81[IQR:29-256] days, p<0.0001), however the difference between groups become insignificant after weighted survival analysis was performed (HR 1.27, 95%CI 0.95-1.69).

Conclusions: Although median post-procedure survival time was longer in the pleurodesis group, this difference was primarily driven by differences in timing of the two procedures. After

adjusting for differences in baseline characteristics we found no significant difference in post-procedure mortality following IPC versus pleurodesis.

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2.2 Introduction

Malignant pleural effusions (MPE) can develop in any advanced stage cancer, including up to 50% of individuals with lung cancer, 65% with disseminated breast cancer and 90% with mesothelioma.(1–6) MPEs are estimated to affect more than 150,000 individuals in the United States each year, based on autopsy case series.(2)

International guidelines recommend either indwelling pleural catheter (IPC) insertion or talc pleurodesis as definitive treatment for symptomatic MPEs.(7, 8) Limited data is available on the how these treatments are being utilized in clinical practice. Both procedures reduce breathlessness and improve quality of life.(9, 10) Pleurodesis requires hospital admission and full lung re-expansion after pleural fluid removal, whereas IPCs can be placed in the outpatient setting and can still be utilized in individuals with a non-expanding lung. IPCs are associated with reduced hospital days and reduced need for repeat ipsilateral interventions due to failed pleurodesis, but increased infectious complications compared to talc pleurodesis.(7–12)

Survival with a MPE depends on the underlying cancer type, cancer treatments, and patient factors, but ranges between 1 to 12 months.(5, 13–15) A network meta-analysis of randomized control trials (RCTs) did not find any significant difference in post-procedure survival between IPCs or talc slurry pleurodesis, although there was a low degree of certainty about the findings.(12) These studies have excluded patients with an expected survival of less than 3 months.(9, 10) Given the poor prognosis in individuals with MPE, these RCTs may not have captured how these procedures are being used in the real world.

Our study aimed to: (1) compare post-procedure all-cause mortality; (2) describe the patterns and patient-, physician- and hospital-characteristics associated with interventions, and (3) compare subsequent pleural procedures between individuals receiving IPC insertion versus pleurodesis for MPEs. We hypothesized that based on existing literature there would be no difference in post-procedure mortality, but IPCs would be associated with reduced repeat pleural procedures.

2.3 Methods

2.3.1 Study design and setting

We performed a retrospective cohort study using provincial health administrative data (Ontario, Canada). The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act (PHIPA), which does not require review by a Research Ethics Board.

2.3.2 Data sources

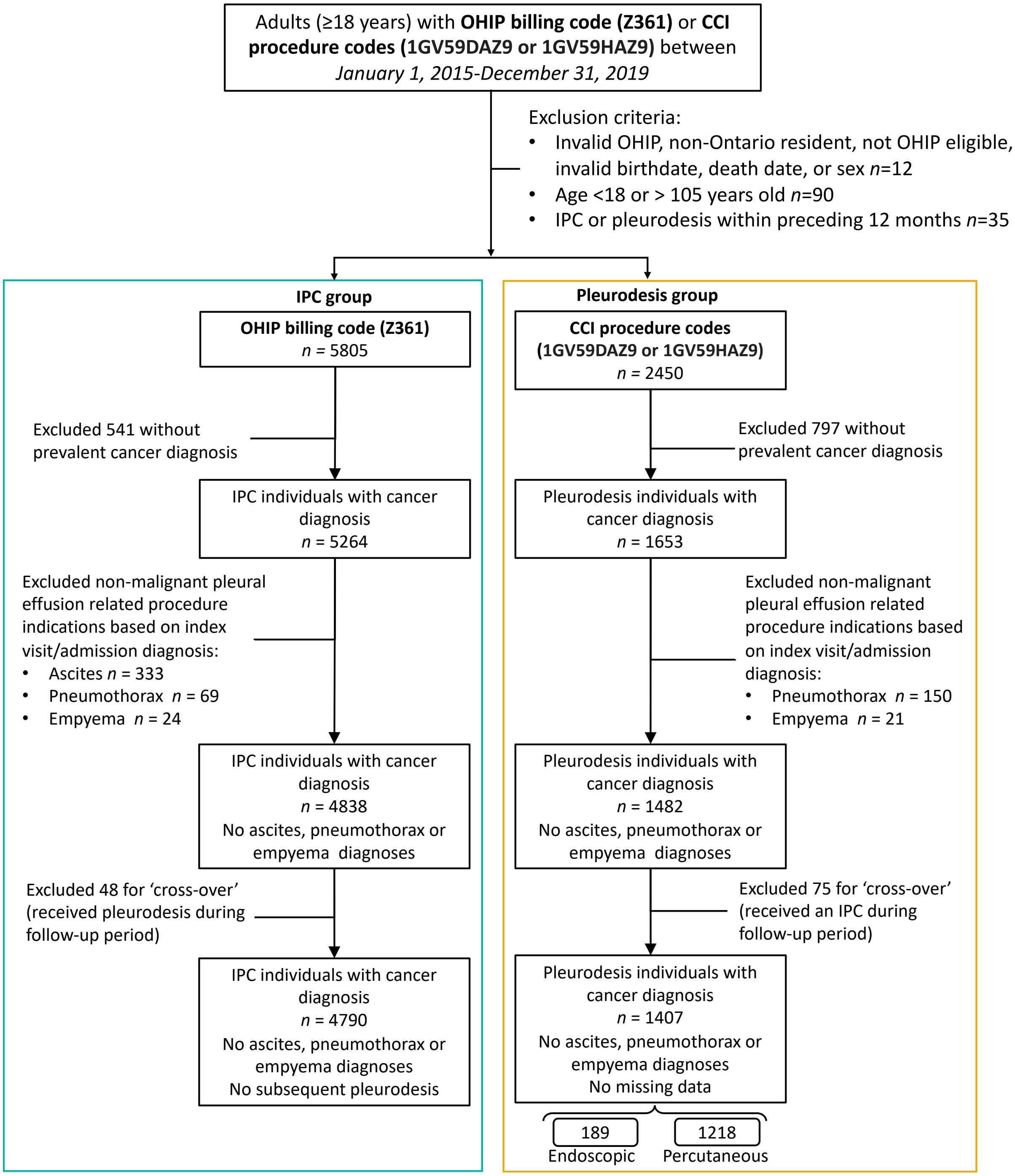
Details of publicly funded health services and individual-level characteristics are retained in health administrative databases housed at ICES, an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. Details of databases used are described in the online data supplement and in Table A1. Datasets were linked using unique encoded identifiers (Figure A1) and analyzed at ICES using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC).

2.3.3 Study population

All adults (≥18 years) who underwent IPC insertion or chemical pleurodesis between January 1, 2015 to December 31, 2019 in Ontario were included (Figure 2.1). Index date was the date of the index procedure (IPC insertion or pleurodesis). Individuals were followed from index to death, end of follow-up (March 31, 2021), or loss of public health insurance eligibility (whichever occurred first). This timeframe was chosen to ensure individuals had at least 2 years of follow-up after their index procedure.

Individuals were excluded if they: (1) had an IPC or pleurodesis in the year prior to the index date to ensure the index procedure was not a repeat procedure; (2) did not have a prevalent cancer diagnosis (i.e. did not have record in the Ontario Cancer Registry with a diagnosis date prior to or including index date)(16) to exclude those without a MPE; (3) diagnosis code of ascites, pneumothorax, or empyema associated with their procedure visit/admission to exclude alternative locations (eg. abdominal IPC placement) or non-malignant indications; (4) had codes for both IPC and pleurodesis procedures to limit the cross-over effect (Figure 2.1; Table A2).

Figure 2.1 Flow chart - Creation of study cohorts: Individuals who received an IPC or pleurodesis procedure for a malignant pleural effusion (Manuscript 1)



IPC: indwelling pleural catheter; OHIP: Ontario Health Insurance Plan; CCI: Canadian Classification of Health Interventions

2.3.4 Outcomes

Our primary outcome was adjusted post-procedure survival. Secondary outcomes included patient-, physician- and hospital-related characteristics associated with either IPC insertion or pleurodesis, rate of IPC removal, and rate of repeat pleural drainage procedures (thoracentesis, chest tube insertion, IPC insertion, pleurodesis).

2.3.5 Covariates

The following covariates were assessed (1) at the index date: age; sex; rurality; neighbourhood income quintile as a measure of socioeconomic status; most recent cancer diagnosis based on ICD-O-3 codes (Table A3); days from initial cancer diagnosis until index procedure; frailty(17) and level of comorbidity based on the preceding 2 years of health service utilization, Johns Hopkins' ACG® System Aggregated Diagnosis Groups (ADG) categories (Version 10.0; https://www.hopkinsacg.org); physician specialty; institution where the procedure was performed; hospital type (community or academic); annual volume of procedures performed at the index institution; (2) prevalent diagnosis of chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and renal failure at index date(18, 19); (3) thoracentesis in the preceding 12 months (Figure A2). Further details on variable definitions available in Table A2.

2.3.6 Analyses

Baseline characteristics were summarised by index procedure using means (standard deviation [SD]), medians (interquartile range [IQR]) or proportions as appropriate. Independent t-test was used to compare means between two groups, Wilcoxon rank-sum test was used to compare medians, and categorical variables were compared using the Chi-square test or Fisher's exact test where appropriate.

Due to significant differences between groups for most baseline covariates, we used inverse probability of treatment weighting (IPTW) using the propensity score, accounting for possible clustering at the institution level, and estimated treatment effect through the average treatment effect (ATE) in the whole study population (please see online data supplement for further details).(20) The selection of variables included in the IPTW were based on existing literature and clinical expertise (Figure A2); however, it was limited by the availability within ICES databases (Table A4). Induced balance was assessed through weighted standard differences for proportions of categorical variables and means of continuous variables, weighted box-plots for continuous variables, and overall by propensity score density plots (Table A4, Figures A3 and A4).(20) We then performed a weighted Cox proportional hazards regression analysis and plotted Kaplan-Meier survival curves based on the weighted cohorts. To assess the robustness of our findings we performed sensitivity analyses using alternate weighting approaches including treatment weights and stabilized IPTW, including 'cross-over' patients, and performed a two-stage analysis where variables with post-weighting standard difference > 0.1 were included in the regression analysis (further details are available in the Online Data Supplement).

Cause-specific Cox models were used to estimate cumulative incidence functions for IPC removal with death as a competing risk.

2.4 Results

We identified 4,790 (77.3%) individuals who underwent IPC insertion and 1,407 (22.7%) treated with pleurodesis (Figure 2.1, Table 2.1). Median follow-up was 90 days (IQR:31-310) in the IPC group and 234 days (IQR: 57-690) in the pleurodesis group. Overall, eight individuals (0.1%) were lost to follow-up.

Table 2.1 Baseline characteristics for individuals receiving (Indwelling pleural catheters) IPCs or pleurodesis

Characteristics, n (%)	IPC (N=4790)	Pleurodesis (N=1407)	p-value
Patient characteristics			
Age in years, mean (SD)	69.1 (12.9)	68.9 (11.7)	0.5732
Female	2722 (56.8)	681 (48.4)	<0.0001
Rural	539 (11.3)	264 (18.8)	<0.0001
Neighbourhood income quintile			0.2787
1 (lowest)	991 (20.7)	297 (21.2)	
2	998 (20.9)	309 (22)	
3	997 (20.9)	273 (19.4)	
4	862 (18)	276 (19.7)	
5 (highest)	931 (19.5)	249 (17.7)	
Number of thoracentesis in 12 months prior to index date			<0.0001
0	1872 (39.1)	799 (56.8)	
1	1585 (33.1)	357 (25.4)	
2	779 (16.3)	143 (10.2)	
≥3	554 (11.6)	108 (7.7)	
Chest tube insertion in preceding 12 months†	916 (19.1)	362 (25.7)	<0.0001
Inpatient for index procedure	1852 (38.7)	1397 (99.3)	<0.0001
Days in hospital prior to index procedure, median (IQR) [n=3249]	4 (1-9)	2 (0-6)	<0.0001
Cancer type			<0.0001
Lung	1889 (39.4)	641 (45.6)	
Breast	751 (15.7)	159 (11.3)	
Mesothelioma	178 (3.7)	153 (10.9)	
Other	1972 (41.2)	454 (32.3)	
Days from cancer diagnosis to index procedure, median (IQR)	243.5 (33-903)	81 (10-737)	<0.0001
COPD	749 (15.6)	306 (21.8)	<0.0001
CHF	679 (14.2)	219 (15.6)	0.1964
Renal failure	207 (4.3)	39 (2.8)	0.0082

Frailty	762 (15.9)	180 (12.8)	0.0041
Aggregated diagnosis groups			0.3350
Low comorbidity (0-5)	106 (2.2)	28 (2)	
Moderate comorbidity (6-9)	1124 (23.5)	306 (21.8)	
High comorbidity (≥10)	3560 (74.3)	1073 (76.3)	
Physician specialty			<0.0001
Pulmonology	3073 (64.2)	56 (4.2)	
Thoracic surgery	832 (17.4)	979 (74)	
General surgery	125 (2.6)	218 (16.5)	
Diagnostic radiology	437 (9.1)	19 (1.4)	
Other	323 (6.7)	51 (3.9)	
Hospital characteristics			
Hospital type			<0.0001
Teaching	2889 (65.1)	796 (56.6)	
Community and Small	1551 (34.9)	611 (43.4)	
Annual volume of IPCs, median (IQR)‡	62 (23-114)	7 (1-14)	<0.0001
Annual volume of pleurodesis, median (IQR)‡	0 (0-6)	51 (22-100)	<0.0001
Annual volume of IPCs‡, categorized			<0.0001
Low (0-49.99)	1677 (37.8)	1276 (90.7)	
High (≥ 50)	2765 (62.3)	131 (9.3)	
Annual volume of pleurodesis‡, categorized			<0.0001
Low (0-49.99)	4369 (98.4)	684 (48.6)	
High (≥ 50)	73 (1.6)	723 (51.4)	

Results are numbers (column percentages) unless otherwise specified. Estimates may not always sum up to 100% due to missing values. The percentage of missing values ranged between 0.2% for rural status to 5.7% for hospital type.
Abbreviations: IPC, indwelling pleural catheter; SD, standard deviation; IQR, interquartile range; COPD, chronic obstructive lung disease; CHF, congestive heart failure
*Based on outpatient visit or hospital admission diagnostic code
†Excluding 3 days prior to index date
‡Number of procedures performed in the calendar year of the index procedure at the institution where the index procedure was performed

2.4.1 Patient characteristics

Patients had a mean age of 69.1 (SD:12.9) and 68.9 years (SD:11.7) in the IPC and pleurodesis groups respectively (Table 2.1). The IPC group had a significantly higher proportion of females (56.8% vs 48.4%, p<0.0001), patients who had undergone a previous thoracentesis

(60.9% vs 43.2%, p<0.0001), and frailty (15.9% v 12.8%, p=0.0041). Median days from initial cancer diagnosis to index procedure was significantly longer for the IPC group (244 vs 81 days, p<0.0001). The most common malignancy was lung, followed by breast cancer. A full listing of assigned cancer types is available in Table A5. Multiple cancer diagnoses were found in 21% of individuals.

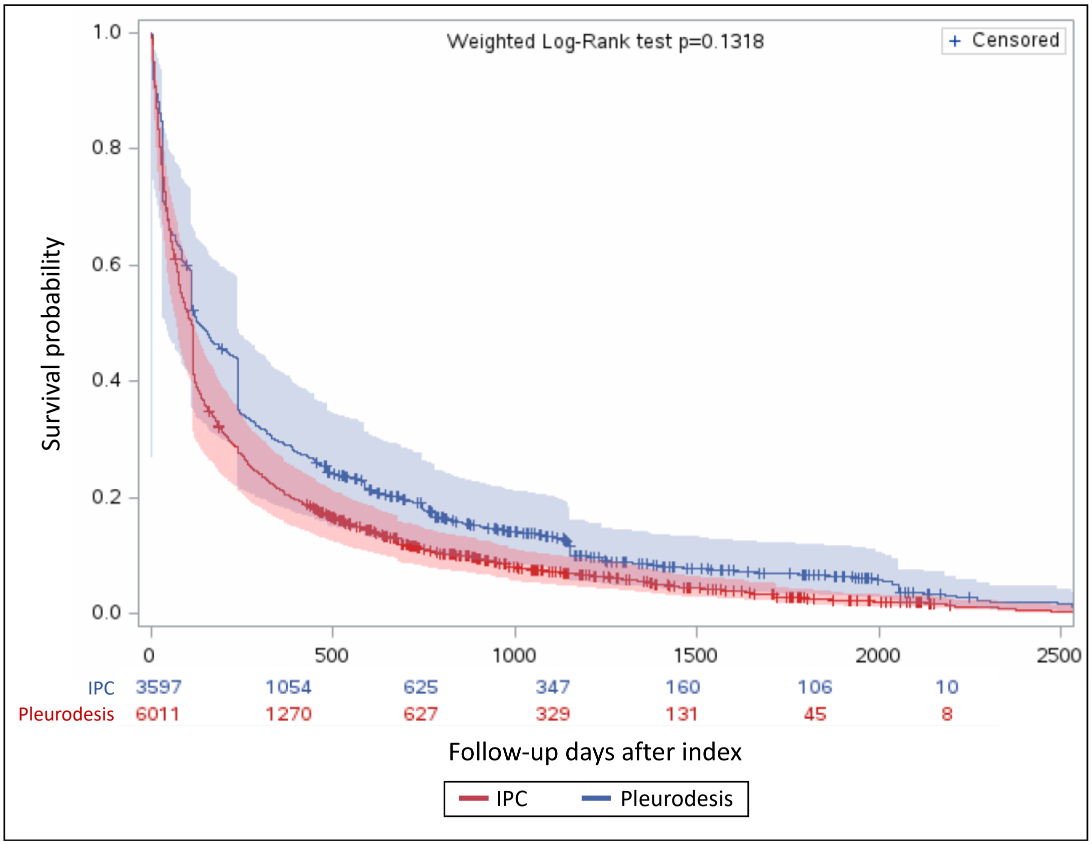
2.4.2 All-cause mortality

Weighted Cox regression revealed no significant difference in adjusted all cause-mortality for individuals with IPC compared to pleurodesis (HR 1.27, 95%CI 0.95-1.69). Weighted Kaplan-Meier survival curves from time of index procedure are presented in Figure 2.2.

In the unweighted sample, during the first 12-months post-procedure 3,726 (77.8%) in the IPC group and 841 (59.8%) in the pleurodesis group died. By the end of follow-up these numbers increased to 4,533 (94.6%) and 1,221 (86.8%) respectively. Median time from index procedure to death was significantly shorter in the IPC group (81 [IQR:29-256] days vs 165 [IQR:48-457] days, p<0.0001). There was no significant difference in median time from initial cancer diagnosis to death between groups (IPC: 486 [IQR:168-1210] days, Pleurodesis: 469 [IQR:171-1206] days; p=0.9878). Crude (unweighted) mortality rate per 1000-person years in the IPC group was 1,329 versus 698 in the pleurodesis group.

Individuals with missing data in any baseline variable were excluded from the weighted survival analysis (7.2% of overall; IPC=358, pleurodesis=87, Table A6). Those with missing data in the IPC group had less mesothelioma and other cancers, in the pleurodesis group they had less mesothelioma and more other cancers. Individuals with missing data in the IPC group also had undergone more thoracenteses prior to their index procedure, and those in the pleurodesis group had less COPD.

Figure 2.2 Kaplan-Meier survival curves after index procedure on weighted sample
At risk numbers by group listed at 1-year intervals



2.4.3 Procedure trends

The number of IPC insertions increased across the 5-years (from 910 in 2015 to 994 in 2019), while pleurodesis procedures decreased in more recent years (from 320 in 2015 to 228 in 2019; Figure A5). All except one regional health authorities performed more IPC insertions than pleurodesis procedures, with significant variation in the ratio between procedures across regional health authorities (Figure A6). The majority (61%) of IPCs were placed in the outpatient setting, this did not significantly change over the 5-year interval. Most procedures were performed at teaching hospitals with Pulmonologists inserting the majority of IPCs and surgeons performing the majority of pleurodesis procedures (Table 2.1). Institutions where individuals received IPCs inserted a median of 62 (IQR:23-114) IPCs annually and performed a median of zero (IQR:0-6) pleurodesis procedures. This trend was reversed for institutions where individuals had undergone pleurodesis.

2.4.4 IPC removal

Over one-quarter (1,677) of individuals in the IPC group had their catheter removed during the study period. Median time to removal was 70 days (IQR:38-120). Figure A7 shows the predicted cumulative incidence function curves for the cause-specific time-to-IPC removal analysis with death as a competing risk.

2.4.5 Repeat pleural drainage procedures

Repeat pleural drainage procedures were performed at a median 33 (IQR 14-97) days after index date in the IPC group compared to 15 (IQR 2-89) days in the pleurodesis group ($p<0.0001$). The number and type of repeat procedures performed within the first 12 months following the index procedure is presented in Table 2.2.

Table 2.2 Repeat pleural procedures within 12 months of index (indwelling pleural catheter) IPC insertion or pleurodesis procedure

Characteristics	**IPC, n(%) (N=4790)**	**Pleurodesis, n(%) (N=1407)**	**p-value**
Thoracentesis	712 (14.9)	119 (8.5)	<0.0001
Chest tube insertion	307 (6.4)	149 (10.6)	<0.0001
IPC insertion	387 (8.1)	-*	
Pleurodesis	-*	112 (8)	

*Patients excluded to prevent cross-over (48 from IPC group, 75 from pleurodesis group)
Abbreviations: IPC, indwelling pleural catheter

2.5 Discussion

In our large population-based study comparing individuals who received IPC insertion to pleurodesis for malignant pleural effusions, no significant difference in post-procedure all-cause mortality was found after balancing baseline characteristics. Although median post-procedure survival time before weighting was longer in the pleurodesis group, this difference was primarily driven by differences in timing of the two procedures, with IPCs inserted significantly later following a cancer diagnosis compared to pleurodesis procedures, and differences in the proportion of frail individuals. In general, IPCs were more commonly used, however there was significant practice variation regionally, at the hospital-level, and by physician specialty. Despite this, the majority of IPCs were still inserted in the outpatient setting.

After adjusting for baseline characteristic imbalances using IPTW, we did not find any significant difference in post-procedure mortality between groups. Post-procedure time-to-death is similar to a previous study of health administrative data in the US which found the median survival from first thoracentesis for MPE was 88 days (IQR, 26-320).(14) The significantly shorter time from index procedure until death in our IPC group compared to pleurodesis group may be explained by the longer time from initial cancer diagnosis to index procedure, as there was no significant difference from time of initial cancer diagnosis until death between groups. Guidelines recommend definitive management for a MPE after an initial thoracentesis if it is symptomatic and recurrent.(7, 8) A previous study of administrative data in the US found that only 24% of individuals received guideline consistent care for MPE.(14) The longer time from cancer diagnosis to index procedure in the IPC group may be partially explained by a higher proportion of IPC patients receiving repeated thoracenteses prior to their index procedure, guideline inconsistent care, compared to pleurodesis patients (27.5% vs 18.1%). There was also a higher proportion of frail individuals in the IPC group. This may be due to more frail individuals being less likely to be offered pleurodesis due to the potential side effects, or a delay in referral for IPC treatment, during which time they become frail, an independent risk factor for mortality.(21) Additionally, the confidence interval from the main analysis and results of the secondary analysis suggested that there may be a higher all-cause mortality associated with IPC insertion, which should be investigated in future studies.

In our study, 50.2% of IPC patients and 31.5% of pleurodesis patients died before 90 days suggesting there is a significant discrepancy between individuals eligible for inclusion in most RCTs (expected survival more than 3 months) compared to those receiving these interventions in the real-world. In previous RCTs and a network meta-analysis comparing these procedures, no significant survival difference has been found, regardless of whether individuals with expected survival of less than 3 months were excluded.(9–12) A retrospective cohort study previously found improved survival from time of index procedure and from time of first effusion in the IPC group, however is limited by the non-contemporaneous time periods during which the procedures were used.(22)

Our study also revealed the drastic practice change which has occurred over the last two decades with increasing IPC use. Between 2015 to 2019 we found IPCs were used to manage MPEs nearly four times more frequently than chemical pleurodesis. This is the opposite found in an earlier observational study from Australia and Spain, where pleurodesis was used twice as often as IPC insertion for MPEs between 2007 to 2013.(25) Our results likely represent an ongoing trend noted from earlier US data, where the proportion of IPCs for definitive treatment of MPEs increased from 15% in 2007 to 28% in 2011, whereas pleurodesis rates declined between 2009 to 2013.(14, 23) The steady level of IPC insertion seen in our study is similar to a multicentre study showing a plateau in IPC use after 2012.(26)

We found significant practice variation by specialty, with pulmonologists more likely to place IPCs and surgeons more likely to treat with pleurodesis. This practice variation is consistent with surveys revealing that the majority of interventional pulmonologists favoured IPCs as the primary intervention while thoracic surgeons preferred pleurodesis.(27, 28) One-quarter of pulmonologists previously reported referring to thoracic surgeons for pleurodesis, potentially contributing to the procedure imbalances between specialities.(29) Consistent with our data showing an increased proportion of females in the IPC group, it has previously been found that women are less likely to be referred to thoracic surgery for definitive management of their MPEs.(30)

Individuals tended to receive the treatment that was performed more frequently at the hospital where their index procedure occurred. We also found practice variation at the level of regional health authorities, with some regions performing similar numbers of IPC and pleurodesis procedures, while others performed many more IPC insertions, and only one performing more pleurodesis procedures. In some regions IPC insertion may be limited due to lack of physician or home nursing expertise to facilitate insertions and home drainage. Expanding training may allow all patients to have more equitable access to these treatments. Although guidelines recommend patient characteristics and preferences be taken into account for deciding between interventions, our results suggest that the choice of procedure may be influenced more by the specialty of the treating physician, and referral and practice patterns within the region.(7, 8)

The number of individuals with missing data excluded from our survival analysis was predominantly driven by missing institutional level data (hospital type and annual procedure volume) in the IPC group receiving outpatient procedures. The majority of baseline characteristics were not significantly different between those with missing data and the analyzed groups. Although more individuals who were excluded from the IPC group had undergone previous thoracenteses, their time from cancer diagnosis to index procedure was not significantly different, suggesting that the procedures were not necessarily performed later in the disease course, and thus not likely to affect the mortality outcomes. In the pleurodesis group, those with missing data represented 6.2% and although the median days to index procedure from initial cancer diagnosis was higher in the missing group, this was not statistically significant. Additionally, the median days from cancer diagnosis to index procedure in the pleurodesis group only changed from 75.5 (IQR: 10-734.5) days to 81 (IQR 10-737) days when those with missing data were included. Therefore, it is not felt that the exclusion of these individuals would have made a significant impact on the observed mortality estimates. Although there were statistically significant differences in cancer types between excluded and included individuals, these differences were still small and not felt to be clinically significant.

Strengths of our study include the use of large databases to identify individuals treated in a variety of real-world clinical settings and practices, and not previously captured in studies utilizing administrative data.(14, 23, 24) Previous population-based studies have assessed individuals with MPE, but lacked codes to identify IPC insertions and only evaluated inpatients.(23, 24) Individuals receiving IPCs represented 77.3% of our cohort with 61% of those procedures performed in the outpatient setting. Another study evaluating characteristics associated with ‘guideline consistent care’ in MPE patients between 2007 to 2011 was limited to Medicare patients older than 65, with IPCs only accounting for up to 28% of definitive procedures.(14) Individuals under 65 represented 36% of our overall cohort and 36% of IPC insertions.

Limitations of our study include potential misclassification bias and unmeasured confounding inherently related to using administrative data. Due to the absence of imaging data, we were not able to evaluate the presence of non-expanding lung, which would typically exclude individuals from receiving pleurodesis, or determine when the MPE first developed. We therefore used patients' initial cancer diagnosis date as a time reference. This may explain the prolonged time from cancer diagnosis to index procedure in some individuals who initially had early-stage disease, before developing recurrence or progression to advanced-stage disease, which ultimately lead to their MPE (Figure A8). The type of sclerosing agent used for pleurodesis was also not available. Johns Hopkins ADG and frailty flag were used as surrogates for performance status, which was not available. These have previously been found to accurately predict one-year mortality.(31) Due to the lack of a validated definition of MPE, previous studies of administrative data have defined MPE using inpatient diagnostic codes, however in order to capture the over 60% of individuals who received their IPC as an outpatient, we used a conservative definition to identify procedures performed for MPEs.(23, 24, 32) In general, patient characteristics in our cohort are similar to those from other population-based studies of patients with MPEs.(14, 23, 24, 32)

2.6 Conclusion

This large population-based study found no significant difference in post-procedure all-cause mortality following IPC insertion versus pleurodesis after adjusting for differences in baseline characteristics. IPCs are inserted later in a disease course compared to pleurodesis procedures. There are significant differences in patient-, physician- and hospital-level characteristics between those who receive IPC compared to chemical pleurodesis for treatment of MPEs, suggesting heterogeneity of health care delivery for these individuals in the real-world setting. The choice of definitive treatment for MPE may be dependent on specialty referral patterns and physician treatment practices. Our findings support further research into what is causing these discrepancies in care and how we can ensure all patients have access to timely guideline-driven care in diverse health care settings.

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Declaration of interest

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Chapter 3. Resource use and costs of indwelling pleural catheters versus pleurodesis for malignant pleural effusions: A population-based study (Manuscript 2)

Chanel Kwok[1,2,3], Kednapa Thavorn[2,3,4], Kayvan Amjadi[1,4], Shawn D. Aaron[1,3,4], Tetyana Kendzerska[1,2,3,4]

[1]Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada; [2]ICES Ottawa;
[3]School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada;
[4]Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

Corresponding author:
Chanel Kwok, MD
The Ottawa Hospital, Division of Respirology
501 Smyth Road, Box 211
Ottawa, ON K1H 8L6
Phone: 613-737-8899 Ext. 79679
chkwok@toh.ca

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3.1 Abstract

Rationale: Malignant pleural effusions (MPE) are associated with significant health service use and healthcare costs, but the current evidence is limited.

Objectives: To compare 12-month post-procedure: (1) health service utilization, and (2) healthcare costs following indwelling pleural catheter (IPC) insertion with at-home drainage performed by homecare nursing services, versus in-hospital chemical pleurodesis.

Methods: We performed a retrospective population-based study on a cohort of adults with MPE who underwent IPC insertion or chemical pleurodesis between January 1, 2015 and December 31, 2019 using provincial health administrative data (Ontario, Canada). Patients were followed from the procedure date until death or until 12-month post-procedure. Inverse probability of treatment weighting (IPTW) was performed to adjust for imbalances in baseline characteristics. Differences in length of stay (LOS), readmissions, emergency department visits, home care visits, and healthcare costs were estimated using weighted regression analysis.

Results: Of 5,752 included individuals, 4432 (77%) underwent IPC insertion and 1320 (23%) had pleurodesis. In the weighted sample, individuals who received an IPC had fewer inpatient days (12.4 days vs 16 days, standardized mean difference 0.229), but a higher proportion of subsequent admissions for empyema (2.7% vs 1.1%, p=0.0002) compared to those undergoing pleurodesis. IPC individuals received more hours of nursing home care (41 hours vs 21.1 hours, standardized mean difference 0.671) but overall had lower average healthcare costs ($40,179 vs $46,640 per patient, standardized mean difference 0.177) than those receiving pleurodesis.

Conclusions: IPCs with home nursing drainage are associated with reduced health resource use compared to pleurodesis in adults with MPE even after controlling for important baseline and clinical characteristics. Given that both procedures have similar health outcomes, our findings

support the ongoing promotion of IPCs to increase outpatient management of patients with MPEs.

Word count: 284/350

3.2 Introduction

Malignant pleural effusions (MPE) are associated with significant morbidity, mortality, and health service use (HSU).(1, 2) In the US, they account for more than 125,000 hospital admissions per year with pleural procedures being performed during 57% of those hospitalizations, and 25% of patients requiring readmission within 30 days.(3–5) The annual cost of these admissions is estimated at over 5 billion USD.(4)

Symptomatic recurrent MPEs can be managed with either indwelling pleural catheter (IPC) insertion or chemical pleurodesis to reduce dyspnea.(1, 2) IPCs are associated with reduced repeat pleural interventions, but increased infectious complications compared to pleurodesis.(1, 2, 6–9) Since the procedure can be done in the outpatient setting, IPC insertion has also been associated with reduced inpatient days.(6, 8, 10)

In the US, home IPC drainage is typically performed by the patients or their relatives. In Canada, drainage is performed by home nursing services funded by the public health care system. Nursing, rather than patient or relative-performed drainage may be associated with lower complication rates, leading to reduced HSU and associated costs. Additionally, as many patients with advanced malignancy are already receiving personal care and symptom support, IPC drainage may only minimally increase the burden on these funded home services.

Limited cost data is available comparing these procedures. Previous cost effectiveness analyses have showed similar cost effectiveness between interventions, except when survival is less than 6 to 14 weeks, when IPCs are more cost effective. These studies are older and do not include the wealth of new data from increased IPC use over the last decade, or are based on a single randomized control trial (RCT), limiting the applicability to real-world use.(11–13)

Published studies to date did not include accurate cost estimates of home nursing care associated with each procedure.

The objectives of our study were to compare post-procedure: (1) health service utilization, and (2) healthcare costs following IPC insertion versus pleurodesis in adults with MPE. We hypothesized that because of the ability to place IPCs in the outpatient setting and previously reported reduced inpatient days after IPC insertion(6, 8, 10), IPCs would be associated with reduced LOS but increased home care services, and that the reduced inpatient costs would offset any increase in healthcare costs due to home nursing services providing drainage. Furthermore, we hypothesized that IPC drainage performed by home nursing services, rather than the patient or their families, would result in reduced infectious complications due to increased health provider assessments and expertise for managing the catheter and site.

3.3 Materials and methods

3.3.1 Study design and setting

We performed a population-based cohort study using provincial health administrative data to compare IPC insertion to pleurodesis for MPE in Ontario, Canada's most populous province. The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act (PHIPA), which does not require review by a Research Ethics Board.

3.3.2 Data sources

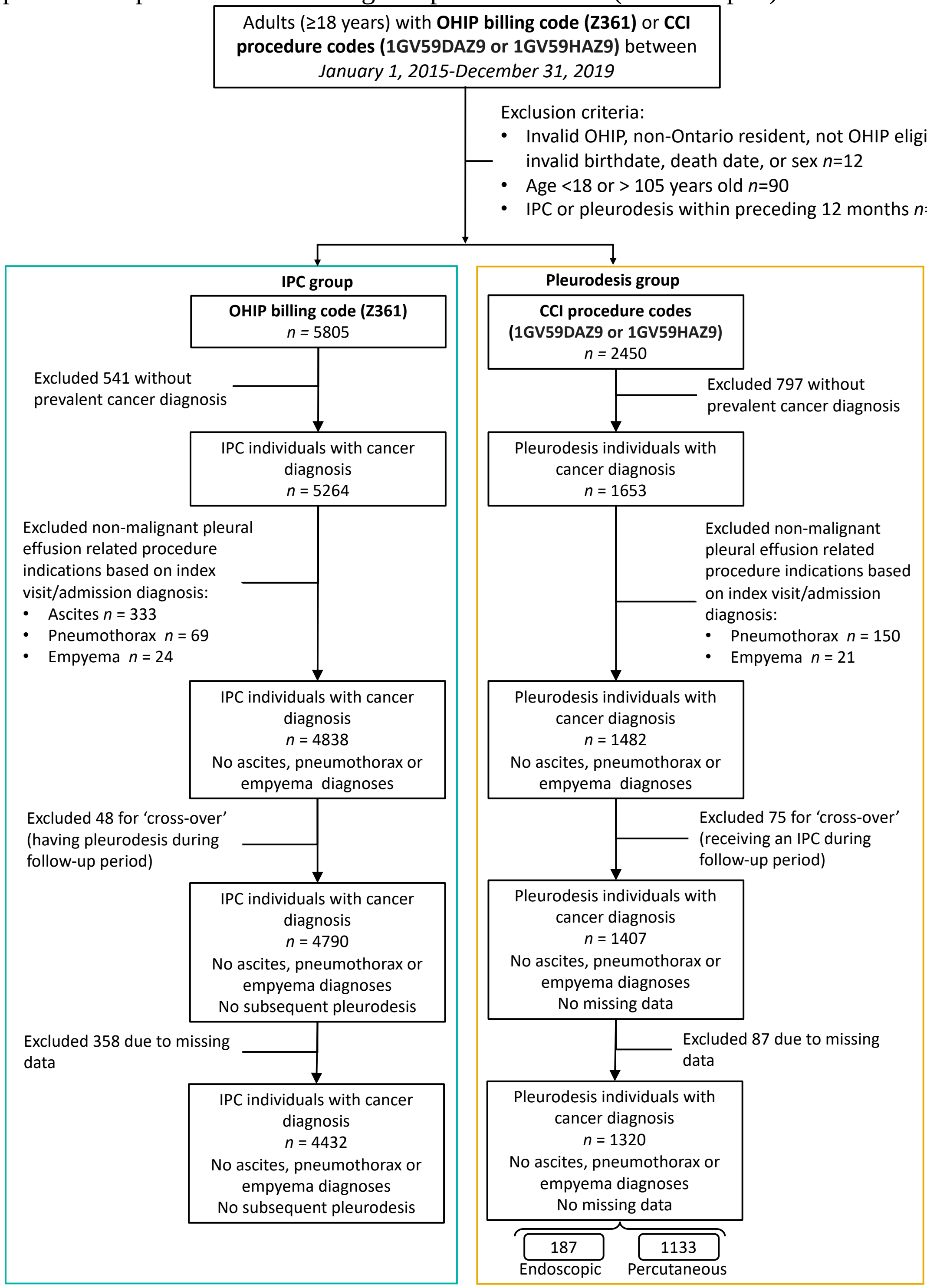
ICES (formerly known as Institute for Clinical Evaluative Sciences) is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. ICES contains data for all individuals covered under the provincial publicly funded health insurance plan, including individual-level characteristics and details on all funded health services (Table B1). Databases were linked using unique patient-level encoded identifiers at ICES (Figure B1).

3.3.3 *Study population (Cohort creation/definition)*

All adults 18 years and older who underwent IPC insertion or chemical pleurodesis between January 1, 2015 to December 31, 2019 were included (Figures 3.1 and B1, Table B2). The index date was the date of the index procedure (IPC insertion or pleurodesis). Patients were followed from index date until 12 months post-index, death, or loss of public health insurance eligibility, whichever occurred first.

Exclusion criteria were: (1) IPC insertion or pleurodesis in the 12 months preceding the index date to exclude repeat procedures; (2) no record in the Ontario Cancer Registry(14) (i.e. to exclude individuals without a known cancer diagnosis at the time of index procedure); (3) diagnosis of ascites, pneumothorax, or empyema associated with outpatient visit or admission to exclude abdominal IPCs and non-malignant treatment indications; (4) codes for opposite procedure during the follow-up period to limit the cross-over effect (i.e. if individual initially had IPC inserted and subsequently received pleurodesis); (5) missing data for any baseline variables (Figure 3.1).

Figure 3.1 Flow chart - Creation of study cohorts: Individuals who received an IPC or pleurodesis procedure for a malignant pleural effusion (Manuscript 2)



IPC: indwelling pleural catheter; OHIP: Ontario Health Insurance Plan; CCI: Canadian Classification of Health Interventions

3.3.4 Outcomes

Our primary outcome was hospital length of stay (LOS) within the first 12 months following the procedure. Secondary outcomes included index admission discharge disposition, time to first readmission and time to first ED visit following the index date, cause-specific post-procedure admissions and ED visits within 12 months, total post-procedure home care visits within 12 months, and 12 month post-procedure healthcare costs. Post-procedure LOS included any inpatient days starting from the day after the index procedure (i.e. if an individual was an inpatient during their index procedure, any subsequent inpatient days related to the same admission, but occurring after the index procedure, were included).

Standard costing methodology developed for Ontario administrative databases was used to determine individual-level healthcare costs from a public payer's perspective.(15) Costs included inpatient admissions, emergency department (ED) visits, same day surgery visits, cancer centre treatments and visits, dialysis, other outpatient care (eg. lab services), physician costs, homecare services, and prescription drugs. All costs were standardized using health sector-specific consumer price indices to their equivalent 2020 Canadian dollar value.(16)

3.3.5 Covariates

Included covariates were assessed: (1) at the time of the index procedure: age; sex; rurality; neighbourhood income quintile as a measure of socioeconomic status; most recent cancer diagnosis (based on ICD-O-3 codes; Table B3); days from initial cancer diagnosis until index procedure; frailty and level of comorbidity (determined using Johns Hopkins' ACG® System Aggregated Diagnosis Groups (ADG) categories based on individual HSU in the previous 2 years; Version 10.0); physician specialty; institution where the procedure was performed; hospital type (community or academic); annual volume of procedures performed at the index institution; prevalent diagnosis of chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), or renal failure; (2) thoracentesis in the preceding 12 months.(17, 18) Additional details on covariate definitions are available in Table B2.

3.3.6 Analysis

Characteristics were summarized by treatment group using means (standard deviation [SD]) or proportions and compared using standardized differences. Across the majority of baseline variables there were significant differences between groups, therefore inverse probability of treatment weighting (IPTW) using the propensity score was used to assigns weights to subjects to estimate the average treatment effect (ATE) in the whole population, and improve the distribution of covariates between groups (please see online supplement for further details).(19) The variables were selected based on existing literature, clinical expertise, and subject to availability within ICES databases (Table 3.1). Weighted standard differences, weighted box-plots, and propensity score density plots were used to assess the balance induced by the weighting strategy (Table 3.1, Figures B2 and B3).(19)

We estimated incremental hospital LOS, homecare visits and healthcare costs using weighted means and standardized mean differences. A standardized mean difference greater than 0.1 was considered significant. Given the high mortality rate in this population, we calculated a weighted sub-distribution hazard ratio with death as a competing risk event for time to first hospital admission and ED visit, and percentage of inpatient days and mean cost per day of follow-up.(20) Proportionality assumption was assessed by Schoenfeld residuals. For individuals who were inpatients at the time of their index procedure, their first hospital admission was their first subsequent admission after discharge from their index stay.

Sensitivity analysis was performed for all outcomes using weights that estimate the average treatment effect among the treated population (ATT), where the treated population was individuals who received an IPC (please see online data supplement for further details). Given previous studies have shown cost benefit for IPCs when survival is limited, home care hours and costs were also compared between groups for individuals who died within 30 days, 6 weeks, and 90 days.

All statistical analyses were performed in the secure environment at ICES using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC).

3.4 Results

Table 3.1 describes baseline individual-, physician- and hospital-level characteristics with unweighted and weighted standard differences after IPTW. Of 5,752 included individuals, 4432 (77%) underwent IPC insertion as their index procedure, and 1320 (23%) had pleurodesis. Mean follow-up time was 150 days (standard deviation [SD], 138d) in the IPC group and 215 days (SD, 145d) in the pleurodesis group. Sixty percent of IPCs were inserted in the outpatient setting. Eighty-six percent of pleurodesis procedures were performed percutaneously via chest tube. Time from initial cancer diagnosis to time of index procedure was significantly longer in the IPC group (244.5 [interquartile range, IQR: 33-897] vs 75.5 [10-734.5] days). Within the 12-month follow-up period 3,60 (78.1%) in the IPC group and 784 (59.4%) in the pleurodesis group died.

Table 3.1 Baseline means, proportions and standard differences of baseline variables before and after inverse probability of treatment weighting*

Characteristics, n (%)	Unweighted comparison: standard difference	Weighted IPC group	Weighted pleurodesis group	Weighted comparison: standard difference
Sample size (N)		6010.8	3597	
Patient characteristics				

Age in years	0.005	70.2	69.8	0.032
Female	0.170	48.8%	61.9%	0.266
Rural	0.239	11.8%	10.3%	0.048
Neighbourhood income quintile				
1 (lowest)	0.012	18.8%	26.7%	0.189
2	0.033	19.1%	33.9%	0.342
3	0.037	19.4%	12.5%	0.191
4	0.048	24.4%	11.8%	0.331
5 (highest)	0.058	18.4%	15.1%	0.086
Thoracentesis in 12 months prior to index date	0.337	58.9%	43.8%	0.306
Cancer type				
Lung	0.136	37.6%	36.8%	0.017
Breast	0.123	12.4%	20.9%	0.231
Mesothelioma	0.286	13.1%	7.2%	0.198
Other	0.210	36.9%	35.1%	0.037
Days from cancer diagnosis to index procedure	0.040	821.3	605.8	0.132
COPD	0.166	22.7%	14.4%	0.215
CHF	0.042	13.9%	10.7%	0.097
Renal failure	0.095	3.8%	1.9%	0.114
Frailty	0.100	15.4%	24.7%	0.236
Aggregated diagnosis groups				
Low comorbidity (0-5)	0.007	1.7%	1.4%	0.022
Moderate comorbidity (6-9)	0.032	21.2%	25.3%	0.096
High comorbidity (≥10)	0.033	77%	73.3%	0.088
Physician specialty				
Pulmonology	1.690	49.4%	32.1%	0.358
Thoracic surgery	1.448	24%	37.7%	0.302
General surgery	0.481	13.2%	7.2%	0.197
Diagnostic radiology	0.334	6.7%	11.8%	0.178
Other	0.144	6.8%	11.2%	0.152
Hospital characteristics				
Hospital type				
Teaching	0.180	69.1%	53.6%	0.322
Community and Small	0.180	30.9%	46.4%	0.322
Annual volume of IPCs†	1.392	61.1	38.5	0.429
Annual volume of pleurodesis†	1.757	17.2	30	0.381

**Weights calculated based on the inverse probability of treatment weighting using the propensity score*

†Number of procedures performed in the calendar year of the index procedure at the institution where the index procedure was performed

Abbreviations: IPC, indwelling pleural catheter; COPD, chronic obstructive lung disease; CHF, congestive heart failure

Individuals with missing data who were excluded from analysis had a higher proportion of lung and breast cancer in the IPC group and decreased proportion of mesothelioma (Table B4). In the pleurodesis group individuals with missing data had lower proportions of lung cancer and mesothelioma. Those in the IPC group with missing data had undergone more thoracentesis and in the pleurodesis group had less COPD, compared to included individuals.

3.4.1 Post-procedure LOS

IPC patients had shorter all-cause LOS over the 12 month post-procedure period compared to individuals who underwent pleurodesis (mean, Table 3.2; median, Table B5). After weighting, 12-month inpatient days in the IPC group was 12.4 days, compared to 16 days in the pleurodesis group (standardized mean difference 0.229). For individuals who were inpatients during their index procedure, there was no significant difference in post-procedure LOS for the index admission (Table 3.3). Weighted mean post-procedure inpatient days as a percentage of follow-up days was lower in the IPC group 22.3% compared to 29.1% (standardized mean difference 0.211).

Table 3.2 Mean 12-month post-procedure health service utilization before and after applying inverse probability of treatment weights

Outcome	Before weighting			After weighting*		
	IPC	Pleurodesis	Standardized mean difference	IPC	Pleurodesis	Standardized mean difference
Total inpatient days in 12 months post procedure	10.1	4.6	0.276	12.4	16	0.229
ED visits	1.5	1.8	0.127	1.5	1.5	0.017
Home care visits, hours						
Nursing visits	38.6	20.3	0.482	41	16.4	0.671
Other visits	34.7	32.4	0.025	33.4	21.1	0.154

Abbreviations: IPC, indwelling pleural catheter; ED, emergency department
*Weights calculated based on the inverse probability of treatment using the propensity score

Table 3.3 Index admission length of stay and discharge disposition for individuals who were inpatients for index procedure

Characteristics, n (%)	**IPC (N=1791)**	**Pleurodesis (N=1320)**	**p-value**
Index admission inpatient days prior to index procedure, median (IQR)	4 (1-9)	2 (0-6)	<0.0001
Index admission inpatient days after index procedure, median (IQR)	4 (2-10)	4 (2-7)	0.5994
Index admission discharge disposition			<0.0001
Home	97 (5.4)	606 (45.9)	
Home with supports	1125 (62.8)	549 (41.6)	
Long term care	145 (8.1)	27 (2.1)	
Died	326 (18.2)	111 (8.4)	
Other	98 (5.5)	27 (2.1)	

Abbreviations: IPC, indwelling pleural catheter; IQR, interquartile range

3.4.2 Index admission discharge disposition

All pleurodesis procedures and 40% of IPC procedures were performed in the inpatient setting. The majority of IPC individuals were discharged with homecare (62.8%, Table 3.3). Nearly half of pleurodesis individuals were discharged home without supports (45.9%). A higher proportion in the IPC group died during their index admission compared to the pleurodesis group (18.2% vs 8.4%).

3.4.3 Time to first admission

Overall rates of subsequent hospital admission within 12 months post-procedure were not significantly different in the IPC group compared to pleurodesis group (51.7% vs 52.6%) (Table 3.4). The weighted subdistribution hazard (SHR) of subsequent all-cause hospital admission for IPC individuals was not significantly different to that of pleurodesis individuals at 12 months (SHR 1.32, 95%CI 0.79-2.18) with death as a competing risk.

Table 3.4 Subsequent all-cause and cause-specific hospital admissions and ED visits, and weighted subdistribution hazards* following (indwelling pleural catheter) IPC insertion or pleurodesis

Outcome	IPC, n (%)	Pleurodesis, n (%)	$SHR_{weighted}$(95%CI)*
Hospital admissions			
All-cause	2289 (51.7)	694 (52.6)	1.32 (0.79-2.18)
Cause-specific			
Pleural effusion	352 (7.9)	98 (7.4)	-
Empyema	121 (2.7)	14 (1.1)	-
ED visits			
All-cause	2745 (61.9)	859 (65.1)	1.44 (0.92-2.25)
Cause-specific			
Pleural effusion	567 (12.8)	140 (10.6)	-
Empyema	47 (1.1)	11 (0.8)	-

Abbreviations: IPC, indwelling pleural catheter; SHR, subdistribution hazard ratio; CI, confidence interval; ED, emergency department

*Weights calculated by inverse probability of treatment weighting and subdistribution hazard calculated with death as a competing risk

3.4.4 Time to first ED visit

IPC individuals had a lower proportion (61.9%) of having at least one post-procedure ED visit within 12 months, compared to pleurodesis individuals (65.1%) (Table 3.4). The weighted subdistribution hazard of time to first ED visit for IPC individuals was not significantly different to that of pleurodesis individuals at 12 months (SHR 1.44, 95%CI 0.92-2.25) with death as a competing risk.

3.4.5 Cause-specific admissions and ED visits

IPC individuals had significantly higher rates of subsequent admission for empyema (2.7% vs 1.1%, p=0.0002) and ED visits for pleural effusions (12.8% vs 10.6%, p=0.0355) compared to pleurodesis individuals within 12 months after their index procedure (Table 3.4). There was no significant difference in pleural-effusion related admissions. Subdistribution hazards could not be calculated due to loss of proportionality assumption for these outcomes.

3.4.6 Home care visits

In the 12 months following their index procedure, IPC individuals received a weighted mean of 41 hours of home care nursing services, compared to pleurodesis individuals 21.1 hours (standardized mean difference 0.671, Table 3.2). Non-nursing home care hours were also higher in the IPC group after weighting.

3.4.7 Healthcare costs

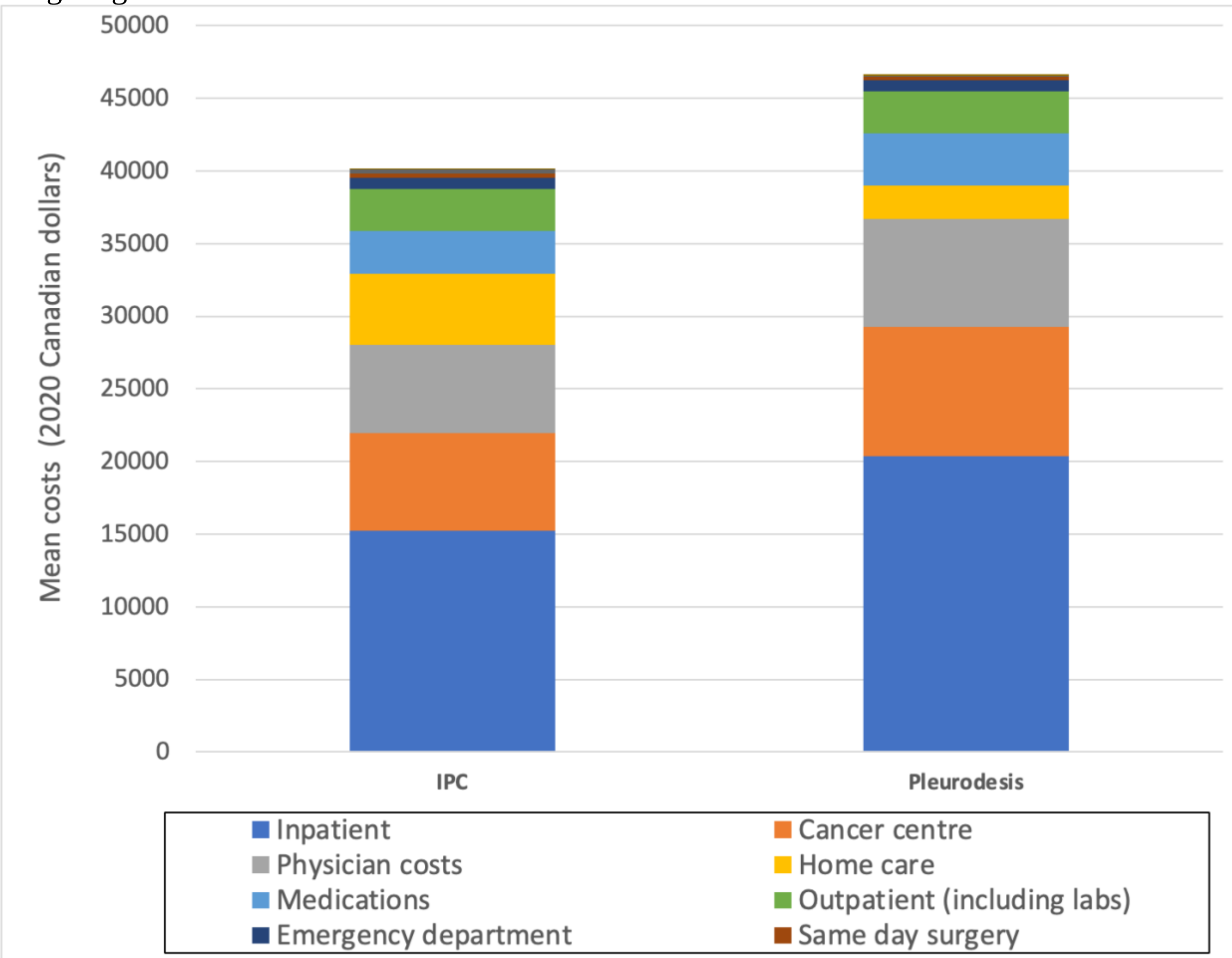
Overall and subdivided healthcare costs after weighting are presented in Table 3.5 (mean), Figure 3.2 and Table B6 (median crude costs). The 12-month post-procedure mean healthcare costs were lower for IPC individuals compared to pleurodesis individuals ($40,179 vs $46,640 per patient, standardized mean difference 0.177). Crude total costs remained lower in the IPC group compared to pleurodesis group for each group of individuals that died within 30 days, 6 weeks, and 90 days post-procedure (Table B7). Mean individual cost per day of follow-up on the weighted sample were $547.87 in the IPC group and $540.13 in the pleurodesis group (standardized difference of weighted means 0.010).

Table 3.5 12-month post-procedure mean and standardized mean difference of total and subdivided healthcare costs by group after weighting* (2020 Canadian dollars)

Costs	**IPC, mean**	**Pleurodesis, mean**	**Standardized mean difference**
Total costs	40,179	46,640	0.177
Subdivided costs			
Inpatient	15,216	20,393	0.234
Cancer centre	6,726	8,888	0.166
Physician costs	6,067	7,421	0.262
Home care	4,930	2,289	0.508
Medications	2,913	3,627	0.061
Outpatient	2,888	2,885	0.001
Emergency department	771	770	0.001
Same day surgery	320	199	0.149
Dialysis	268	71	0.064
Other	82	97	0.090

Abbreviations: IPC, indwelling pleural catheter
*Weights calculated based on the inverse probability of treatment using the propensity score

Figure 3.2 Mean post-procedure sub-divided costs (2020 Canadian dollars) by group after weighting*



*Weights calculated based on the inverse probability of treatment using the propensity score

3.5 Discussion

This is the first study to use routinely collected data to capture post-procedure health services use and healthcare costs following IPC insertion or pleurodesis for MPE. Our population-based study of adults with MPE found that IPC individuals had shorter overall post-procedure LOS and lower healthcare costs in the 12-months following their index procedure compared to those who underwent pleurodesis. A small proportion of patients required subsequent admission for complication due to empyema. For LOS, these results support findings from other RCT and observational studies.(6, 8, 10) Only one other study has directly compared the costs between these procedures, and was limited to only looking at costs related to the initial intervention, ongoing IPC drainage, and adverse events captured during a RCT, and they found no significant difference in overall mean costs between groups.(21)

Twelve-month all-cause post-procedure LOS in our population was similar to that from the AMPLE international multi-site RCT (weight mean, IPC 12 days vs pleurodesis 16 days), but shorter than that found in a cohort study of US administrative data (median, IPC 23 days, pleurodesis 25-34 days).(8, 22) This may be due to the fact that the US study only included older patients aged 66 to 90 years, with increasing age likely associated with longer LOS, as has been seen in the post-surgical lung cancer population.(23, 24)

One main benefit of IPCs is their ability to be inserted in the outpatient setting, while pleurodesis requires admission. The longer duration of hospital days prior to the index procedure being performed and high rates of in-hospital mortality in the inpatient IPC group (41% of IPC group) suggests that they may have been admitted to hospital for reasons other than their MPE. Median LOS before pleurodesis however was only 1 day, which is the time required to insert a chest tube and ensure drainage of the pleural space and lung apposition before instilling a sclerosing agent. This short pre-procedure LOS suggests that these patients were more likely admitted directly for this procedure.

To the best of our knowledge this is the first study to evaluate home care nursing services which assist in the management of IPCs in Canada. Hours of homecare services, both nursing and non-nursing services, were higher in the IPC group. Given the higher rate of mortality in the IPC group, to assess the possible impact of mortality on this result, we assessed home care hours limited to individuals who only survived 30 days, 6 weeks, and 90 days (Table B8). For all three intervals, and for both nursing and non-nursing home care services, IPC individuals utilized more hours.

Pleural catheters, and especially IPCs, are associated with increased rates of pleural empyema. An international retrospective review of 1,318 individuals receiving IPC for MPE found 4% (95% CI, 3–5%) developed deep pleural infection, with the vast majority (88%) requiring inpatient treatment.(25) Previous RCTs found that between 2.7% to 9.6% of IPC participants required inpatient treatment for pleural infections, compared to 1.4% and 1.9% of pleurodesis subjects.(6, 8) In contrast, our study found the rate of admission for empyema following index procedures (2.7% after IPC, 1.1% after pleurodesis) to be lower than described elsewhere in the literature. We hypothesize that infection rates are lower in Ontario compared to internationally, because in Ontario IPC drainage is performed by home nursing services, rather than by the patient or their families. This may result in reduced infectious complications due to health provider expertise in managing the catheter and site.

Previous costing studies comparing IPCs to pleurodesis have shown similar costs and cost-effectiveness between groups, with IPCs more favourable (lower costs or more cost-effective) in patients with shorter survival (6-14 weeks).(11–13, 21, 26) These studies have been limited by the use of data from a single RCT, and/or not including or only estimating home care costs, and only including costs related to the procedures and any complications themselves, rather than total healthcare costs. Our results showed that total costs were lower in the IPC group, both overall and when restricted to individuals who had limited survival. This is likely explained by the higher inpatient costs, but lower home care costs in the pleurodesis group.

Strengths of our study include the use of large administrative databases which allowed us to capture comprehensive health service use, including admissions and ED visits at sites outside of where the index procedure was performed, and home care services. The latter is especially important given their role in providing home IPC care and drainage, and not previously being reported in the literature. Capturing individual-level health care costs from the perspective of the public payer is also a strength. Due to the structure of our publicly funded healthcare system, costs captured are very comprehensive for all HSU, and similar data has not previously been reported in this patient population. Our results will allow us to perform a cost-effectiveness analysis in the future.

There are several limitations to our study. Misclassification bias can result from the use of billing codes, which may lack specificity. Additionally, in order to capture the large number of outpatient IPC insertions, we were unable to utilize the inpatient MPE definition previously used in health administrative database studies, and despite conservative exclusion criteria, this may have resulted in inclusion of patients receiving the interventions for non-MPE conditions.(27–29) Given the high mortality and resource use for individuals with MPE, the erroneous inclusion of individuals with non-malignant effusions would be expected to lower healthcare use and costs. The high mortality is also a limitation, as those dying during follow-up would not contribute to further HSU and costs. We aimed to address this by assessing outcomes per day of follow-up and in those with only limited survival (30 days, 6 weeks, 90 days). Results were consistent in these analyses.

Due to limitations in visit coding, we are not able to determine whether nursing visits were solely for IPC drainage and care or other additional services. We hypothesized that given the advanced stage disease of these individuals, it is likely that they may require home care support for other aspects of their care, and that the additional burden of visits for IPC management would be minimal. Unmeasured confounding may be introduced by the inability to determine which patients had trapped lung and would be ineligible for pleurodesis, which sclerosing agent was used for pleurodesis, and the date of radiographic or symptomatic onset of MPE. Our treatment groups had significant baseline imbalances in baseline characteristics, and we were able to improve this balance using IPTW. Our results were consistent when treatment weights were applied instead, suggesting the robustness of our findings.

Individuals with missing data were predominantly excluded due to missing hospital-level data. Although there were some statistically significant differences between these individuals and those included, the differences overall were small, for example small differences in proportions of cancer types affecting both groups, which was not felt to likely affect the results since all patients with advanced malignancy have been shown to have high HSU due to significant morbidity and mortality associated with their disease.(30)

3.6 Conclusions

The results of this prospective observational population-based study highlight the high health care utilization of individuals with advanced malignancy requiring IPC insertion or pleurodesis. We found that IPCs with home nursing drainage are associated with reduced LOS and health care costs compared to pleurodesis, even in individuals with limited post-procedure survival. Results support the ongoing use of IPCs to allow outpatient management of MPEs and limit the inpatient days required of this population with high morbidity and mortality. Future research should examine the value for money of IPC compared to pleurodesis and assess the impact of modifiable factors, such as specialized pleural clinics, on the high resource use.

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Declaration of interest

CK received financial support from The Ottawa Hospital Department of Medicine Academic Scholarship while completing this project. She has previously received and honorarium from AstraZeneca for participation in the MultiDisciplinary Team meeting (MDT) Aid Program unrelated to the submitted work.

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Chapter 4. Economic evaluation protocol for comparing cost effectiveness of indwelling pleural catheter insertion to chemical pleurodesis

4.1 Introduction

MPEs are associated with significant morbidity and mortality. IPC insertion or chemical pleurodesis can be used for recurrent and symptomatic MPEs to reduce dyspnea and improve quality of life.(1–4) Previous RCT's have not found a significant difference between groups for these outcomes. Guidelines recommend patient preferences guide the procedure choice, however given the significant regional and physician specialty variation noted between procedures in the first manuscript, it suggests that this is more driven by factors external to the patient. IPCs have been developed more recently, with increasing use since their approval two decades ago. The physician and nursing expertise are required to insert and manage IPCs may not be equally available for all patients. To receive pleurodesis, individuals need to have an expanding lung following pleural fluid drainage and be admitted to hospital.

RCTs have previously shown that IPCs are associated with reduced inpatient days and repeat ipsilateral pleural drainage, but compared to talc pleurodesis, they have increased infection risk.(1–6) Although 12-month mortality rate is high among individuals with MPEs, these studies were not powered to detect a difference in post-procedure all-cause mortality.

Direct costs associated with IPC insertion include the cost of insertion, ongoing drainage bottles and home nursing hours. Direct costs of pleurodesis include the cost of inpatient admission and pleurodesis procedure which is performed at the bedside or in the operating room. Additional post-procedure costs relate to complications such as infections or recurrence of the MPE requiring repeated pleural drainage intervention(s). The total costs captured, include all post-procedure healthcare costs (eg. hospital admissions, ED visits, outpatient visits and services, home care, medications), and provide a better assessment of the real-world healthcare use by individuals with MPE, which includes contact beyond the index procedure, and have not previously been reported.

There are few economic evaluations comparing IPC insertion to pleurodesis with which decision makers can use to assess trade-offs between interventions, and very limited costing data.(7, 8)

The objective of this study will be to integrate the outcomes observed in the first and second manuscript with existing literature to assess the cost-effectiveness following IPC insertion compared to pleurodesis for individuals with MPE.

4.2 Methods

4.2.1 Decision problem

The decision problem relates to the incremental cost and effect trade-off of two interventions (IPC insertion and pleurodesis) for managing symptomatic MPEs.

4.2.2 Target population

Adult (≥18 years) patients with recurrent symptomatic MPEs in Ontario, Canada.

4.2.3 Intervention and comparators

The intervention will be IPC insertion and the comparator will be chemical pleurodesis.

4.2.4 Form of analysis

As recommended by the Canadian Agency for Drugs and Technologies in Health (CADTH) *Guidelines for the Economic Evaluation of Health Technologies* a CUA with outcomes expressed as cost per QALY gained will be conducted.(9)

4.2.5 Perspective

The economic evaluation will be conducted from the perspective of the publicly funded health care payer which will incorporate costs borne to Canada's healthcare system.

4.2.6 Time Horizon

Given the relevant decision-makers and high mortality in this population, a CUA over a lifetime horizon (i.e. until death).

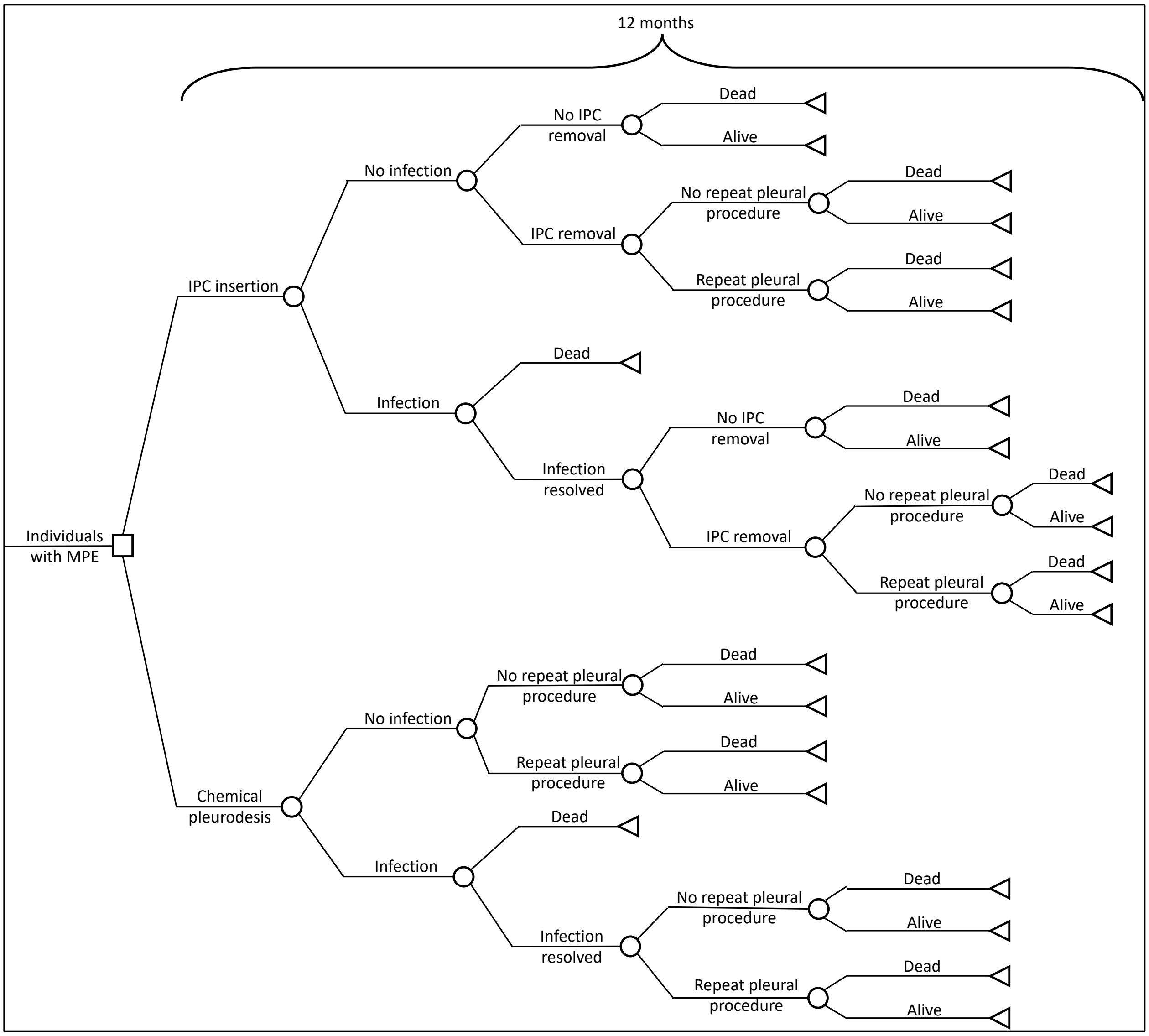
4.2.7 Outcome measures

The primary outcome will be the incremental cost per QALYs gained, as per CADTH guidelines.(9) An ICER will be calculated by dividing the difference in total costs (incremental cost) by the difference in health outcome (QALY) based on the expected values of costs and outcomes for each intervention.

4.2.8 Model structure

A decision tree model has been developed which incorporates major post-procedure patient outcomes including, infectious complications (the most common complication), IPC removal, effusion recurrence requiring a repeat pleural procedure, and death (Figure 4.1), and all healthcare costs related to these outcomes. The model occurs over a 12-month period, consistent with our data from the first and second components.

Figure 4.1 Decision tree model for economic evaluation comparing individuals receiving (indwelling pleural catheter) IPC or pleurodesis for MPE (12 months)



Abbreviations: MPE, malignant pleural effusion, IPC, indwelling pleural catheter

We will derive transition probabilities and cost data from the first and second manuscripts, which were population-based retrospective studies of adults with MPE receiving IPC insertion or pleurodesis between January 1, 2015, to December 31, 2019 in Ontario, Canada.

Costs

Costs will be based on the results of the second manuscript, which calculated individual-level direct healthcare costs from the public payer's perspective using standard costing methodology.(10) Hospital admissions, emergency department visits, same day surgery visits, cancer centre treatments and visits, dialysis, other outpatient care (eg. labs services), physician costs, homecare services, prescription drugs (covered by Ontario Drug Benefit program for eligible individuals) costs were included. Costs were converted to and presented in 2020 Canadian dollars.(11)

Utilities

We will conduct a targeted literature review to identify health utility associated with each procedure. Health utility is a measure of an individual's health-related quality of life. It is typically measured on a scale of 0 to 1, with 0 representing death and 1 representing perfect health. Health utility scores for individuals can be determined using questionnaires, such as the EuroQol EQ-5D, which asks about an individual's mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.(12, 13) The scores obtained from these questionnaires can then be used to estimate the change in health-related quality of life associated with a healthcare intervention. Our searches will focus on studies conducted in Canada and countries with similar healthcare system, such as United Kingdom.

Discounting

If required, an annual discount rate of 1.5% will be applied, as per CADTH guidelines.(9)

Stratified analyses

Subgroups that will be considered for stratified analyses will include survival time (less than: 30 days, 42 days, and 90 days) given the poor survival in this population and previous economic evaluations suggesting cost benefit for IPCs if survival is less than 14 weeks, and cancer type (lung, breast, mesothelioma, other), given the known variation in survival time between MPEs caused by different cancers.

Sensitivity analysis

Sensitivity analyses will be performed in the form of threshold analysis, to determine the levels of rates of infection, repeat procedures, and utility values, at which one procedure is preferred over the other.

Scenario analysis may also be performed at different rates of IPC removal based on data from the published literature.

4.3 Discussion

There is limited data to guide physicians and patients on the optimal treatment strategy for MPEs. Guidelines suggest either IPC insertion or pleurodesis, as both have been shown to improve dyspnea, but the comparative costs of each treatment strategy are uncertain. Additionally, the effectiveness of IPCs (i.e. time to removal and risk of recurrent MPE after removal) and infection risk, are likely affected by local factors such as drain management by home nursing services rather than patients and family members. Therefore, it is important to evaluate these interventions using Canadian outcome and cost data.

Previous economic evaluations comparing IPCs to pleurodesis have significant limitations in their applicability to the Canadian, and real-world setting. Olfert et al. calculated costs based on the direct procedure, ongoing drainage and adverse event costs from individuals who were enrolled in a randomized control trial in the United Kingdom.(12) They found IPCs to be cost effective over pleurodesis with an ICER of US$ 10,870 per QALY gained.(12) This result however had a low degree of certainty, and costs of home care hours were only estimated, as this resource use had not been recorded in the study. In participants (n=16 IPC, 22 pleurodesis) with limited survival (<14 weeks), the probability of IPC being cost-effective (ICER < £30 000) was greater than 95%.

Other economic evaluations are based on data from small older observational studies.(14, 15) Puri et al. found IPCs to be more cost effective over pleurodesis when survival was limited to 3 months.(6) Their decision tree model included costs for an IPC to be placed in an operating theatre with moderate sedation provided by an anesthesiologist, which is a greater cost than if the IPC was placed in an outpatient clinic without sedation, as is more often the practice here. Additionally, the success rates for pleurodesis (73% for bedside pleurodesis and 87% for thorascopic pleurodesis) are higher than typically reported using more recent literature. Olden and Holloway found that IPCs were more cost-effective than pleurodesis only when survival was less than 6 weeks, but defined cost effective as an ICER of less than US$ 100,000/QALY, a higher threshold than is usually accepted in Canada (CAD$ 50,000).(14)

By using population-based data to calculate post-procedure costs, we are able to capture a more complete assessment of health system costs that may relate to a procedure, such as complications requiring hospital admission and further procedures, as well as home care costs for IPC drainage. Our economic evaluation will provide insight into cost-effective management of adults with MPE in Canada, allowing us to improve the care of this population in the future.

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Chapter 5. Overall conclusions and knowledge translation

5.1 Summary of findings

This thesis includes two population-based cohort studies comparing individuals receiving IPCs to individuals receiving pleurodesis for MPEs between 2015 and 2019. The overall objectives of the cohort studies were to compare post-procedure mortality, post-procedure healthcare utilization, and overall health system costs in patients who received an IPC versus those who received pleurodesis. Analysis of the data collected in these studies will help to facilitate a future economic evaluation comparing the two procedures, which is outlined in chapter 4 of the thesis. My ultimate goal will be to uses these clinical and economic evaluations to support the development of provincial and/or national guidelines for treatment of malignant pleural effusions.

The first manuscript described and compared post-procedure mortality, procedural trends, IPC removal rates and repeat pleural procedures. We found significant differences across a number of baseline characteristics. In order to compare post-procedure outcomes between groups, IPTW using the propensity score were calculated and weighted analyses performed. Despite individuals with IPCs having their index procedure performed later after an initial cancer diagnosis and having higher rates of frailty, after weighting, we found no significant difference in post-procedure mortality, with high 12-month mortality rates in both groups. Overall, IPCs were used more often than pleurodesis, with some regional exceptions, and mostly inserted by pulmonologists and at institutions where IPCs were the preferred procedure. This suggests that intervention choice may be dependent on specialty referral patterns and physician treatment practices.

The second manuscript focused on post-procedure HSU and healthcare costs. Individuals who underwent IPC insertion had fewer post-procedure inpatient days and healthcare costs but required more subsequent admissions for empyema and outpatient nursing care hours, compared to those who received pleurodesis. Although the IPC group had a higher mortality rate during the follow-up period which could lead to reduced inpatient days or healthcare costs, the results were similar when restricted to individuals with limited survival and when assessed 'per day of follow-up' to account for differential censoring as a result of death.

These studies are the first to use routinely collected health administrative data to compare post-procedure mortality, health services use and healthcare costs following IPC insertion or pleurodesis for MPE. Limitations include imbalances in baseline characteristics between treatment groups, which we were able to minimize by using IPTW. Other limitations included the inability to determine when the MPE first developed or became symptomatic, and high mortality during follow-up, which differentially affected the IPC group.

The economic evaluation protocol described in chapter 4 aims to build on the results of the first and second manuscripts to compare the cost effectiveness of IPC insertion to pleurodesis from the perspective of the publicly funded health care payer. Data from the first and second manuscript as well as data from the existing literature will be incorporated into the model to increase the robustness of the findings compared to previous cost-effectiveness studies which have lacked real-world data.

5.2 Clinical/policy implications

The findings of our study show significant variation in MPE management. IPCs were inserted significantly later after an initial cancer diagnosis, suggesting there is room for improvement with respect to earlier referrals for MPE management in this population. Access to providers who can perform these interventions, and the development of local guidelines may reduce the variations in management we identified. Earlier referral may also help to reduce the need for repeated thoracenteses, which were higher in the IPC group in our study. This can help to reduce the discomfort and risks associated with repeat procedures, and reduce the number of healthcare visits required for pleural effusion management. The results of our study add to the existing literature to help inform individuals and their physicians with respect to the trade-offs between IPCs and pleurodesis. IPCs can be inserted in the outpatient setting but require home care for drainage and are associated with increased infectious complications compared to pleurodesis. Our results suggest that IPC drainage performed by home nursing services in Ontario is associate with fewer infectious complications compared to historical infection rates reported with patient/caregiver drainage, suggesting that drainage may be safer when performed by trained healthcare personnel.

5.3 Recommendations for future research

Our proposed economic evaluation based on the included manuscripts and existing literature will provide valuable insights into the cost-effectiveness of these procedures. Our results will be disseminated at national and international society meetings and through manuscript publication. In addition to completing the economic evaluation, other avenues of future research include comparing individuals receiving IPCs in the inpatient versus outpatient setting and comparing alternative IPC management strategies and alternative drainage frequencies. The results of these studies will help to support the development of provincial and/or national guidelines for the management of MPEs, which do not currently exist.

APPENDICES

Appendix A – Supplementary materials for Manuscript 1

Methods

Data sources

Residents of Ontario have access to publicly funded health care through the government-run Ontario Health Insurance Plan (OHIP) which pays for services that are medically necessary. Details of services provided, and individual-level characteristics are retained in health administrative databases housed at ICES (formerly known as Institute for Clinical Evaluative Sciences). ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. Descriptions of available databases are available at https://datadictionary.ices.on.ca/Applications/DataDictionary/.

Cohort creation and data linkage

Physician billing codes, including the date of service, are captured in the OHIP database. Procedures performed during hospital admissions and in Same Day Surgery are captured through Canadian Classification of Health Interventions (CCI) codes in the Canadian Institute for Health Information-Discharge Abstract Database (CIHI-DAD) and CIHI-Same Day Surgery Database (SDS). Individuals over the age of 18 years with an OHIP billing code for IPC insertion (Z361) were identified for the IPC group, and those with a CCI procedure code of 1GV59DAZ9 or 1GV59HAZ9 in CIHI-DAD or CIHI-SDS were identified for the pleurodesis group if the procedure was performed between January 1, 2015 and December 31, 2019, and they had not had either of the procedures in the preceding one year (please see Figure 2.1 in the main manuscript). The procedure date was used as the index date.

These datasets were then linked using unique encoded identifiers to other datasets for analysis, including: Registered Persons Database (RPDB) which contains information on patient demographics such as sex, year of birth, date of death and postal codes, about anyone who has ever received an Ontario health card number; Ontario Cancer Registry (OCR) which contains information on all incident cancer diagnoses based on hospital discharge and day surgery summaries, pathology reports, patient records from Cancer Care Ontario's eight Regional Cancer Centres or the Princess Margaret Hospital, and death certificates; other records in CIHI-DAD containing admission dates, diagnoses, and procedures; other records in CIHI-SDS containing admission dates, diagnoses, and procedures; other records in OHIP containing billing and diagnosis codes; Home care database (HCD) for dates, hours and type of home care visit; Ontario health care institutions database (INST) containing hospital information such as the type of hospital and used to calculate annual procedure volumes; ICES Physician Database (IPDB) containing physician specialty; National Ambulatory Care Registry System (NACRS) records for ED visit dates and diagnoses; and ICES-derived disease-specific chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF) databases.

Inverse probability of treatment weighting using propensity score

The propensity score (PS) is the probability that a patient will receive a particular intervention, based on the patient-, physician-, and institutional-level covariates. Individuals in both groups with the same PS will have similar distributions of covariates. PS methods can be used to reduce the bias created due to confounding by indication (characteristics influencing procedure choice). Using multivariable hierarchical logistic regression model (receiving treatment with IPC as the dependent variable, covariates as predictors, and considering potential hospital-level clustering), the PS (0 to 1) was calculated. The PS was then used to calculate statistical weights for the study population.

Inverse probability of treatment weighting (IPTW) assesses the average treatment effect (ATE) in the whole population of study individuals (compares effectiveness of IPC to pleurodesis) and was therefore chosen as our primary weighting method. IPTW defines weights as the inverse probability of receiving the treatment actually received: 1/PS for IPC group and 1/(1-PS) for pleurodesis group. Therefore, a patient who received an IPC receives a larger weight if their PS for IPC is small and a smaller weight if their PS is large. For example, if most individuals with certain characteristics usually get pleurodesis but an individual with those same characteristics received an IPC, they would receive a larger weight. This weighting aims to adjust for over/underrepresentation of individuals with certain characteristics in each group, such that the distribution of covariates between groups is similar in the weighted sample. After weights were assigned, weighted Cox proportional hazards regression analysis was performed, and Kaplan-Meier survival curves based on the weighted cohorts were plotted.

Sensitivity analyses

A sensitivity analysis was performed using treatment weights to estimate the average treatment effect among the treated (IPC) population (ATT). While IPTW estimates the effect of moving the entire population from receiving IPC to receiving pleurodesis, treatment weights estimate the effect of moving all IPC patients from receiving pleurodesis to receiving IPC. For treatment weights, all IPC patients were assigned a weight of 1, and pleurodesis patients were assigned a weight based on the odds of treatment (PS/(1-PS)). Furthermore, due to the possibility of extreme weights using IPTW, another sensitivity analysis was performed using stabilized

IPTW where the marginal probability (MargP) was incorporated into the numerator (IPC_{weight}= MargP /PS; $Pleurodesis_{weight}$=[1- MargP]/[1-PS]).

A two-stage adjustment to compare post-procedure mortality between groups was performed where any variables with a standard difference greater than 0.1 after weights were applied were included in the weighted cox regression analysis.

All analyses were repeated on groups which included 'cross-over' individuals (e.g. IPC individuals who had pleurodesis during follow-up, or pleurodesis individuals who had an IPC inserted during follow-up). Individuals were assigned to the group based on the earliest procedure they received.

To assess the possible impact of the COVID pandemic on mortality rates, individuals who a procedure before 2019 to those who had it during 2019, the latter group being more likely to still be alive at the start of the pandemic and therefore affected by it, were compared.

Results

Sensitivity analysis (ATT)

Treatment weights were calculated on the same individuals and using the same variables as for the IPTW. Weighted Cox regression analysis and Kaplan-Meier survival curves based on weights assigned using treatment weights revealed no significant difference in mortality between groups (HR 1.11, 95%CI 0.75-1.64).

Sensitivity analysis (stabilized IPTW)

Stabilized weights were calculated on the same individuals and using the same variables as for the IPTW. The standardized differences for all included variables were no different for stabilized IPTW compared to IPTW. With stabilized weights applied, there was no significant difference between groups in all-cause mortality (HR 1.26, 95%CI 0.94-1.68).

Sensitivity analysis (two-stage adjustment)

When a weighted cox regression was performed including covariates which had standard difference more than 0.1 after weights were applied, individuals in the IPC group had a significantly higher hazard of post-procedure mortality (HR 1.29, 95%CI 1.05-1.58).

Analyses including 'cross-over' individuals

All trends in baseline characteristics when 'cross-over' individuals were included were the same as the main cohorts. After IPTW were applied, weighted Cox regression analysis and Kaplan-Meier survival curves did not reveal any significant difference in mortality between groups (HR 1.26, 95%CI 0.95-1.66).

Effect of COVID on mortality

In the overall cohort only 6 individuals in the IPC group were noted to have positive COVID polymerase chain reaction tests. All procedures were performed prior to the start of the pandemic. Of the 5,754 (93% of overall cohort) who died during follow-up, 5161 (90%) had died before March 1, 2020 (start of the pandemic).

In the IPC group there was no significant difference in time to death (median 81 days pre-2019 vs 80 days in 2019, p=0.2948). In the pleurodesis group, median time to death for those who had a procedure before 2019 was 171 days vs after 2019 was 129 days (p=0.0256). For those that had procedures before 2019, overall 12-month mortality rate was 78.7% vs 82.2% for those who had procedures in 2019. In the IPC group (82% pre-2019 vs 84%, p=0.1204), and in the pleurodesis group (68% pre-2019 vs 73%, p=0.2570).

Discussion

All sensitivity analyses were consistent with the findings of the primary analyses except the two-staged analysis which showed higher mortality in the IPC group, which should be investigated in future studies.

Overall, only a relatively small percentage of individuals in our cohort were still alive at the start of the COVID pandemic and there was no difference in 12-month mortality rates in either group for those individuals who received procedures in 2019 and would've been more likely to still be alive during, and thus affected by the pandemic, compared to those who received them before 2019. Therefore it is not felt that pandemic-associated excess mortality had a significant impact on our results.

Tables

Table A1. ICES database descriptions

Database	Description
Ontario Health Insurance Plan Claims Database (OHIP)	Information on all physician billing claims in the province.
Canadian Institute for Health Information-Discharge Abstract Database (CIHI-DAD)	Information on all acute care hospitalizations in Canada
Canadian Institute for Health Information-Same Day Surgery Database (CIHI-SDS)	Patient-level data for day surgery at institutions in Ontario
Ontario Cancer Registry (OCR)	Database of all cases of cancer diagnosed among Ontario residents
Registered Persons Database (RPDB)	Basic demographic information (e.g., sex, year of birth, date of death where applicable and postal codes) about anyone who has ever received an Ontario health card number
National Ambulatory Care Registry System (NACRS)	Information on Emergency Department (ED), Dialysis and Cancer Clinic visits
ICES Physician Database (IPDB)	Yearly information about all physicians in Ontario
Home Care Database (HCD)	Information on home care services provided including date and type of service and associated diagnosis
Ontario health care institutions database (INST)	Information about Ontario health care institutions funded by the Ministry of Health and Long-Term Care (MOHLTC).
ICES-derived disease-specific databases	Chronic obstructive pulmonary disease (COPD)(1) Congestive heart failure (CHF)(2)

Additional details of available ICES databases are available at https://datadictionary.ices.on.ca/Applications/DataDictionary/.

Table A2. Variable definitions from health administrative databases for main exposure, exclusion criteria and covariates

Cohort creation definitions	
Main exposures	– IPC insertion (OHIP billing code Z361) – Chemical pleurodesis (CCI procedure codes 1GV59DAZ9 or 1GV59HAZ9)
Ascites, pneumothorax, or empyema diagnoses (exclusion criteria)	– Ascites: OHIP diagnosis code (787) – Pneumothorax: OHIP diagnosis code (512) or ICD-10 code J93, J930, J931, J938, J939 during index admission – Empyema: ICD-10 code J86, J860, J869 during index admission
Baseline Characteristics	
Baseline demographics	– Age, sex – Location of residence (urban vs. rural) – Neighbourhood income quintile as a marker of socioeconomic status: A patient's postal code is used to identify the nearest census dissemination area (DA), for which an average after tax income per single-person equivalent has been calculated. To account for cost-of-living differences, DAs are compared within census metropolitan areas or census agglomerations and classified into quintiles. Income quintile 1 contains the lowest incomes; income quintile 5 contains the highest incomes.(3)
Pleural effusion in previous 3 months	– Any diagnosis of pleural effusion during an admission (DAD, ICD-10 code J90, J91) or outpatient visit (OHIP, Diagnosis code 163, 511) in 3 months prior to index procedure
Procedure codes (OHIP billing codes)	– Thoracentesis (Z331, Z332) – Chest tube insertion (Z341)
Inpatient status (DAD)	– Index procedure date on or between any admission and discharge dates in DAD
Days in hospital prior to index procedure	– For patients categorized as admitted during their index procedure, admission date to the day prior to index
Cancer type (OCR)	ICD-O-3 codes(4) – Lung cancer: topography code C340, C341, C342, C343, C348, C349 – Breast cancer: topography code C500, C501, C502, C503, C504, C505, C506, C508, C509 – Mesothelioma: morphology code 90500, 90503, 90510, 90513, 90520, 90523, 90533, 90540, 90550, 90551 – Other: all other topography and morphology codes The OCR contains information about all Ontario residents who have been diagnosed with or died from cancer.
COPD	Prevalent COPD from the ICES-derived COPD specific cohort(1)

CHF	Prevalent CHF from the ICES-derived COPD specific cohort(2)
Frailty	Frailty indicator as defined in Johns Hopkins Adjusted Clinical Groups (ACG) software based on previous 2 years of health service utilization. Identifies an individual as frail if they are classified into one of the any expanded diagnostic clusters of malnutrition, dementia, impaired vision, decubitus ulcer, incontinence of urine or feces, loss of weight, obesity, poverty, barriers to access of care and difficulty walking.
Comorbidities	Calculated using Johns Hopkins Aggregated Diagnostic Groups (ADGs)(5, 6) in 2 years prior to index date and divided into categories based on total number of ADGs: - Low comorbidity: 0-5 ADGs - Moderate comorbidity: 6-9 ADGs - High comorbidity: ≥ 10 ADGs ADG comorbidity classification had been shown accurate for prediction of one-year mortality in patients with chronic diseases.(7, 8)
End stage renal disease, hemodialysis in the last 5 years prior the index date (from DAD, SDS, NACRS, and/or OHIP databases)	• Any diagnosis code from admission/visit in DAD, SDS, or NACRS: – ICD-10: I12, I13, N18.3, 18.4, 18.5, 18.6, 18.9, E08.22, E09.22, E10.22, E11.22, E13.22, Z99.2 • Any visit with OHIP codes: G860, G861, G862, G863, G864, G865, G866(9, 10)
Physician specialty	• Specialty of the physician assigned to CCI procedure or billing for the procedure
Hospital size	• Teaching as defined by Ontario Academic Health Science Centre definition from HealthForceOntario (https://www.health.gov.on.ca/en/common/system/services/hosp/group_a.aspx) • Community: Small or large community hospitals
Outcome Definitions	
IPC removal	• OHIP billing code (Z362)

Abbreviations: IPC-indwelling pleural catheter; OHIP-Ontario Health Insurance Plan Database; CCI-Canadian Classification of Health Interventions; DAD- Canadian Institute for Health Information- Discharge Abstract Database); OCR- Ontario Cancer Registry; COPD- Chronic obstructive pulmonary disease; CHF- congestive heart failure; NACRS- Canadian Institute for Health Information-National Ambulatory Care Reporting System

Table A3. Cancer diagnosis classification codes based on ICD-O-3

Cancer type	**ICD-O-3/SEER Code Grouping**(4)
Lip	[C00.0-C00.9]
Tongue	[C02.0-C02.9]
Other mouth, gum, pharynx	[C03.0-C03.9, C05.0, C05.8-C05.9, C06.0-C06.9, C09.0-C09.9, C14.0-C14.8]
Salivary gland	[C07.9-C08.9]
Floor of mouth	[C04.0-C04.9]
Nasopharynx	[C11.0-C11.9]
Oropharynx	[C01.9, C05.1-C05.2, C10.0-C10.9]
Hypopharynx	[C12.9, C13.0-C13.9]
Esophagus	[C15.0-C15.9]
Stomach	[C16.0-C16.9]
Small intestine	[C17.0-C17.9]
Colon and rectum	[C18.0-C18.9, C19.9, C20.9, C26.0]
Anus, anal canal and anorectum	[C21.0-C21.8]
Liver	[C22.0]
Gallbladder	[C23.9]
Pancreas	[C25.0-C25.9]
Other digestive system	[C22.1, C24.0-C24.9, C26.8-C26.9, C48.0-C48.8]
Larynx	[C32.0-C32.9]
Lung and bronchus	[C34.0-C34.9]
Other respiratory system	[C30.0-C30.1, C31.0-C31.9, C33.9, C38.1-C38.8, C39.0-C39.9]
Bones and joints	[C40.0-C41.9]
Soft tissue (including heart)	[C38.0, C47.0-C47.9, C49.0-C49.9]
Melanoma of the skin	[C44.0-C44.9, M-8720-M-8790]
Other non-epithelial skin	[C44.0-C44.9]
Breast	[C50.0-C50.9]
Cervix uteri	[C53.0-C53.9]
Corpus uteri	[C54.0-C54.9]
Uterus, not otherwise specified	[C55.9]
Ovary	[C56.9]
Other female genital system	[C51.0-C51.9, C52.9, C57.0-C58.9]
Prostate	[C61.9]
Testis	[C62.0-C62.9]
Penis	[C60.0-C60.9]

Other male genital organs	[C63.0-C63.9]
Urinary bladder (including in situ)	[C67.0-C67.9]
Kidney and renal pelvis	[C64.9, C65.9]
Ureter	[C66.9]
Other urinary organs	[C68.0-C68.9]
Eye and orbit	[C69.0-C69.9]
Brain and other nervous system	[C71.0-C71.9, C70.0-C70.9, C72.0-C72.9]
Thyroid	[C73.9]
Other endocrine	[C37.9, C74.0-C74.9, C75.0-C75.9]
Hodgkin lymphoma	[M-9650-M-9667]
Non-Hodgkin lymphoma	[M9590-9597, M-9670-9671, M-9673, M-9675, M-9678-9680, M-9684, M-9687, M-9689-9691, M-9695, M-9698-9702, M-9705, M-9708-9709, M-9714-9719, M-9727-9729; M-9823, M-9827]
Myeloma	[M-9731, M-9732, M-9734]
Acute lymphocytic leukemia	[M-9826, M-9835-9836;C42.0, M-9811-9818, M-9837;C42.1, M-9811-9818, M-9837;C42.4, M-9811-9818, M-9837]
Chronic lymphocytic leukemia	[C42.0, M-9823; C42.1, M-9823; C42.4, M-9823]
Acute monocytic leukemia	[M-9891]
Acute myeloid leukemia	[M-9840,M-9861,M-9865,M-9866,M-9867,M-9869,M-9871-M-9874,M-9895-M-9897,M-9898,M-9910,M-9911,M-9920]
Chronic myeloid leukemia	[M-9863, M-9875, M-9876, M-9945, M-9946]
Mesothelioma	[M-9050-M-9055]
Kaposi sarcoma	[M-9140]

Table A4. Means, proportions and standard differences of baseline variables before and after inverse probability of treatment weighting*

Characteristics, n (%)	Standard difference before weighting	Weighted IPC group	Weighted pleurodesis group	Standard difference after weighting
Sample size (N)		6010.8	3597	
Patient characteristics				
Age in years	0.005	70.2	69.8	0.032
Female	0.170	48.8%	61.9%	0.266
Rural	0.239	11.8%	10.3%	0.048
Neighbourhood income quintile				
1 (lowest)	0.012	18.8%	26.7%	0.189
2	0.033	19.1%	33.9%	0.342
3	0.037	19.4%	12.5%	0.191
4	0.048	24.4%	11.8%	0.331
5 (highest)	0.058	18.4%	15.1%	0.086
Thoracentesis in 12 months prior to index date	0.337	58.9%	43.8%	0.306
Cancer type				
Lung	0.136	37.6%	36.8%	0.017
Breast	0.123	12.4%	20.9%	0.231
Mesothelioma	0.286	13.1%	7.2%	0.198
Other	0.210	36.9%	35.1%	0.037
Days from cancer diagnosis to index procedure	0.040	821.3	605.8	0.132
COPD	0.166	22.7%	14.4%	0.215
CHF	0.042	13.9%	10.7%	0.097
Renal failure	0.095	3.8%	1.9%	0.114
Frailty	0.100	15.4%	24.7%	0.236
Aggregated diagnosis groups				
Low comorbidity (0-5)	0.007	1.7%	1.4%	0.022
Moderate comorbidity (6-9)	0.032	21.2%	25.3%	0.096
High comorbidity (≥10)	0.033	77%	73.3%	0.088
Physician specialty				
Pulmonology	1.690	49.4%	32.1%	0.358
Thoracic surgery	1.448	24%	37.7%	0.302
General surgery	0.481	13.2%	7.2%	0.197
Diagnostic radiology	0.334	6.7%	11.8%	0.178
Other	0.144	6.8%	11.2%	0.152
Hospital characteristics				
Hospital type				
Teaching	0.180	69.1%	53.6%	0.322
Community and Small	0.180	30.9%	46.4%	0.322
Annual volume of IPCs	1.392	61.1	38.5	0.429
Annual volume of pleurodesis	1.757	17.2	30	0.381

Abbreviations: IPC, indwelling pleural catheter; COPD, chronic obstructive lung disease; CHF, congestive heart failure
*Weights calculated using inverse probability of treatment weights

Table A5. Type of cancer by group (all cancer types)

Cancer type	IPC group, n	Pleurodesis group, n
Lung and bronchus	1889	641
Breast	751	159
Ovary	311	48
Mesothelioma	178	153
Non-Hodgkin lymphoma	202	66
Colon and rectum	195	38
Pancreas	179	19
Kidney and renal pelvis	125	42
Stomach	103	24
Corpus uteri	110	10
Prostate	73	31
Other digestive system	86	10
Melanoma of the skin	67	13
Esophagus	54	22
Liver	52	6
Urinary bladder (including in situ)	45	13
Soft tissue (including heart)	33	9
Myeloma	25	9
Thyroid	22	9
Other female genital system	23	7
Cervix uteri	18	8
Other endocrine	17	6
Other respiratory system	13	7
Small intestine	14	<6
Other mouth, gum, pharynx	12	<6
Salivary gland	13	<6
Hodgkin lymphoma	9	<6
Bones and joints	6	6
Gallbladder	12	<6
Chronic myeloid leukemia	9	<6
Other non-epithelial skin	7	<6
Other urinary organs	10	<6
Tongue	9	<6
Anus, anal canal and anorectum	8	<6
Acute myeloid leukemia	7	<6
Larynx	6	<6
Other	97	25

Table A6. Available baseline characteristics for those with and without missing data

Characteristics, n (%)			
IPC individuals	**No missing data (N=4432)**	**Missing data (N=358)**	**Standard difference**
Patient characteristics			
Age in years, mean (SD)	69 (12.9)	70.2 (12.7)	0.094
Female	2511 (56.7)	211 (58.9)	0.046
Rural	475 (10.7)	-	-
Neighbourhood income quintile			
1 (lowest)	926 (20.9)		
2	923 (20.8)	-	-
3	925 (20.9)		
4	796 (18)		
5 (highest)	862 (19.5)		
Thoracentesis in 12 months prior to index date	2647 (59.7)	271 (75.7)	0.347
Chest tube insertion in preceding 12 months†	855 (19.3)	61 (17)	0.058
Inpatient for index procedure	1791 (40.4)	-	-
Cancer type			
Lung	1733 (39.1)	156 (43.6)	0.091
Breast	685 (15.5)	66 (18.4)	0.079
Mesothelioma	171 (3.9)	7 (2)	0.113
Other	1843 (41.6)	129 (36)	0.114
Days from cancer diagnosis to index procedure, median (IQR)	244.5 (33-897)	223 (32-960)	0.040
COPD	703 (15.9)	46 (12.9)	0.086
CHF	632 (14.3)	47 (13.1)	0.033
Renal failure	195 (4.4)	12 (3.4)	0.054
Frailty	716 (16.2)	46 (12.9)	0.094
Aggregated diagnosis groups			
Low comorbidity (0-5)	95 (2.1)	11 (3.1)	0.058
Moderate comorbidity (6-9)	1033 (23.2)	91 (25.4)	0.049
High comorbidity (≥10)	3304 (74.6)	256 (71.5)	0.069
Physician specialty			
Pulmonology	2918 (65.8)		
Thoracic surgery	695 (15.7)	-	-
General surgery	119 (2.7)		
Diagnostic radiology	384 (8.7)		
Other	316 (7.1)		
Hospital characteristics			
Hospital type			
Teaching	2882 (65)	-	-
Community and Small	1550 (35)		

Annual volume of IPCs, median (IQR)[‡]	62 (23-114)	-	-
Annual volume of pleurodesis, median (IQR)[‡]	0 (0-6)	-	-
Annual volume of IPCs[‡], categorized			
Low (0-49.99)	1673 (37.8)	-	-
High (≥ 50)	2759 (62.3)		
Annual volume of pleurodesis[‡], categorized			
Low (0-49.99)	4360 (98.4)	-	-
High (≥ 50)	72 (1.6)		
Pleurodesis individuals	**No missing data (N=1320)**	**Missing data (N=87)**	**Standard difference**
Patient characteristics			
Age in years, mean (SD)	69 (11.6)	68.1 (12.8)	0.069
Female	636 (48.2)	45 (51.7)	0.071
Rural	253 (19.2)	-	-
Neighbourhood income quintile			
1 (lowest)	282 (21.4)		
2	293 (22.2)	-	-
3	256 (19.4)		
4	262 (19.9)		
5 (highest)	227 (17.2)		
Previous thoracentesis in 12 months prior to index date	569 (43.1)	39 (44.8)	0.035
Chest tube insertion in preceding 12 months[†]	336 (25.5)	26 (29.9)	0.099
Inpatient for index procedure	1320 (100)	-	-
Cancer type			
Lung	605 (45.8)	36 (41.4)	0.006
Breast	149 (11.3)	0-10	0.090
Mesothelioma	150 (11.4)	0-10	0.306
Other	416 (31.5)	38 (43.7)	0.253
Days from cancer diagnosis to index procedure, median (IQR)	75.5 (10-734.5)	193 (20-1076)	0
COPD	295 (22.4)	11 (12.6)	0.258
CHF	208 (15.8)	11 (12.6)	0.089
Renal failure	35 (2.7)	<6	0.104
Frailty	167 (12.7)	13 (14.9)	0.066
Aggregated diagnosis groups			
Low comorbidity (0-5)	27 (2.1)	0-20	0.072
Moderate comorbidity (6-9)	290 (22)	0-20	0.089
High comorbidity (≥10)	1003 (76)	70 (80.5)	0.109
Physician specialty			

Pulmonology	56 (4.2)		
Thoracic surgery	977 (74)	-	-
General surgery	217 (16.4)		
Diagnostic radiology	19 (1.4)		
Other	51 (3.9)		
Hospital characteristics			
Hospital type			
Teaching	743 (56.3)	-	-
Community and Small	577 (43.7)		
Annual volume of IPCs, median (IQR)‡	7 (1-14)	-	-
Annual volume of pleurodesis, median (IQR)‡	52 (23-100)	-	-
Annual volume of IPCs‡, categorized			
Low (0-49.99)	1220 (92.4)	-	-
High (≥ 50)	100 (7.6)		
Annual volume of pleurodesis‡, categorized			
Low (0-49.99)	614 (46.5)	-	-
High (≥ 50)	706 (53.5)		

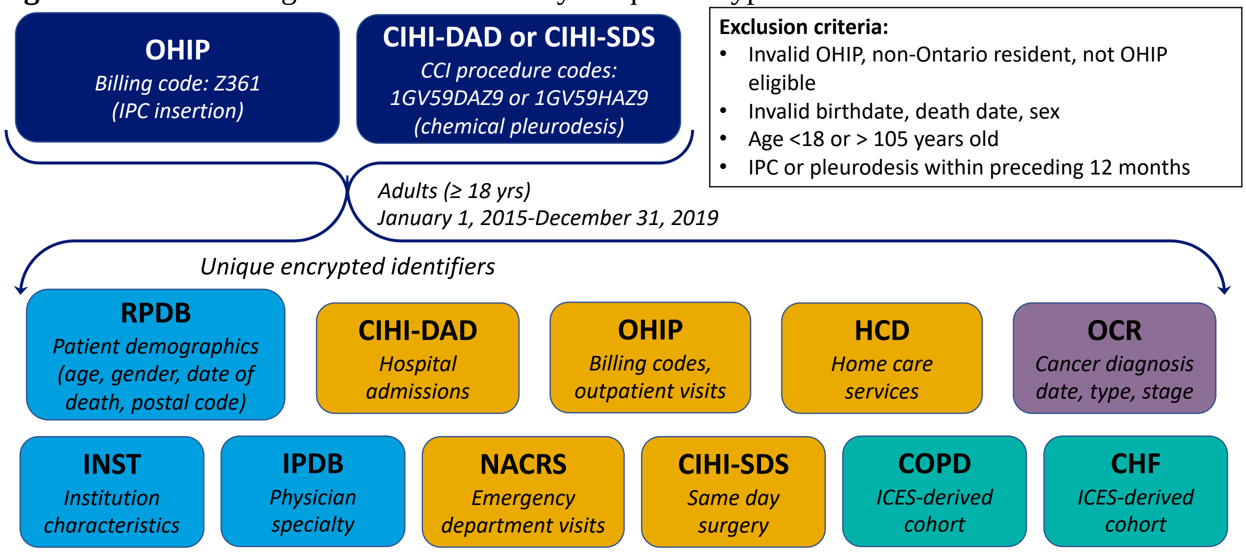
Abbreviations: IPC, indwelling pleural catheter; IQR, interquartile range; COPD, chronic obstructive lung disease; CHF, congestive heart failure

*p<0.5 in IPC individuals

†Excluding 3 days prior to index date

‡p<0.5 in pleurodesis individuals

Figure A1. Data linkage of ICES datasets by unique encrypted identifiers



OHIP: Ontario Health Insurance Plan claims database; IPC: indwelling pleural catheter; CIHI-DAD: Canadian Institute for Health Information-Discharge Abstract Database; SDS: Same Day Surgery database; CCI: Canadian Classification of Health Interventions; RPDB: Registered Persons Database; HCD: Home Care Database; OCR: Ontario Cancer Registry; INST: Institution database; IPDB: ICES Physician Database; NACRS: National Ambulatory Care Reporting System; COPD: Chronic Obstructive Pulmonary Disease database; CHF: Congestive Heart Failure database

Figure A2. Relationship of covariates between malignant pleural effusions and mortality outcome

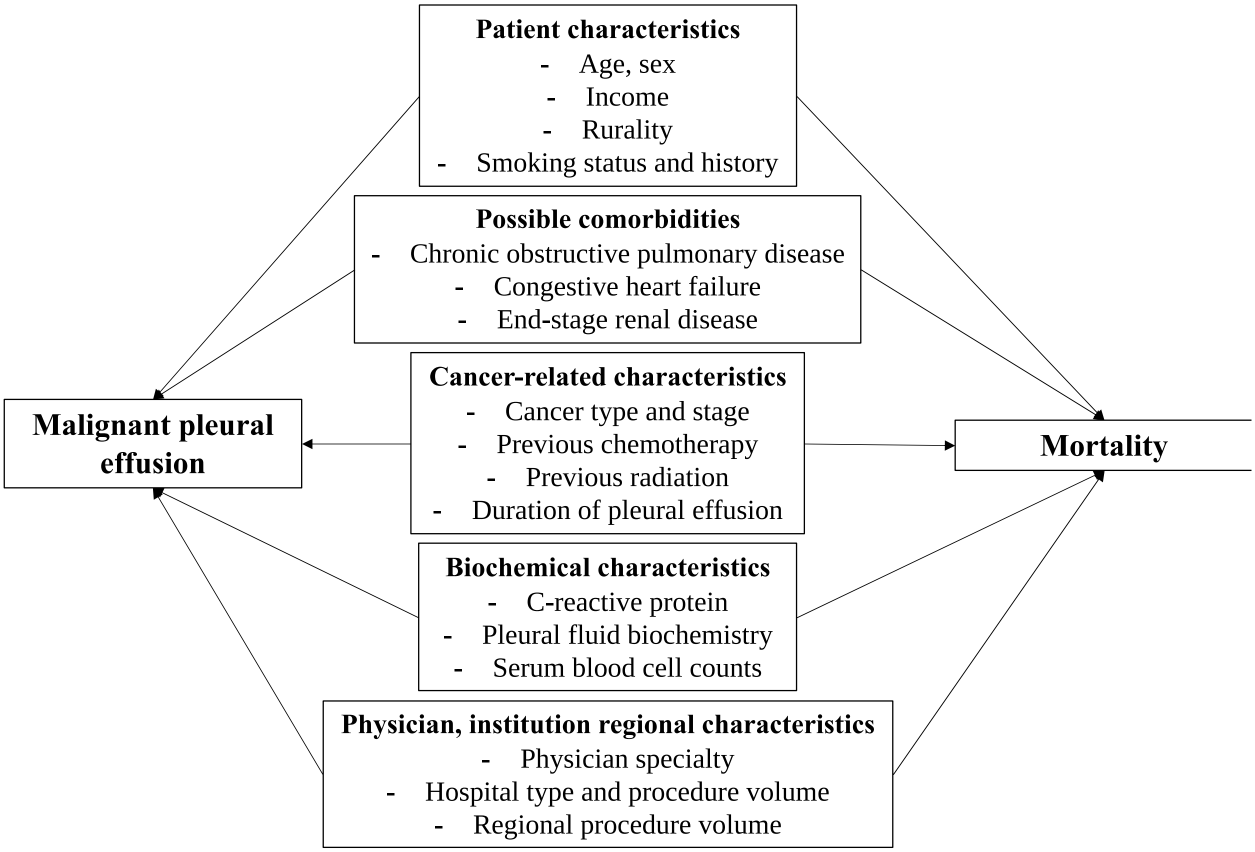


Figure A3. Box plots of continuous variables before and after propensity score weighting by inverse probability of treatment weighting (IPTW)

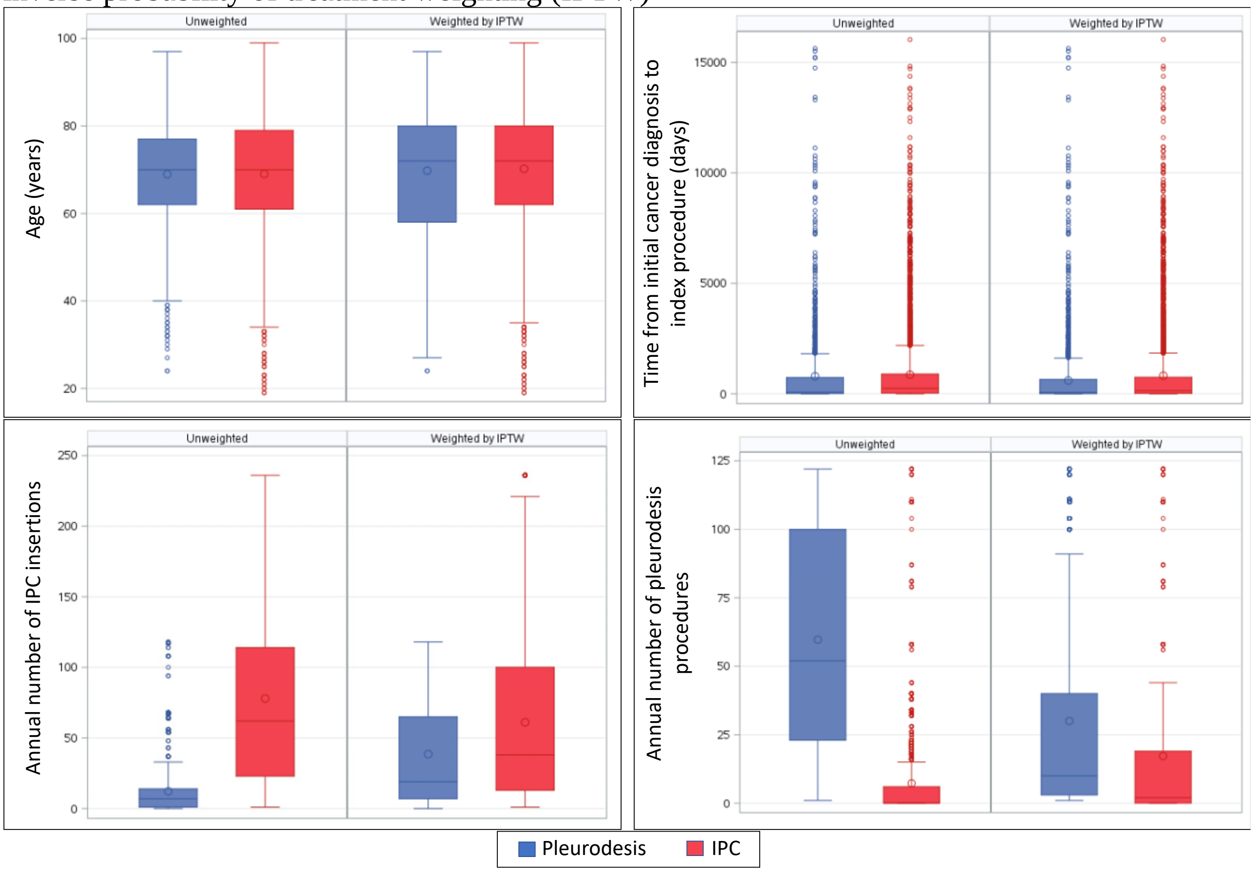


Figure A4. Density Plots of propensity scores before and after inverse probability of treatment weighting

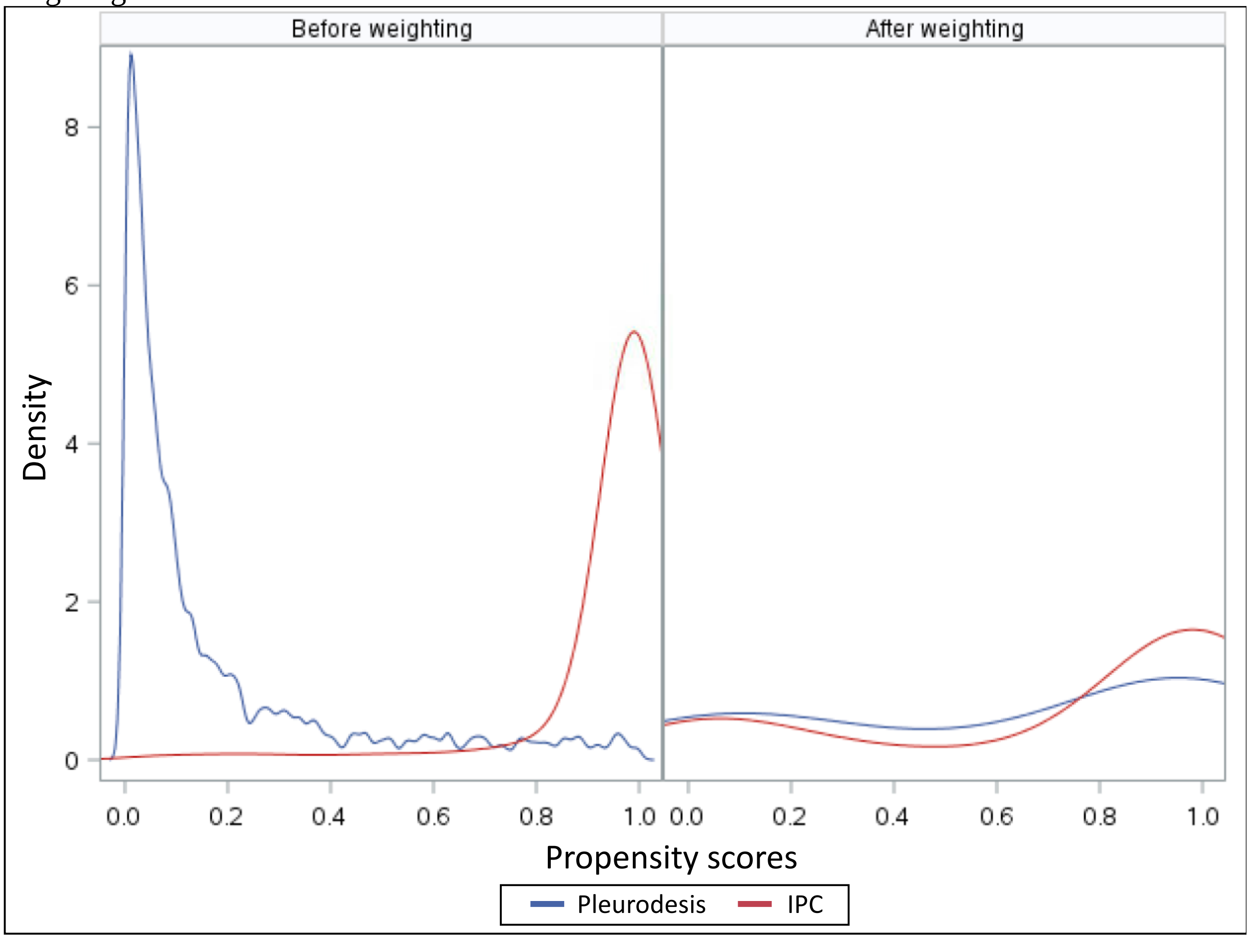


Figure A5. Annual number of indwelling pleural catheters (IPC) and pleurodesis procedures performed between 2015 – 2019

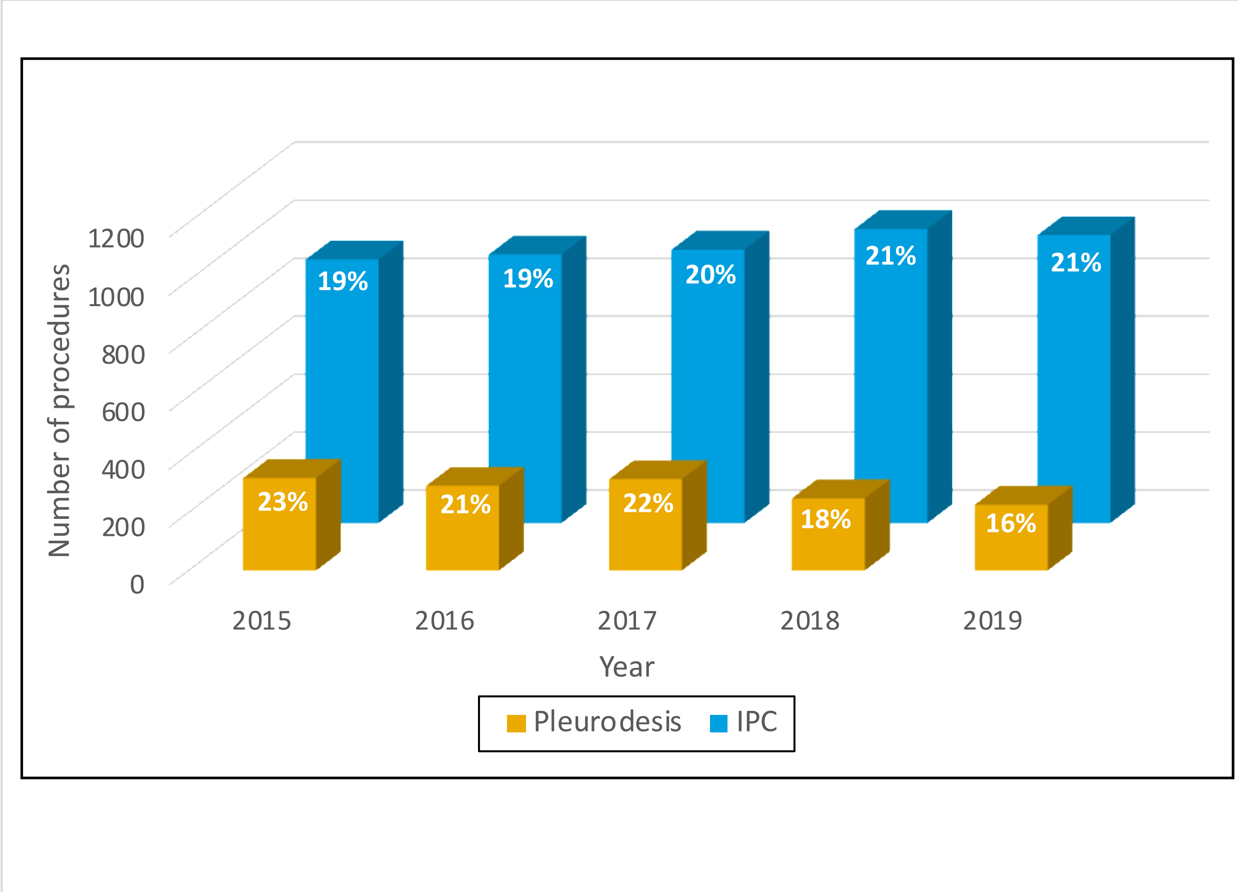


Figure A6. Number of procedures performed by regional health authority (responsible for providing home care services)

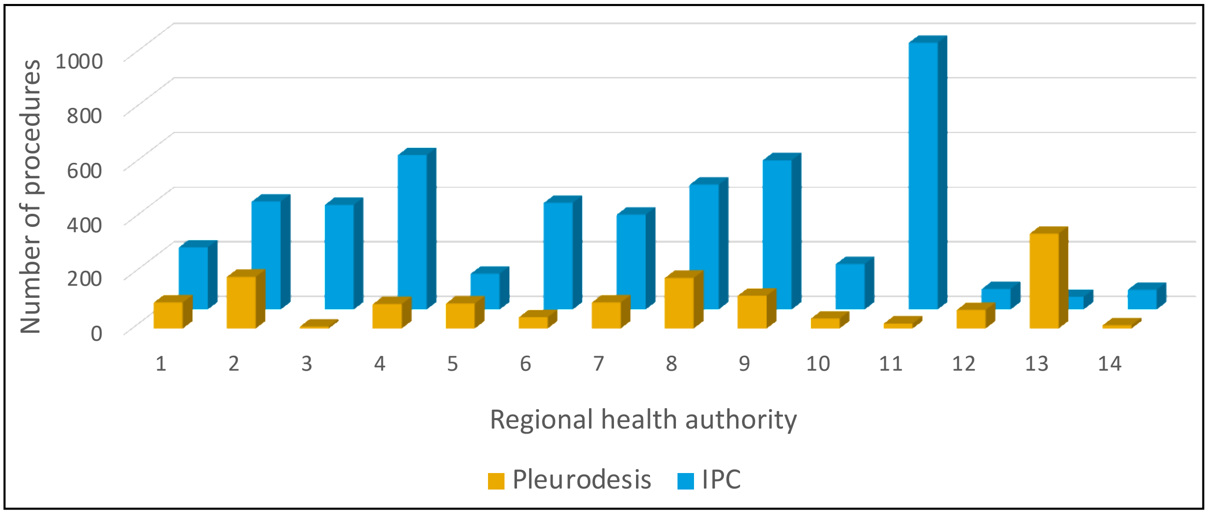


Figure A7. Stacked curve of competing risk analysis for (indwelling pleural catheter) IPC removal (IPC group only)
Graph of cumulative incidence function demonstrating probability of IPC removal over time, with death as a competing risk.

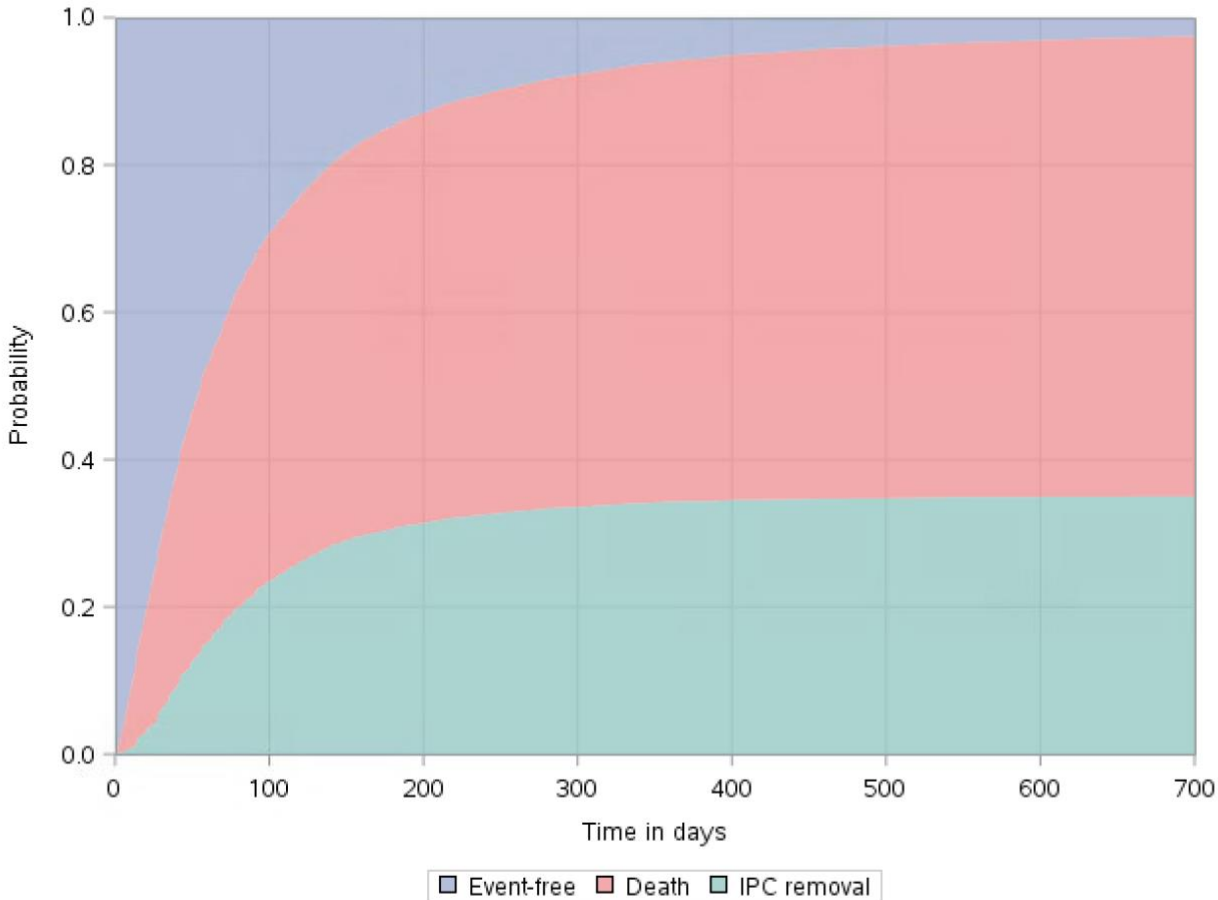
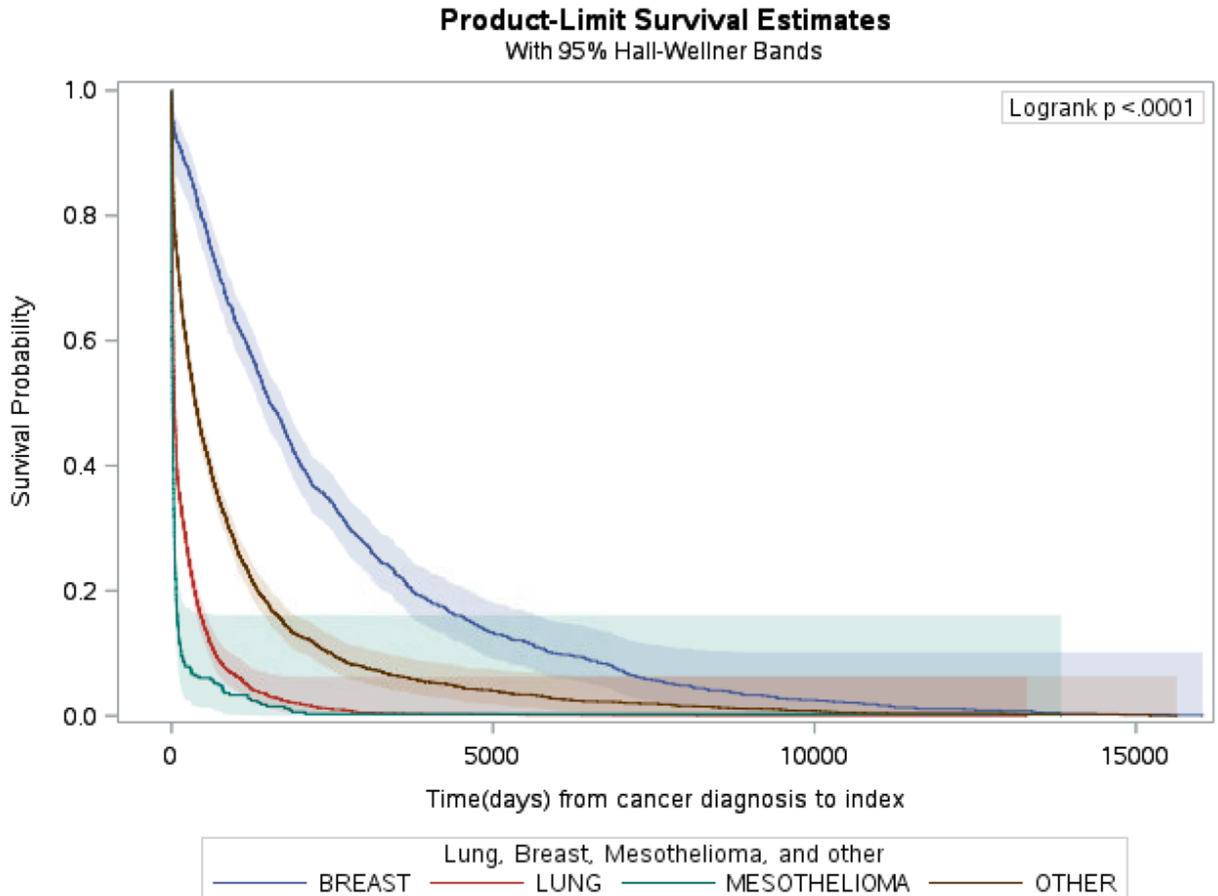


Figure A8. Kaplan-Meier curve of days from cancer diagnosis to index procedure by cancer type for all study individuals



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Appendix B – Supplementary material for Manuscript 2

Methods

Inverse probability of treatment weighting using propensity score

The probability that an individual will receive an intervention based on baseline covariates is the propensity score (PS). It can be used to minimize the bias introduced by the patient-, physician-, and/or hospital-level characteristics that can influence treatment choice (confounding by indication). A PS of 0 to 1 was calculated for each individual using multivariable hierarchical logistic regression model with receiving an IPC as the dependent variable, baseline covariates as predictors, and including potential hospital-level clustering. Inverse probability of treatment weighting (IPTW) using the PS was then performed to assess the average treatment effect (ATE) in the whole population of study individuals. For IPTW, a weight of 1/PS was assigned to the IPC group, and 1/(1-PS) for pleurodesis group; the inverse probability of receiving the treatment actually received. This form of weighting the study population aims to improve the balance of covariates between groups, by assigning larger weights to individuals who receive one intervention, but have characteristics that would statistically suggest they would typically receive the other intervention (i.e. have a small PS).

An alternative method to calculate weights, is using treatment weights (TW) to estimate the average treatment effect among the treated (IPC) population (ATT). This was performed as a sensitivity analysis. All IPC patients were assigned a weight of 1, and pleurodesis patients a weight based on the odds of treatment (PS/(1-PS)). Stabilized weights can also be calculated to reduce the influence of subjects with very large weights. These incorporate the marginal probability (margP) into the weight calculation (IPC_{weight}= MargP /PS; $Pleurodesis_{weight}$=[1-MargP]/[1-PS]).

Results

Sensitivity analysis (ATT)

A sensitivity analysis was performed use TW instead of IPTW for all weighted outcomes. All results showed consistent treads and significance. After TW were applied, individuals in the IPC group spent 10.13 days versus 16.76 days in the pleurodesis as inpatients during the follow-up period (standard difference 0.448). Total costs were $39,505 in the IPC group compared to $46,188 in the pleurodesis group (standard difference 0.316).

Sensitivity analysis (stabilized IPTW)

After stabilized IPTW were calculated and applied, IPC individuals spent 12.37 days versus 15.97 days in the pleurodesis groups as inpatients during the 12-months post-procedure (standard difference 0.229). Total post-procedure healthcare costs were $40,179 in the IPC group compared to $46,640 in the pleurodesis group (standard difference 0.177).

Tables

Table B1. ICES database descriptions

Database	Description
Ontario Health Insurance Plan Claims Database (OHIP)	Information on all physician billing claims in the province.
Canadian Institute for Health Information-Discharge Abstract Database (CIHI-DAD)	Information on all acute care hospitalizations in Canada
Canadian Institute for Health Information-Same Day Surgery Database (CIHI-SDS)	Patient-level data for day surgery at institutions in Ontario
Ontario Cancer Registry (OCR)	Database of all cases of cancer diagnosed among Ontario residents
Registered Persons Database (RPDB)	Basic demographic information (e.g., sex, year of birth, date of death where applicable and postal codes) about anyone who has ever received an Ontario health card number
National Ambulatory Care Registry System (NACRS)	Information on Emergency Department (ED), Dialysis and Cancer Clinic visits
ICES Physician Database (IPDB)	Yearly information about all physicians in Ontario
Home Care Database (HCD)	Information on home care services provided including date and type of service and associated diagnosis
Ontario health care institutions database (INST)	Information about Ontario health care institutions funded by the Ministry of Health and Long-Term Care (MOHLTC).
ICES-derived disease-specific databases	Chronic obstructive pulmonary disease (COPD)(1) Congestive heart failure (CHF)(2)

Additional details of available ICES databases are available at https://datadictionary.ices.on.ca/Applications/DataDictionary/.

Table B2. Variable definitions from health administrative databases for main exposure, exclusion criteria and covariates

Cohort creation definitions	
Main exposures	– IPC insertion (OHIP billing code Z361) – Chemical pleurodesis (CCI procedure codes 1GV59DAZ9 or 1GV59HAZ9)
Ascites, pneumothorax, or empyema diagnoses (exclusion criteria)	– Ascites: OHIP diagnosis code (787) – Pneumothorax: OHIP diagnosis code (512) or ICD-10 code J93, J930, J931, J938, J939 during index admission – Empyema: ICD-10 code J86, J860, J869 during index admission
Baseline Characteristics	
Baseline demographics	– Age, sex – Location of residence (urban vs. rural) – Neighbourhood income quintile as a marker of socioeconomic status: A patient's postal code is used to identify the nearest census dissemination area (DA), for which an average after tax income per single-person equivalent has been calculated. To account for cost-of-living differences, DAs are compared within census metropolitan areas or census agglomerations and classified into quintiles. Income quintile 1 contains the lowest incomes; income quintile 5 contains the highest incomes.(3)
Pleural effusion in previous 3 months	– Any diagnosis of pleural effusion during an admission (DAD, ICD-10 code J90, J91) or outpatient visit (OHIP, Diagnosis code 163, 511) in 3 months prior to index procedure
Procedure codes (OHIP billing codes)	– Thoracentesis (Z331, Z332) – Chest tube insertion (Z341)
Inpatient status (DAD)	– Index procedure date on or between any admission and discharge dates in DAD
Days in hospital prior to index procedure	– For patients categorized as admitted during their index procedure, admission date to the day prior to index
Cancer type (OCR)	ICD-O-3 codes(4) – Lung cancer: topography code C340, C341, C342, C343, C348, C349 – Breast cancer: topography code C500, C501, C502, C503, C504, C505, C506, C508, C509 – Mesothelioma: morphology code 90500, 90503, 90510, 90513, 90520, 90523, 90533, 90540, 90550, 90551 – Other: all other topography and morphology codes The OCR contains information about all Ontario residents who have been diagnosed with or died from cancer.
COPD	Prevalent COPD from the ICES-derived COPD specific cohort(1)
CHF	Prevalent CHF from the ICES-derived COPD specific cohort(2)

Frailty	Frailty indicator as defined in Johns Hopkins Adjusted Clinical Groups (ACG) software based on previous 2 years of health service utilization. Identifies an individual as frail if they are classified into one of the any expanded diagnostic clusters of malnutrition, dementia, impaired vision, decubitus ulcer, incontinence of urine or feces, loss of weight, obesity, poverty, barriers to access of care and difficulty walking.
Comorbidities	Calculated using Johns Hopkins Aggregated Diagnostic Groups (ADGs)(5, 6) in 2 years prior to index date and divided into categories based on total number of ADGs: - Low comorbidity: 0-5 ADGs - Moderate comorbidity: 6-9 ADGs - High comorbidity: ≥ 10 ADGs ADG comorbidity classification had been shown accurate for prediction of one-year mortality in patients with chronic diseases.(7, 8)
End stage renal disease, hemodialysis in the last 5 years prior the index date (from DAD, SDS, NACRS, and/or OHIP databases)	• Any diagnosis code from admission/visit in DAD, SDS, or NACRS: – ICD-10: I12, I13, N18.3, 18.4, 18.5, 18.6, 18.9, E08.22, E09.22, E10.22, E11.22, E13.22, Z99.2 • Any visit with OHIP codes: G860, G861, G862, G863, G864, G865, G866(9, 10)
Physician specialty	• Specialty of the physician assigned to CCI procedure or billing for the procedure
Hospital size	• Teaching as defined by Ontario Academic Health Science Centre definition from HealthForceOntario (https://www.health.gov.on.ca/en/common/system/services/hosp/group_a.aspx) • Community: Small or large community hospitals
Outcome Definitions	
IPC removal	• OHIP billing code (Z362)

Abbreviations: IPC-indwelling pleural catheter; OHIP-Ontario Health Insurance Plan Database; CCI-Canadian Classification of Health Interventions; DAD- Canadian Institute for Health Information- Discharge Abstract Database); OCR- Ontario Cancer Registry; COPD- Chronic obstructive pulmonary disease; CHF- congestive heart failure; NACRS- Canadian Institute for Health Information-National Ambulatory Care Reporting System

Table B3. Cancer diagnosis classification codes based on ICD-O-3

Cancer type	**ICD-O-3/SEER Code Grouping**(4)
Lip	[C00.0-C00.9]
Tongue	[C02.0-C02.9]
Other mouth, gum, pharynx	[C03.0-C03.9, C05.0, C05.8-C05.9, C06.0-C06.9, C09.0-C09.9, C14.0-C14.8]
Salivary gland	[C07.9-C08.9]
Floor of mouth	[C04.0-C04.9]
Nasopharynx	[C11.0-C11.9]
Oropharynx	[C01.9, C05.1-C05.2, C10.0-C10.9]
Hypopharynx	[C12.9, C13.0-C13.9]
Esophagus	[C15.0-C15.9]
Stomach	[C16.0-C16.9]
Small intestine	[C17.0-C17.9]
Colon and rectum	[C18.0-C18.9, C19.9, C20.9, C26.0]
Anus, anal canal and anorectum	[C21.0-C21.8]
Liver	[C22.0]
Gallbladder	[C23.9]
Pancreas	[C25.0-C25.9]
Other digestive system	[C22.1, C24.0-C24.9, C26.8-C26.9, C48.0-C48.8]
Larynx	[C32.0-C32.9]
Lung and bronchus	[C34.0-C34.9]
Other respiratory system	[C30.0-C30.1, C31.0-C31.9, C33.9, C38.1-C38.8, C39.0-C39.9]
Bones and joints	[C40.0-C41.9]
Soft tissue (including heart)	[C38.0, C47.0-C47.9, C49.0-C49.9]
Melanoma of the skin	[C44.0-C44.9, M-8720-M-8790]
Other non-epithelial skin	[C44.0-C44.9]
Breast	[C50.0-C50.9]
Cervix uteri	[C53.0-C53.9]
Corpus uteri	[C54.0-C54.9]
Uterus, not otherwise specified	[C55.9]
Ovary	[C56.9]
Other female genital system	[C51.0-C51.9, C52.9, C57.0-C58.9]
Prostate	[C61.9]
Testis	[C62.0-C62.9]
Penis	[C60.0-C60.9]

Other male genital organs	[C63.0-C63.9]
Urinary bladder (including in situ)	[C67.0-C67.9]
Kidney and renal pelvis	[C64.9, C65.9]
Ureter	[C66.9]
Other urinary organs	[C68.0-C68.9]
Eye and orbit	[C69.0-C69.9]
Brain and other nervous system	[C71.0-C71.9, C70.0-C70.9, C72.0-C72.9]
Thyroid	[C73.9]
Other endocrine	[C37.9, C74.0-C74.9, C75.0-C75.9]
Hodgkin lymphoma	[M-9650-M-9667]
Non-Hodgkin lymphoma	[M9590-9597, M-9670-9671, M-9673, M-9675, M-9678-9680, M-9684, M-9687, M-9689-9691, M-9695, M-9698-9702, M-9705, M-9708-9709, M-9714-9719, M-9727-9729; M-9823, M-9827]
Myeloma	[M-9731, M-9732, M-9734]
Acute lymphocytic leukemia	[M-9826, M-9835-9836;C42.0, M-9811-9818, M-9837;C42.1, M-9811-9818, M-9837;C42.4, M-9811-9818, M-9837]
Chronic lymphocytic leukemia	[C42.0, M-9823; C42.1, M-9823; C42.4, M-9823]
Acute monocytic leukemia	[M-9891]
Acute myeloid leukemia	[M-9840,M-9861,M-9865,M-9866,M-9867,M-9869,M-9871-M-9874,M-9895-M-9897,M-9898,M-9910,M-9911,M-9920]
Chronic myeloid leukemia	[M-9863, M-9875, M-9876, M-9945, M-9946]
Mesothelioma	[M-9050-M-9055]
Kaposi sarcoma	[M-9140]

Table B4. Available baseline characteristics for those with and without missing data

Characteristics, n (%)			
IPC individuals	**No missing data (N=4432)**	**Missing data (N=358)**	**Standard difference**
Patient characteristics			
Age in years, mean (SD)	69 (12.9)	70.2 (12.7)	0.094
Female	2511 (56.7)	211 (58.9)	0.046
Rural	475 (10.7)	-	-
Neighbourhood income quintile			
1 (lowest)	926 (20.9)		
2	923 (20.8)	-	-
3	925 (20.9)		
4	796 (18)		
5 (highest)	862 (19.5)		
Thoracentesis in 12 months prior to index date	2647 (59.7)	271 (75.7)	0.347
Chest tube insertion in preceding 12 months[†]	855 (19.3)	61 (17)	0.058
Inpatient for index procedure	1791 (40.4)	-	-
Cancer type			
Lung	1733 (39.1)	156 (43.6)	0.091
Breast	685 (15.5)	66 (18.4)	0.079
Mesothelioma	171 (3.9)	7 (2)	0.113
Other	1843 (41.6)	129 (36)	0.114
Days from cancer diagnosis to index procedure, median (IQR)	244.5 (33-897)	223 (32-960)	0.040
COPD	703 (15.9)	46 (12.9)	0.086
CHF	632 (14.3)	47 (13.1)	0.033
Renal failure	195 (4.4)	12 (3.4)	0.054
Frailty	716 (16.2)	46 (12.9)	0.094
Aggregated diagnosis groups			
Low comorbidity (0-5)	95 (2.1)	11 (3.1)	0.058
Moderate comorbidity (6-9)	1033 (23.2)	91 (25.4)	0.049
High comorbidity (≥10)	3304 (74.6)	256 (71.5)	0.069
Physician specialty			
Pulmonology	2918 (65.8)		
Thoracic surgery	695 (15.7)	-	-
General surgery	119 (2.7)		
Diagnostic radiology	384 (8.7)		
Other	316 (7.1)		
Hospital characteristics			
Hospital type			
Teaching	2882 (65)	-	-
Community and Small	1550 (35)		

Annual volume of IPCs, median (IQR)‡	62 (23-114)	-	-
Annual volume of pleurodesis, median (IQR)‡	0 (0-6)	-	-
Annual volume of IPCs‡, categorized Low (0-49.99) High (≥ 50)	 1673 (37.8) 2759 (62.3)	-	-
Annual volume of pleurodesis‡, categorized Low (0-49.99) High (≥ 50)	 4360 (98.4) 72 (1.6)	-	-
Pleurodesis individuals	**No missing data (N=1320)**	**Missing data (N=87)**	**Standard difference**
Patient characteristics			
Age in years, mean (SD)	69 (11.6)	68.1 (12.8)	0.069
Female	636 (48.2)	45 (51.7)	0.071
Rural	253 (19.2)	-	-
Neighbourhood income quintile 1 (lowest) 2 3 4 5 (highest)	 282 (21.4) 293 (22.2) 256 (19.4) 262 (19.9) 227 (17.2)	-	-
Previous thoracentesis in 12 months prior to index date	569 (43.1)	39 (44.8)	0.035
Chest tube insertion in preceding 12 months†	336 (25.5)	26 (29.9)	0.099
Inpatient for index procedure	1320 (100)	-	-
Cancer type Lung Breast Mesothelioma Other	 605 (45.8) 149 (11.3) 150 (11.4) 416 (31.5)	 36 (41.4) 0-10 0-10 38 (43.7)	 0.006 0.090 0.306 0.253
Days from cancer diagnosis to index procedure, median (IQR)	75.5 (10-734.5)	193 (20-1076)	0
COPD	295 (22.4)	11 (12.6)	0.258
CHF	208 (15.8)	11 (12.6)	0.089
Renal failure	35 (2.7)	<6	0.104
Frailty	167 (12.7)	13 (14.9)	0.066
Aggregated diagnosis groups Low comorbidity (0-5) Moderate comorbidity (6-9) High comorbidity (≥10)	 27 (2.1) 290 (22) 1003 (76)	 0-20 0-20 70 (80.5)	 0.072 0.089 0.109
Physician specialty			

Pulmonology	56 (4.2)	-	-
Thoracic surgery	977 (74)		
General surgery	217 (16.4)		
Diagnostic radiology	19 (1.4)		
Other	51 (3.9)		
Hospital characteristics			
Hospital type			
Teaching	743 (56.3)	-	-
Community and Small	577 (43.7)		
Annual volume of IPCs, median (IQR)‡	7 (1-14)	-	-
Annual volume of pleurodesis, median (IQR)‡	52 (23-100)	-	-
Annual volume of IPCs‡, categorized			
Low (0-49.99)	1220 (92.4)	-	-
High (≥ 50)	100 (7.6)		
Annual volume of pleurodesis‡, categorized			
Low (0-49.99)	614 (46.5)	-	-
High (≥ 50)	706 (53.5)		

Abbreviations: IPC, indwelling pleural catheter; SD, standard deviation; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure

*p<0.5 in IPC individuals

†Excluding 3 days prior to index date

‡p<0.5 in pleurodesis individuals

Table B5. Crude median 12-month post-procedure health service utilization

Outcome	IPC, Median (IQR)	Pleurodesis, Median (IQR)
Total inpatient days in 12 months post procedure	5 (0-14)	9 (4-19)
ED visits	1 (0-2)	1 (0-2)
Home care visits		
Nursing visits	25 (7-55)	8 (0-29)
Other visits	10 (3-28)	7 (1-23)

Abbreviations: IPC, indwelling pleural catheter; IQR, interquartile range; ED, emergency department

Table B6. Crude 12-month post-procedure healthcare costs (2020 Canadian dollars), median

Costs	IPC, median (IQR)	Pleurodesis, median (IQR)
Total costs	28,798 (14,166.5-54,346.5)	38,597.5 (22,941-64,593)
Subdivided costs		
Inpatient	7,886.5 (0-17,251)	14,016 (7,752.5-24,800.5)
Cancer centre	810.5 (0-9,797)	557 (0-10,812)
Physician costs	4,805.5 (2,588-8,073)	6,722.5 (3,841-9903.5)
Home care	3,021 (907.5-6,534)	1,124.5 (0-3,839)
Medications	678 (103-2,104)	969.5 (127.5-2,954.5)
Outpatient	2,010.5 (692-4,359)	2,028 (742-4,085.5)
Emergency department	530 (0-1,118)	535 (0-1,198.5)
Same day surgery	0 (0-440)	0 (0-0)
Dialysis	0 (0-0)	0 (0-0)
Other	0 (0-68)	36.5 (0-128)

Abbreviations: IPC, indwelling pleural catheter; IQR, interquartile range

Table B7. Crude mean post-procedure healthcare costs (2020 Canadian dollars) by survival time

Died within	IPC			Pleurodesis		
	n (%)	Mean (SD)	Median (IQR)	n (%)	Mean (SD)	Median (IQR)
30 days	1298 (29.3)	21,119 (25,226)	13,393.5 (6,534-14,171)	357 (27.1)	33,080 (28,009)	24,017 (13,319-42553)
6 weeks	1634 (36.9)	20,972 (23,524)	14,255 (6,885-24,665)	422 (32)	31,844 (26,256)	23,934.5 (13,839-39,138)
90 days	2476 (55.9)	23,376 (23,172)	17,309 (8,829-29,736)	588 (44.6)	33,921 (28,059)	26,527 (15,738.5-42,823.5

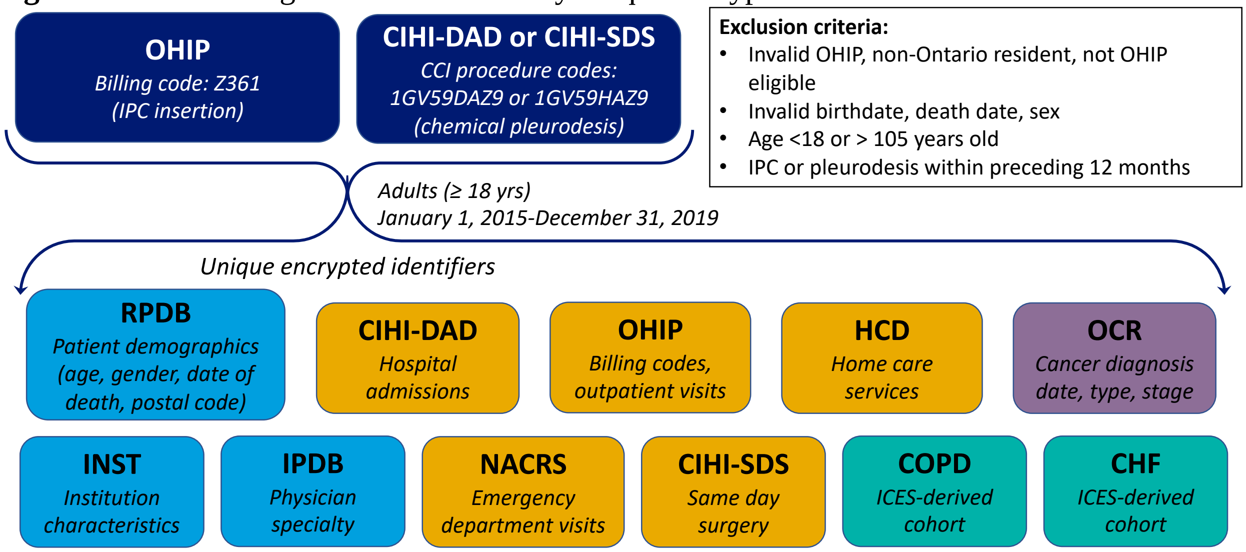
Abbreviations: IPC, indwelling pleural catheter; SD, standard deviation; IQR, interquartile range

Table B8. Crude hours of post-procedure home care services by survival time

Died within	IPC		Pleurodesis	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Nursing services				
30 days	12.8 (26)	4 (0-13)	9.3 (25.8)	0 (0-7)
6 weeks	13 (23.7)	5 (0-15)	8.9 (23.9)	0 (0-8)
90 days	17.1 (22.5)	11 (0-25)	10.9 (22.2)	2 (0-13)
Non-nursing services				
30 days	10.3 (30.1)	3 (0-8)	8,5 (28.8)	1 (0-5)
6 weeks	12.1 (30.5)	4 (0-11)	9.3 (27.8)	2 (0-7)
90 days	19.1 (42.1)	6 (1-17)	14.8 (39)	4 (0-12)

Abbreviations: IPC, indwelling pleural catheter; SD, standard deviation; IQR, interquartile range

Figure B1. Data linkage of ICES datasets by unique encrypted identifiers



OHIP: Ontario Health Insurance Plan claims database; IPC: indwelling pleural catheter; CIHI-DAD: Canadian Institute for Health Information-Discharge Abstract Database; SDS: Same Day Surgery database; CCI: Canadian Classification of Health Interventions; RPDB: Registered Persons Database; HCD: Home Care Database; OCR: Ontario Cancer Registry; INST: Institution database; IPDB: ICES Physician Database; NACRS: National Ambulatory Care Reporting System; COPD: Chronic Obstructive Pulmonary Disease database; CHF: Congestive Heart Failure database

Figure B2. Box plots of continuous variables before and after propensity score weighting by inverse probability of treatment weighting (IPTW)

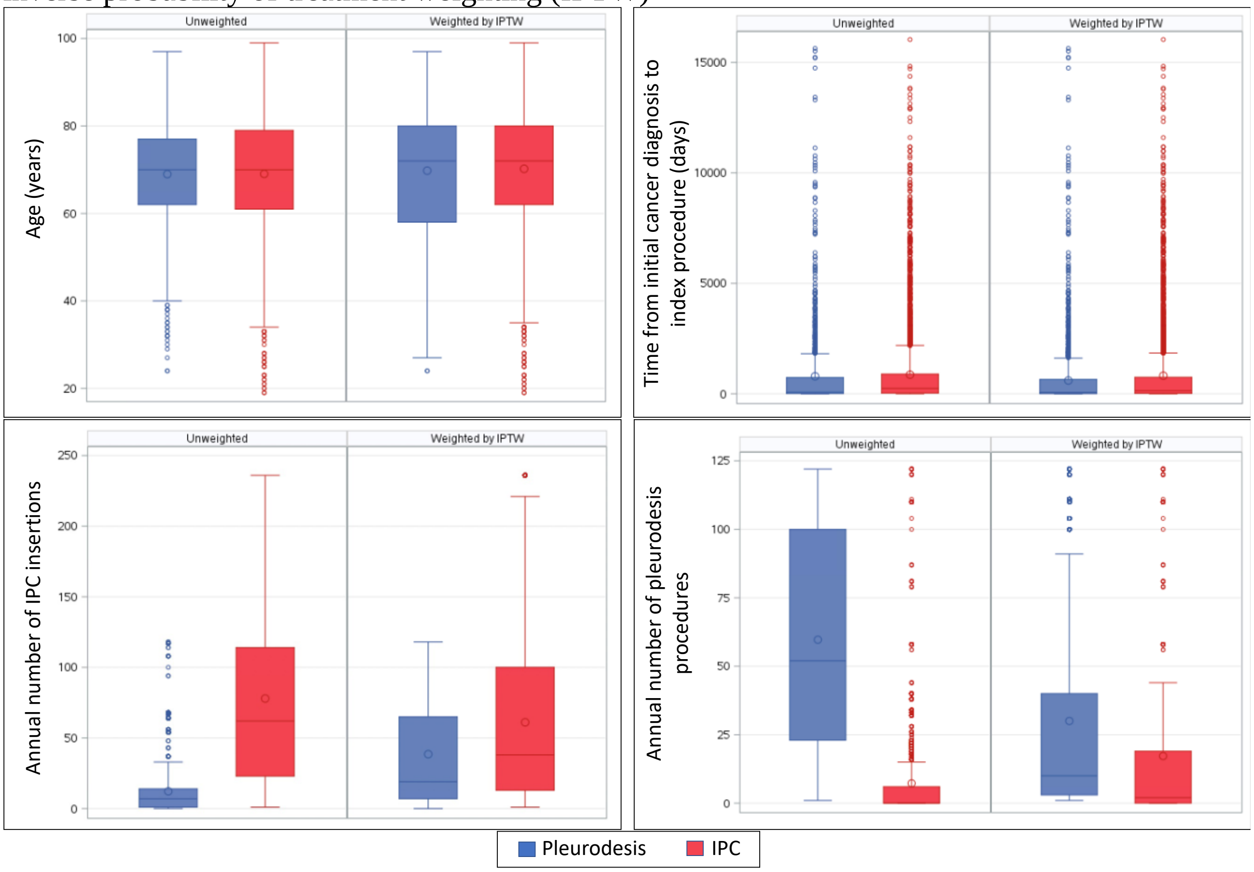
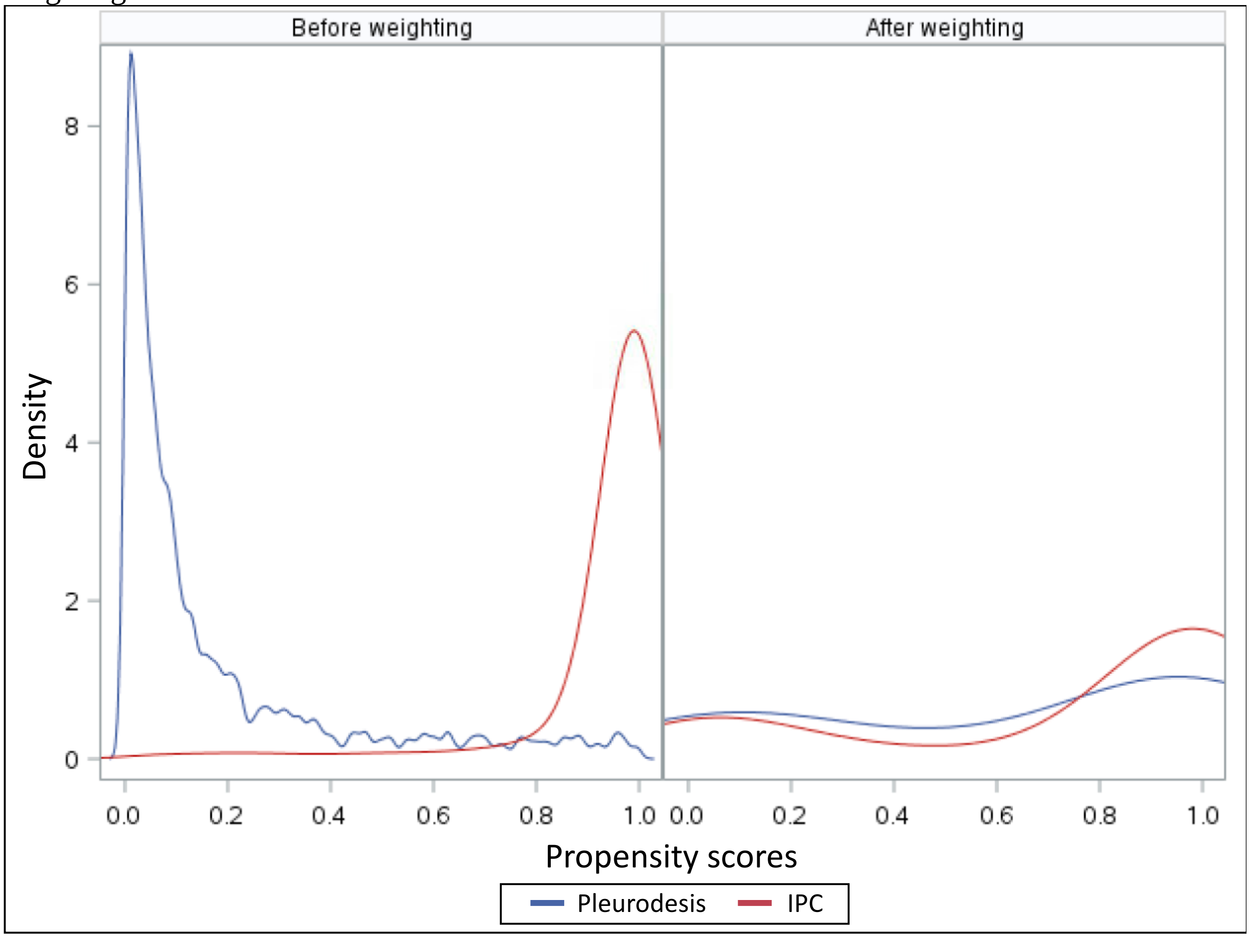


Figure B3. Density Plots of propensity scores before and after inverse probability of treatment weighting



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