CHEST

The Clinical and Economic Implications of Different Treatment Pathways for Patients With Rapidly Recurrent Malignant Pleural Effusion

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BACKGROUND: Malignant pleural effusion (MPE) is a common cancer complication. Clinical and economic implications of different recurrent MPE treatment pathways have not been evaluated fully.

RESEARCH QUESTION: What clinical outcomes, complications, health care resource use, and costs are associated with various rapidly recurrent MPE treatment pathways?

STUDY DESIGN AND METHODS: This retrospective cohort study using Surveillance, Epidemiology and End Results Medicare data (2011-2015) included patients 66 to 90 years of age with rapidly recurrent MPE. Rapid recurrence was defined as receipt of a second pleural procedure within 14 days of the first thoracentesis, including nondefinitive repeated thoracentesis or a definitive treatment option including chest tube, indwelling pleural catheter (IPC), or thoracoscopy.

RESULTS: Among 8,378 patients with MPE, 3,090 patients (36.9%) had rapidly recurrent MPE (mean $\pm$ SD age, 75.9 $\pm$ 6.6 years; 45.6% male; primary cancer, 62.9% lung and 37.1% other). Second pleural procedures were nondefinitive thoracentesis (62.3%), chest tube (17.1%), IPC (13.2%), or thoracoscopy (7.4%). A third pleural procedure was required more frequently if the second pleural procedure was nondefinitive thoracentesis vs chest tube placement, IPC placement, or thoracoscopy (70.3% vs 44.1% vs 17.9% vs 14.4%, respectively). The mean number of subsequent pleural procedures over the patient's lifetime varied significantly among the procedures (1.74, 0.82, 0.31, and 0.22 procedures for patients receiving thoracentesis, chest tube, IPC, and thoracoscopy, respectively; $P < .05$). Average total costs after the second pleural procedure to death adjusted for age at primary cancer diagnosis, race, year of second pleural procedure, Charlson comorbidity index, cancer stage at primary diagnosis, and time from primary cancer diagnosis to diagnostic thoracentesis were lower with IPC ($37,443; $P < .0001$) or chest tube placement ($40,627; $P = .004$) vs thoracentesis ($47,711). Patients receiving thoracoscopy ($45,386; $P = .5$) incurred similar costs as patients receiving thoracentesis.

INTERPRETATION: Early definitive treatment was associated with fewer subsequent procedures and lower costs in patients with rapidly recurrent MPE.

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KEY WORDS: cancer; cost; health care burden; indwelling pleural catheter; malignant pleural effusion; pleural procedure; pleurodesis; rapid recurrence; thoracentesis; thoracoscopy

Take-home Points

Study Question: What clinical outcomes, complications, health care resource use, and costs are associated with various rapidly recurrent malignant pleural effusion (MPE) treatment pathways?

Results: Among 3,090 patients (36.9%) with rapidly recurrent MPE from the Surveillance, Epidemiology, and End Results Medicare database, only 37.7% received definitive pleural procedures (chest tube placement, 45.3%; indwelling pleural catheter [IPC] placement, 35.0%; and thoracoscopy, 19.7%), yet definitive treatment was shown to result in fewer mean subsequent pleural procedures (thoracoscopy, 0.22; IPC placement, 0.31; chest tube placement, 0.82; and thoracentesis, 1.74) and lower average total costs (IPC placement, $37,443; chest tube placement, $40,627; thoracoscopy, $45,386; and thoracentesis, $47,711).

Interpretation: Guideline-consistent care, defined as definitive treatment for rapidly recurrent MPE, was associated with fewer subsequent procedures and lower costs.

Malignant pleural effusion (MPE) is a complication of cancer most commonly occurring among patients with lung cancer, breast cancer, lymphoma, and primary pleural malignancy (mesothelioma).[1,2] Patients with MPE typically have a poor prognosis (mean survival, 4-7 months[3,4]) and use significant health care resources.[2,5,6] In the United States, MPE results in > 125,000 hospital admissions and $5 billion in inpatient hospital charges annually.[2] Although evidence has shown that annual MPE hospitalization rates per 100,000 population have been decreasing over time (33.4 in 2007 vs 31.9 in 2016),[7] MPE still poses a significant health care burden.[2,5,6]

MPE often recurs after initial thoracentesis, and diagnostic yield for molecular tumor markers is modest.[8,9] Treatment options available for the management of recurrent MPE include repeat thoracentesis, chest tube, indwelling pleural catheter (IPC), and thoracoscopy.[5,6] A prior study published in 2018 showed that guidelines for recurrent MPE, which recommend cost-effective[10] definitive procedures such as IPC placement or pleurodesis over repeat thoracentesis, generally are not followed.[11] However, patients with rapidly recurring MPEs who receive guideline-consistent care using definitive procedures underwent fewer subsequent pleural procedures, experienced fewer complications, and underwent emergency department (ED) procedures compared with patients who undergo repeat thoracentesis.[11]

This study sought to update prior analyses and to evaluate further the outcomes of patients with recurrent MPE beyond the initial therapeutic pleural procedure. The specific objectives of this study were: (1) to evaluate the different longitudinal patient treatment pathways after initial MPE thoracentesis and (2) to illustrate the differences in clinical outcomes, complications, health care resource use, and economic burden across the various treatment pathways.

Study Design and Methods

This retrospective cohort study evaluated patients with cancer who had rapidly recurrent MPE, defined as requiring a second pleural procedure within 14 days of diagnostic thoracentesis, in the Surveillance, Epidemiology, and End Results (SEER) Medicare-linked database.

Study Population

Patients aged 66 to 90 years at cancer diagnosis were included if they had the first malignant primary cancer diagnosed from 2011 through 2015; histologic confirmation of cancer (e-Appendix 1), ≥ 1 MPE diagnosis after the primary cancer diagnosis (e-Appendix 2), thoracentesis as the first pleural procedure (e-Appendix 3),

ABBREVIATIONS: aOR = adjusted OR; IPC = indwelling pleural catheter; IQR = interquartile range; MPE = malignant pleural effusion; SEER = Surveillance, Epidemiology, and End Results

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continuous enrollment 6 months before the index (first thoracentesis; baseline period) to the earliest of patient death or 12 months after the index (follow-up period), and second pleural procedure within 14 days of diagnostic thoracentesis (rapid recurrence).[12] Additionally, patients were excluded if a cancer diagnosis was made at autopsy or on the death certificate.

Definitions

Four possible pleural procedures were identified using Current Procedural Terminology codes (e-Appendix 3): thoracentesis, chest tube placement, IPC placement, or thoracoscopy with pleurodesis (ie, thoracoscopy). Thoracentesis was considered a nondefinitive procedure, whereas chest tube placement, IPC placement, and thoracoscopy were considered definitive procedures. If multiple pleural procedures were performed on the same day, treatments were grouped as follows: thoracoscopy plus any other pleural procedure equated to thoracoscopy, chest tube placement plus thoracentesis equated to chest tube placement, IPC placement plus thoracentesis equated to IPC placement, chest tube placement plus IPC equated to IPC, and IPC placement plus chemical pleurodesis equated to IPC. Chemical pleurodesis procedure codes without a chest tube or IPC placement procedure code on the same day were excluded.

Outcomes

Baseline characteristics evaluated included age, sex, race and ethnicity, marital status, reason for Medicare entitlement, SEER registry geographic location, primary health care payer, Charlson comorbidity index score,[8] year of cancer diagnosis, primary cancer site, and primary cancer stage. The outcomes that were evaluated were selected because the study sought to evaluate the clinical implications, health care resource use, and costs associated with the various procedural pathways. Primary outcomes were proportions of patients requiring subsequent pleural procedures after the second pleural procedure and numbers of subsequent pleural procedures after the second pleural procedure (per patient and per patient day of life, overall and by site of service). Subsequent pleural procedures were defined as procedures administered after the second pleural procedure (third treatment and beyond). Survival time was calculated as the time between the second pleural procedures and end of follow-up (ie, 12 months from first thoracentesis or from the first thoracentesis to death).

Secondary outcomes were the proportions of patients requiring hospitalization, the proportions of hospitalizations associated with early procedures (MPE-related procedures), the numbers of inpatient days associated with pleural procedures, the numbers of survival days after the second pleural procedure, the rate of pneumothoraces per patient day of life (diagnosis codes in e-Appendix 4), and the total costs of care after the second pleural procedure (overall and per patient day of life). Because patients with MPE may be hospitalized for other comorbid conditions, early pleural procedure during an inpatient stay (ie, days 0-2 of hospitalization according to Ost et al[11]) was used as a measure of whether the MPE was the initial reason for hospitalization. Inpatient hospitalizations with missing discharge dates were excluded. Treatment-related pneumothoraces were defined as pneumothoraces diagnosed 0 to 2 days after subsequent thoracenteses or IPC placement. Rate of pneumothorax per subsequent pleural procedure (third treatment and beyond) was calculated as the number of treatment-related pneumothoraces diagnosed within 2 days of thoracentesis or IPC placement divided by the number of subsequent thoracentesis procedures, the number of IPCs placed, or both (third treatment and beyond). The average number of pneumothoraces per patient (third treatment) was the number of treatment-related pneumothoraces divided by type of second pleural procedure.

Total costs were calculated using the Medicare payment amount for any inpatient, outpatient, carrier, hospice, home health administration, and durable medical equipment care claim between the second pleural procedure date and the end of patient follow-up, regardless of whether a pleural procedure was performed. When analyzing total costs and total costs per day of life, only patients who died during follow-up were included, given that cost per day of life follows a U-shaped pattern, with the most expensive days being at the end of life.[13] Patients who were alive at 1 year were censored from the analyses. Hence, these costs are for the 84% of patients with cancer and MPE who died within 1 year of the second pleural intervention. Specific variables and SEER Medicare data files used for these cost calculations were those evaluated by Bremner et al.[14] Patients with total costs of $0 were excluded from the analysis.

Statistical Analyses

Descriptive statistics were reported for all baseline characteristics. Means, SDs, medians, and interquartile ranges (IQRs) summarized continuous variables, and frequencies and percentages summarized categorical variables. A Sankey diagram illustrated patient treatment pathways, with block sizes at each node reflecting the proportions of patients receiving each procedure.

Kruskal-Wallis tests assessed differences between medians, and the analysis of variance tested differences in means. Means were compared with IPC placement as a reference (because it is considered definitive treatment and the only outpatient definitive treatment) and Student t tests with Bonferroni correction. We used χ^2 tests to evaluate differences in proportions.

Survival analysis compared survival among treatments. The cumulative incidence of MPE recurrence requiring a third pleural procedure while accounting for competing risk of death was assessed using Gray's test.

Logistic regression models were fit to assess factors associated with the choice of definitive or nondefinitive treatment for the second pleural procedure. γ Regression models were fit to quantify the average total costs after the second pleural procedure and were restricted to patients who died during follow-up. Variables with $P \leq .2$ in the univariable analyses were considered candidate variables a priori for multivariable models. The final multivariable models were built using backward selection, and variables with $P < .05$ were retained.

Statistical analyses were conducted using SAS version 9.4 software (SAS Institute), and the Sankey diagram was created in R version 4.2.1 software (R Foundation for Statistical Computing). Per SEER Medicare requirements, results with fewer than 11 outcomes were suppressed to ensure confidentiality.

Ethics Review

Use of this database was determined to be exempt from institutional review board approval by the Western Institutional Review Board (Identifier: 2594930-44438733).

Results

Among 8,378 patients with MPE, 3,090 patients (36.9%) had rapidly recurrent MPE (Fig 1). Table 1 presents patient baseline demographic and clinical characteristics.

Patient Treatment Pathways

Variations in treatment pathways were observed for patients with rapidly recurrent MPE (Fig 2). Only 37.7% of patients received a definitive procedure as their second pleural procedure (chest tube placement, 17.1%; IPC placement, 13.2%; and thoracoscopy, 7.4%). After this initial treatment, patients with thoracentesis were more likely to require subsequent MPE treatment (70.3% vs 44.1% for chest tube placement, 17.9% for IPC placement, and 14.4% for thoracoscopy) (Fig 3A) and underwent significantly more subsequent pleural procedures (1.74 vs 0.31 for IPC placement and 0.22 for thoracoscopy; $P < .0001$) (Table 2). Among patients requiring a third pleural procedure, patients with thoracentesis for both the second and third procedures showed the greatest burden (average additional procedures, 2.13) (Fig 3B). The findings of greater numbers of subsequent pleural procedures with thoracentesis also were confirmed and illustrated in a competing risk model (e-Fig 1) and were consistent by type of cancer and site of service (e-Tables 1).

The median length of survival in days from the second pleural procedure to the end of follow-up or death was statistically significantly higher among patients who received a thoracoscopy (64 days) or thoracentesis (63 days) vs in those who underwent chest tube placement (43 days) or IPC placement (45 days; $P < .0001$) (Table 3). Survival probability was higher among patients who received a nondefinitive thoracentesis to treat the first recurrence relative to those who received a definitive pleural procedure (e-Fig 2A, 2B). Median survival among patients who died during follow-up (n = 2,589) was highest among patients who underwent a thoracoscopy as the second pleural procedure (49.5 days; IQR, 20.5-100.5 days), followed by thoracentesis (41.0 days; IQR, 17.0-109.5 days), IPC placement (40.0 days; IQR, 13.0-91.0 days), and chest tube placement (35.5 days; IQR, 20.5-100.5 days; $P = .0072$). Despite differences in survival, the previously shown pattern of subsequent pleural procedures was consistent in that patients who received a thoracentesis as the second pleural procedure underwent the highest overall number of subsequent pleural procedures per patient day of life, with chest tube placement, IPC, and thoracoscopy having lower rates (0.0133 vs 0.0078 vs 0.0035 vs 0.0018 procedures per patient day of life, respectively [$P < .0001$]) (Table 4).

Inpatient Hospitalization and Inpatient Days

Patients who received a thoracentesis as the second pleural procedure were most likely to be hospitalized during the follow-up period after the second pleural procedure (64.5%), followed by thoracoscopy (60.4%),

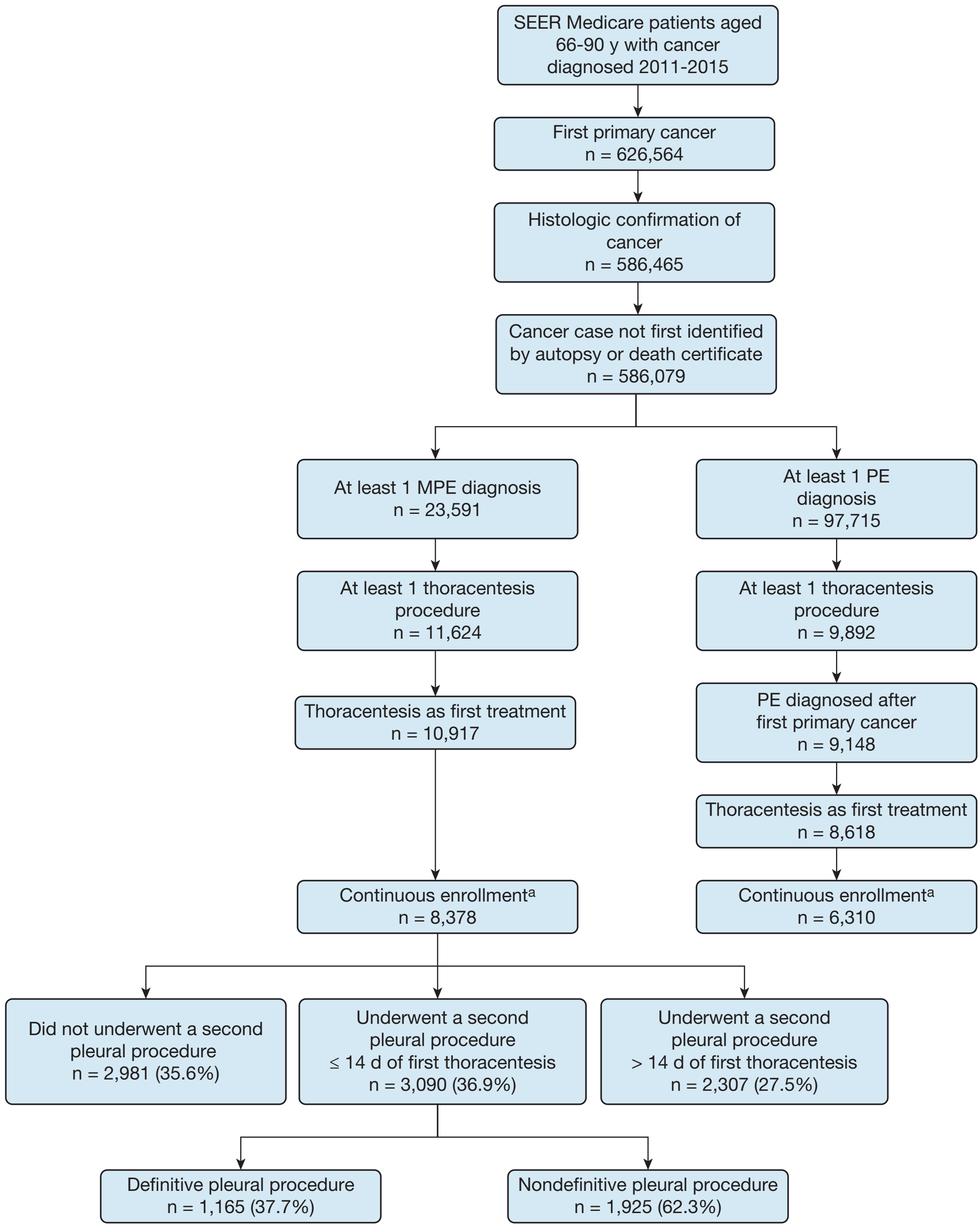

Figure 1 – *Flow diagram showing patient selection and attrition.* [a]*Patients with continuous enrollment were enrolled in Medicare Parts A and B, with no health maintenance organization enrollment, for at least 6 months before the first thoracentesis and for the earliest of 12 months after the first thoracentesis or date of death. MPE = malignant pleural effusion; PE=pleural effusion; SEER = Surveillance, Epidemiology, and End Results.*

chest tube placement (53.2%), and IPC placement (51.4%; $P < .0001$). Additionally, a greater proportion of patients who received thoracentesis as the second pleural procedure underwent hospitalizations with early pleural procedures (43.4%) vs patients who underwent chest tube placement (26.7%), thoracoscopy (12.2%), or IPC placement (12%; $P < .0001$). The median total inpatient days did not differ among treatment groups (Table 3) or by lung cancer vs other cancer types (e-Table 2).

TABLE 1] Patient Demographic and Clinical Characteristics by MPE Diagnosis Type

Variable	Patients With ≥ 1 MPE Diagnosis (n = 8,378)	Patients With Rapidly Recurrent MPE (n = 3,090)
Age at cancer diagnosis, y	76.2 ± 6.6	75.9 ± 6.6
Male sex	3,760 (44.9)	1,410 (45.6)
Race		
White	6,996 (83.5)	2,559 (82.8)
Black	724 (8.6)	262 (8.5)
Other[a]	658 (7.9)	269 (8.7)
Ethnicity		
Hispanic	502 (6.0)	177 (5.7)
Non-Hispanic	7,876 (94.0)	2,913 (94.3)
Marital status at primary cancer diagnosis		
Married	4,098 (48.9)	1,585 (51.3)
Unmarried	3,861 (46.1)	1,356 (43.9)
Unknown	419 (5.0)	149 (4.8)
Charlson Comorbidity Index score[b]		
0	2,285 (27.3)	885 (28.6)
1	2,104 (25.1)	785 (25.4)
2	1,409 (16.8)	491 (15.9)
3	904 (10.8)	327 (10.6)
4	609 (7.3)	221 (7.2)
≥ 5	789 (9.4)	281 (9.1)
Missing[b]	278 (3.3)	100 (3.2)
Primary cancer site		
Lung	5,362 (64.0)	1,943 (62.9)
Breast	497 (5.9)	198 (6.4)
Lymphoma	464 (5.5)	200 (6.5)
Colorectal	217 (2.6)	69 (2.2)
Prostate	142 (1.7)	55 (1.8)
Other[c]	1,696 (20.2)	625 (20.2)
Primary cancer stage at cancer diagnosis		
0	65 (0.8)	22 (0.7)
I	467 (5.6)	176 (5.7)
II	509 (6.1)	173 (5.6)
III	1,099 (13.1)	370 (12.0)
IV	5,884 (70.2)	2,217 (71.8)
Occult	33 (0.4)	14 (0.5)

(Continued)

TABLE 1] *(Continued)*

Variable	Patients With ≥ 1 MPE Diagnosis (n = 8,378)	Patients With Rapidly Recurrent MPE (n = 3,090)
Unknown	249 (3.0)	90 (2.9)
Not available	72 (0.9)	28 (0.9)

Data are presented as No. (%) or mean ± SD. MPE = malignant pleural effusion.
[a]Includes Native American or Alaskan Native, Asian or Pacific Islander, and unknown.
[b]The Charlson comorbidity index was calculated using the 2014 version of the Comorbidity SAS Macro developed by the National Cancer Institute, Information Management Services (IMS). Currently, the macro only incorporates International Classification of Diseases, Ninth Revision, diagnosis and procedure codes into its algorithm. To ensure proper calculation of the Charlson comorbidity index, all patients with at least one International Classification of Diseases, Tenth Revision, diagnosis or procedure code were excluded from this analysis (n = 511).
[c]Includes ovarian, pancreatic, kidney, endometrial, stomach, esophageal, melanoma, head and neck, bladder, cervical, uterine, vulvar, anal, liver, penile, vaginal, endocrine, small intestine, leukemia, etc.

Complications

Overall, 62 pneumothoraces occurred among the 1,925 patients who underwent a nondefinitive thoracentesis as a second pleural procedure and fewer than 11 pneumothoraces occurred among the 1,165 patients who underwent a definitive procedure. Among patients with nondefinitive thoracentesis and definitive procedures, the rate of pneumothorax per subsequent pleural procedure (third treatment and beyond) was 0.022 and < 0.027, respectively. The average number of pneumothoraces per patient (third treatment and beyond) was 0.032 for patients who received a nondefinitive procedure and < 0.009 for patients who received definitive procedures (Table 5).

Factors Associated With Use of Definitive Treatment as Second Pleural Procedure

In the multivariable adjusted model, type of cancer, location of first thoracentesis, and time from first thoracentesis to second pleural procedure were associated with second pleural procedure type (Table 6). Patients with lung cancer were more likely than those with other types of cancer to have a definitive treatment as the second pleural procedure (adjusted OR [aOR], 1.60; 95% CI, 1.37-1.86; $P < .0001$). Patients who underwent an initial thoracentesis in the outpatient setting were less likely than those in the ED to undergo a definitive treatment as the second pleural procedure (aOR, 0.59; 95% CI, 0.42-0.82; $P = .002$). Patients with a second pleural procedure within 3 to 5 days or 6 to

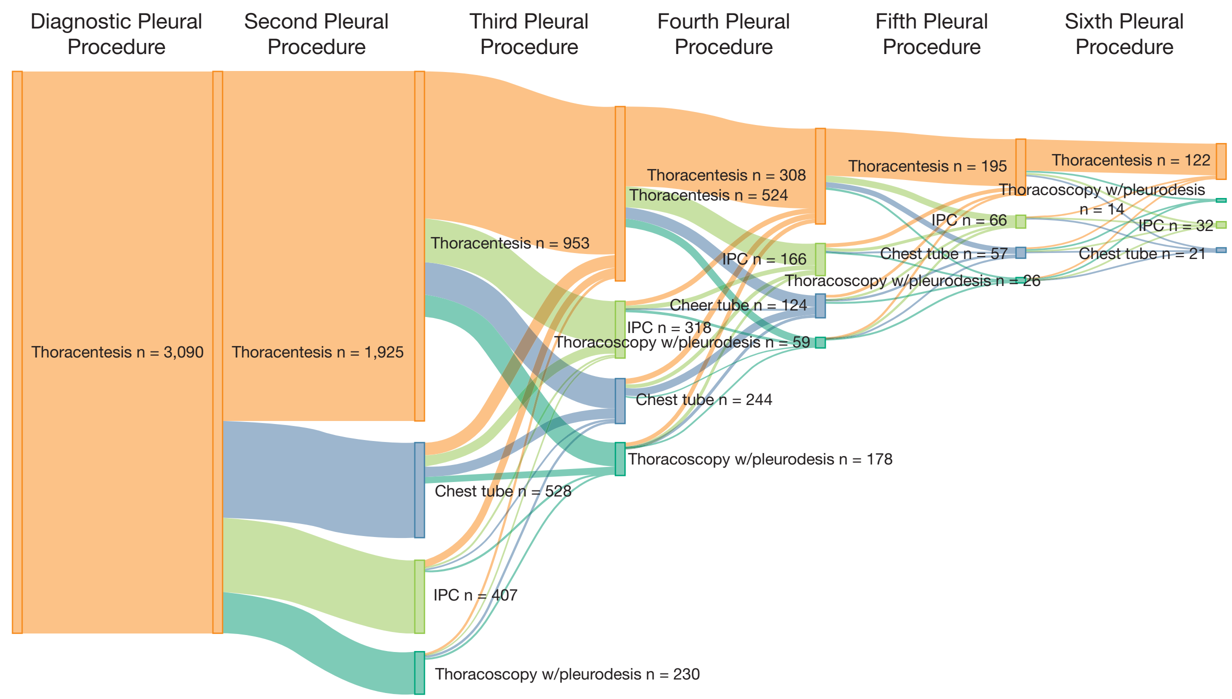

Figure 2 – *Sankey diagram showing treatment patterns among patients with rapidly recurrent malignant pleural effusion (MPE) created for those with MPE who underwent ≤ 6 pleural procedures during the follow-up period, accounting for 96.4% of the patients in the sample.*

9 days after the first thoracentesis were more likely than those with a second pleural procedure within 1 to 2 days afterward to undergo a definitive treatment as the second pleural procedure (aOR, 1.78 [95% CI, 1.44-2.19; $P < .0001$] and aOR, 1.34 [95% CI, 1.08-1.65; $P = .007$], respectively) (Table 6).

Costs After Second Pleural Procedure

Among patients who died during follow-up (n = 2,589), the median total costs from the second pleural procedure to the end of patient follow-up were higher with thoracentesis ($23,889; IQR, $8,476-$49,673) and thoracoscopy ($24,343; IQR, $8,491-$46,765) compared with chest tube placement ($16,982; IQR, $4,833-$41,169) and IPC placement ($17,410; IQR, $4,888-$39,032; $P < .0001$) (Table 7). As would be expected, median total costs per patient day of life for these patients were consistent with the total cost findings (thoracentesis, $416; chest tube placement, $372; IPC placement, $338; and thoracoscopy, $419; $P = .0008$). Among patients who underwent a second procedure (n = 3,090), patients who moved to IPC placement for the third treatment incurred the lowest average costs and those who moved to thoracentesis incurred the highest average costs (all patients, n = 3,090) (Fig 3C).

Factors Associated With Costs After the Second Pleural Procedure

Among 3,090 patients with rapid recurrence of MPE, 83.8% of patients (n = 2,589) died during follow-up. In the final multivariable model, second pleural procedure type, age at primary cancer diagnosis, race, year of second pleural procedure, Charlson comorbidity index score, cancer stage at primary cancer diagnosis, and time from cancer diagnosis to first thoracentesis were associated with average total costs after the second pleural procedure. Adjusted average total costs were higher for patients treated for the first recurrence of MPE with nondefinitive thoracentesis ($47,711) compared with patients treated with definitive IPC placement ($37,443) or chest tube placement ($40,627). Patients 66 to 70 years of age incurred higher adjusted average total costs ($48,024) compared with patients 76 to 80 years of age ($41,267) and patients 80 to 90 years of age ($35,705). Adjusted average total cost was lower with Charlson comorbidity index score of 3 vs 0 ($38,863 vs $51,201) and > 6 months vs ≤ 6 months from cancer diagnosis to first thoracentesis ($38,914 vs $46,640) (Table 8).

Discussion

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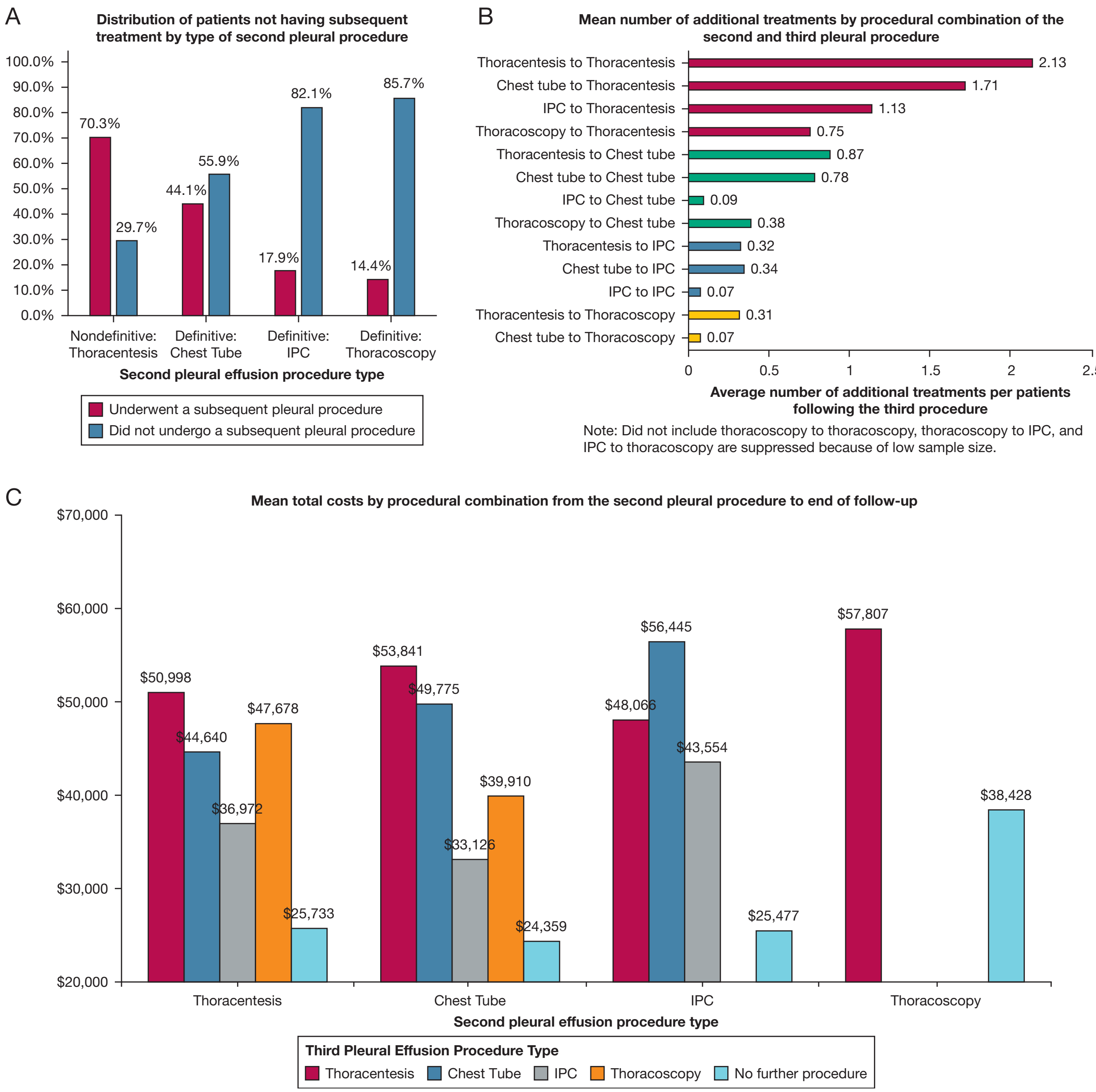

Figure 3 – *Bar graphs showing treatment characteristics and average costs for each pleural procedure combination. A, Distribution of patients not having subsequent treatment by type of second pleural procedure. B, Mean number of additional treatments by procedural combination of the second and third pleural procedure. C, Mean total costs by procedural combination from the second pleural procedure to end of follow-up. IPC = indwelling pleural catheter.*

guidelines recommend the use of definitive treatment as the first-line intervention for symptomatic recurrent MPE.[4] The current analysis of 3,090 patients with rapidly recurrent MPE from 2011 through 2015 SEER Medicare data found that a minority of patients (37.7%) received definitive pleural procedures (chest tube placement, 45.3%; IPC placement, 35.0%; and thoracoscopy, 19.7%) and 62.3% of patients underwent repeat nondefinitive thoracentesis procedures as the second pleural procedure. The previously published evaluation[11] using 2007 through 2011 SEER Medicare data found that only 23.9% of patients received guideline-consistent definitive care (IPC placement, 17%; thoracoscopy, 23%; and chest tube placement, 60%). Hence, the proportion of patients with recurrent MPE receiving definitive care has increased since the prior study, primarily because of an increase in the use of IPC placement, which more than doubled (from 7.4% to 16.5%), whereas the proportions of patients

TABLE 2] Subsequent Pleural Procedures (Third Treatment and Beyond) by Procedure Used to Treat First Recurrence and Site of Service

Pleural Procedure Chosen to Treat First Recurrence of MPE	All Patients With Rapid Recurrence (n = 3,090)				
	No.	Overall Subsequent Pleural Procedures per Patient[a,b]	Subsequent Pleural Procedures per Patient Performed in the ED[a,c]	Subsequent Pleural Procedures per Patient Performed in an Inpatient Setting[a,d]	Subsequent Pleural Procedures per Patient Performed in an Outpatient Setting[a,e]
Thoracentesis	1,925	1.74	0.05	0.86	0.82
Chest tube placement	528	0.82	0.04	0.55	0.23
IPC placement	407	0.31	0.01	0.19	0.11
Thoracoscopy	230	0.22	0.02	0.18	0.02

ED = emergency department; IPC = indwelling pleural catheter; MPE = malignant pleural effusion.
[a]$P < .0001$ by analysis of variance.
[b]Overall number of subsequent pleural procedures administered as third treatment and beyond comprises those treatments that were administered in the ED, inpatient setting, and outpatient settings.
[c]$P = .0006$ by analysis of variance.
[d]Inpatient setting is an inpatient hospital of a skilled nursing facility.
[e]Outpatient setting is an outpatient hospital, ambulatory surgical center, or doctor's office.

receiving the other definitive procedures decreased (chest tube placement, from 22.1% to 14.9%; thoracoscopy, from 11.2% to 5.6%). The proportion of patients receiving thoracentesis remained relatively stable during the years of our study (from 59.3% in 2011 to 63.0% in 2015) (e-Fig 3).

Compared with patients who received a nondefinitive second pleural procedure, patients who underwent definitive pleural procedures underwent fewer overall subsequent pleural procedures per patient day of life; fewer subsequent pleural procedures in the ED, inpatient, and outpatient settings per patient day of life; and fewer hospitalizations with early pleural procedures. The findings regarding the number of subsequent pleural procedures are similar to those observed by Ost et al.[11]

Additionally, this study evaluated the economic implications of the various treatment pathways, which

TABLE 3] Inpatient Days by Procedure Used to Treat First Recurrence

Second Pleural Procedure Type	No. of Unique Patients	Survival Days From Second Pleural Procedure to End of Follow-up[a]	Summary of Patients With Any Inpatient Hospitalization From Second Pleural Procedure (n = 1,871)		
			Ever Inpatient Hospitalization From Second Pleural Procedure[b,c,d]	Per Patient Total Inpatient Days[e] From Second Pleural Procedure to End of Follow-up[f]	Patients With Early Pleural Procedures[c,g,h]
Thoracentesis	1,925	63.0 (22.0-240.0)	1,242 (64.5)	11.0 (5.0-23.0)	539 (43.4)
Chest tube placement	528	43.0 (16.0-148.0)	281 (53.2)	13.0 (5.0-28.0)	75 (26.7)
IPC placement	407	45.0 (15.0-121.0)	209 (51.4)	10.0 (4.0-27.0)	25 (12.0)
Thoracoscopy	230	64.0 (24.0-219.0)	139 (60.4)	10.0 (5.0-22.0)	17 (12.2)

Data are presented as No. (%) or median (interquartile range) unless otherwise indicated. IPC = indwelling pleural catheter.
[a]$P < .0001$ by Kruskal-Wallis test.
[b]Twenty-five patients with missing total inpatient days (because of missing discharge date) were excluded from this analysis.
[c]$P < .0001$ by χ^2 test.
[d]The percentage is of the of subgroup.
[e]Total inpatient days was defined as the sum of all days spent in the hospital from the time of first recurrence of malignant plural effusion (second pleural procedure date, not inclusive) to the end of patient follow-up (inclusive), regardless of whether a pleural procedure was performed.
[f]$P = .07$ by Kruskal-Wallis test.
[g]Early pleural procedures were defined as pleural procedures performed within the first 2 days of an inpatient hospitalization (days 0-2 of the hospital encounter).
[h]The percentage is of any inpatient hospitalization.

TABLE 4] Rate of Subsequent Pleural Procedures per Patient Day of Life Administered as Third Treatment and Beyond by Procedure Used to Treat First Recurrence and by Site of Service

	All Patients With Rapid Recurrence (n = 3,090)				
Pleural Procedure Chosen to Treat First Recurrence of MPE	No.	Overall Subsequent Pleural Procedures per Patient Day of Life[a,b]	Subsequent Pleural Procedures per Patient Day of Life Performed in the ED[a,c]	Subsequent Pleural Procedures per Patient Day of Life Performed in an Inpatient Setting[a,d]	Subsequent Pleural Procedures per Patient Day of Life Performed in an Outpatient Setting[a,e]
Thoracentesis	1,925	0.0133	0.0004	0.0066	0.0062
Chest tube placement	528	0.0078	0.0004	0.0053	0.0022
IPC placement	407	0.0035	0.0001	0.0022	0.0012
Thoracoscopy	230	0.0018	0.0002	0.0015	0.0001

ED = emergency department; IPC = indwelling pleural catheter; MPE = malignant pleural effusion.
[a]$P < .0001$ by analysis of variance.
[b]Overall number of subsequent pleural procedures administered as third treatment and beyond comprises those treatments that were administered in the ED, inpatient setting, and outpatient settings.
[c]$P = .05$ by analysis of variance.
[d]Inpatient setting is an inpatient hospital of a skilled nursing facility.
[e]Outpatient setting is an outpatient hospital, ambulatory surgical center, or doctor's office.

has not been evaluated previously using SEER Medicare data. Overall, total median costs from a second nondefinitive pleural procedure to the end of follow-up were significantly higher than the total median costs for definitive pleural procedures. These findings were consistent when evaluated for lung vs other cancers and across sites of care. Among patients who underwent thoracentesis for the second pleural procedure, costs for a definitive third procedure were lower compared with those of patients who underwent a nondefinitive third procedure.

The reasons patients are not receiving guideline-based care likely are multifactorial. Access to care may be a barrier given that procedural expertise, anesthesia support, and special monitoring are needed for some definitive MPE treatments.[6] Patients seeking treatment at the ED or physicians' offices may receive thoracentesis because it can be performed easily in an outpatient setting without extensive resources or training, dyspnea and pain are reduced almost immediately, and the patient can return home shortly thereafter.[6] Patient and doctor preference and disease progression also may dictate the treatment for rapidly recurrent MPE. Patients with poor performance status will not be eligible for thoracoscopy, and some patients may not agree to definitive treatment based on their perceptions regarding quality of life associated with the treatments. These aspects are not captured in the dataset and are beyond the scope of this study[15,16]; however, future research evaluating the reasons for recurrent MPE treatment selection are warranted.

A strength of this study is the use of SEER Medicare data (2011-2015), which enabled efficient longitudinal analysis of large numbers of diverse patients cared for in the real world.[17] The burden of MPE is rising, given the increasing global prevalence of cancer and the availability of improved systemic therapies that prolong patients' lives and potentially increase the numbers of patients experiencing MPE.[5,18] Clinical

TABLE 5] Pneumothoraces by Procedure Used to Treat First Recurrence

Pleural Procedure Chosen to Treat First Recurrence of MPE	No.	Subsequent Thoracentesis, IPC, or Both Administered as Third Treatment and Beyond	Pneumothoraces Diagnosed 0-2 d After Subsequent Thoracenteses or IPC	Rate of Pneumothoraces per Subsequent Pleural Procedure (Third Treatment and Beyond)	Average No. of Pneumothoraces per Patient (Third Treatment and Beyond)
Nondefinitive: thoracentesis	1,925	2,784	62	0.022	0.032
Definitive	1,165	407	< 11	< 0.027	< 0.009

According to Centers for Medicare and Medicaid Services cell size suppression policy, strata with n = 10 are reported as < 11 and were suppressed to ensure confidentiality of Medicare and Medicaid beneficiaries. IPC = indwelling pleural catheter; MPE = malignant pleural effusion.

TABLE 6] Factors Associated With Selection of Definitive vs Nondefinitive Treatment for Second Pleural Procedure

Variable	Univariable Analysis		Multivariable Analysis	
	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Age at primary cancer diagnosis, y[a]				
66-70	(Reference)	Reference	NA	NA
71-75	1.07 (0.88-1.31)	.5	NA	NA
76-80	1.07 (0.88-1.32)	.5	NA	NA
80-90	1.05 (0.86-1.29)	.6	NA	NA
Race[b]				
White	(Reference)	Reference	NA	NA
Black	1.47 (1.14-1.90)	.003	NA	NA
Other	1.21 (0.93-1.56)	.2	NA	NA
Unknown	3.48 (0.32-38.41)	.3	NA	NA
Sex[a]				
Female	(Reference)	Reference	NA	NA
Male	1.07 (0.93-1.24)	.4	NA	NA
Marital status[a]				
Married	(Reference)	Reference	NA	NA
Unmarried	1.14 (0.98-1.32)	.1	NA	NA
Unknown	1.00 (0.70-1.41)	1	NA	NA
Charlson Comorbidity Index score[b]				
0	(Reference)	Reference	NA	NA
1	1.04 (0.85-1.27)	.7	NA	NA
2	1.27 (1.02-1.60)	.04	NA	NA
3	1.15 (0.89-1.50)	.3	NA	NA
4	1.08 (0.80-1.47)	.6	NA	NA
5+	1.43 (1.09-1.88)	.01	NA	NA
Missing	1.08 (0.70-1.66)	.7	NA	NA
Cancer type				
Others	(Reference)	Reference	(Reference)	Reference
Lung	1.60 (1.37-1.86)	< .0001	1.60 (1.37-1.87)	< .0001
Location of first thoracentesis				
ED	(Reference)	Reference	(Reference)	Reference
Inpatient	1.18 (0.86-1.61)	.3	1.13 (0.82-1.55)	.4
Outpatient	0.59 (0.42-0.82)	.002	0.59 (0.42-0.83)	.003
Cancer stage at primary cancer diagnosis[a]				
0	(Reference)	Reference	NA	NA
I	1.94 (0.68-5.50)	.2	NA	NA
II	1.62 (0.57-4.63)	.4	NA	NA
III	2.09 (0.76-5.79)	.2	NA	NA
IV	2.08 (0.77-5.66)	.2	NA	NA
Occult	3.39 (0.80-14.41)	.1	NA	NA
Unknown	2.48 (0.84-7.31)	.1	NA	NA
Not available	2.20 (0.63-7.68)	.2	NA	NA

(Continued)

TABLE 6] (Continued)

Variable	Univariable Analysis		Multivariable Analysis	
	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Time from diagnostic thoracentesis to second pleural procedure, d				
1-2	(Reference)	Reference	(Reference)	Reference
3-5	1.98 (1.61-2.43)	< .0001	1.78 (1.44-2.19)	< .0001
6-9	1.31 (1.07-1.62)	.01	1.34 (1.08-1.65)	.007
10-14	1.09 (0.88-1.36)	.4	1.11 (0.89-1.39)	.4

We decided a priori to include variables that were associated at the 0.2 level in univariable analysis in the multivariable analysis. For the multivariable model, we used backward selection only to retain variables with a level of significance of $P < .05$. CCI = Charlson Comorbidity Index; ED = emergency department; NA = not applicable.
[a]Variable was excluded after univariable analysis because $P > .2$.
[b]Variable was excluded from multivariable model based on backward selection criteria ($P > .05$).

studies have provided evidence for the management of MPE[19-21]; however, a need still exists for this type of comparative effectiveness research, where patients are not selected carefully and may be sicker and not receiving the same level of follow-up. This study helped to elucidate the real-world clinical and economic implications of different treatment pathways for patients with recurrent MPE.

The use of SEER Medicare data also has limitations because the purpose of the database is for billing and not specifically for research. As described earlier, claims databases lack clinical variables that could be important in accounting for differences among groups. Data for chest tube placement is based purely on Centers for Medicare and Medicaid Services billing data, which do not fully capture patient care. Although we expect, based on clinical experience, that most of the patients with chest tubes had pleurodesis, only 15% had a code for pleurodesis. The true number of patients who had pleurodesis may be underestimated.

Patients who undergo thoracoscopy will have better performance status, thus living longer and accruing more costs. We adjusted by calculating costs per day of life (Table 7); however, costs at the end of life are higher per day.[13] Treatments with shorter survival time will have lower total costs but higher per day costs because patients are closer to the end of life. Hence, unadjusted comparisons of total or per-day-of-life costs should be viewed as preliminary. γ Regression models were fit to evaluate factors associated with costs after the second pleural procedure. Data were adjusted using an array of patient demographics, comorbidities, and disease history characteristics; however, other variables unmeasured may lead to residual confounding even after adjustment. Another limitation is that specific costs of the MPE and its associated management cannot be calculated because

TABLE 7] Total Costs and Total Cost per Patient Day of Life by Procedure Used to Treat First Recurrence Among Patients Who Died During Follow-Up

Pleural Procedure Chosen to Treat First Recurrence of MPE	All Patients With Rapid Recurrence Who Died During Follow-up (n = 2,589)		
	No.	Total Costs From Second Pleural Procedure to End of Patient Follow-up[a,b]	Total Costs per Patient Day of Life[c]
Thoracentesis	1,560	$23,889 ($8,476-$49,673)	$441
Chest tube placement	462	$16,982 ($4,833-$41,169)	$387
IPC placement	375	$17,410 ($4,888-$39,032)	$360
Thoracoscopy	192	$24,343 ($8,491-$46,765)	$447

Data are presented as median (interquartile range) unless otherwise indicated. IPC = indwelling pleural catheter; MPE = malignant pleural effusion.
[a]Total costs (rounded to the nearest dollar) were defined as the sum of all Medicare payment amounts for claims dated between the second pleural procedure and the end of patient follow-up (inclusive of both dates). Claims were pulled from the Medicare Provider Analysis and Review (inpatient), National Claims History (carrier), outpatient, home health agency, hospice, and durable medical equipment files.
[b]$P < .0001$ by Kruskal-Wallis test.
[c]$P = .0007$ by Kruskal-Wallis test.

TABLE 8] Factors Associated With Total Costs After Second Pleural Procedure Among Patients Who Died During Follow-Up

Variables	Univariable		Multivariable	
	Unadjusted Mean (95% CI)	*P* Value	Adjusted Mean (95% CI)	*P* Value
Pleural procedure chosen to treat first recurrence of MPE				
Nondefinitive				
Thoracentesis	$35,773 ($33,927-$37,720)	Reference	$47,711 ($34,446-$66,084)	Reference
Definitive				
Chest tube placement	$29,811 ($27,045-$32,860)	.001	$40,627 ($29,136-$56,650)	.004
IPC placement	$27,393 ($24,586-$30,519)	< .0001	$37,443 ($26,638-$52,630)	< .001
Thoracoscopy with pleurodesis	$34,271 ($29,466-$39,859)	.60	$45,386 ($31,721-$64,938)	.54
Age at primary cancer diagnosis, y				
66-70	$37,664 ($34,730-$40,845)	Reference	$48,024 ($34,398-$67,047)	Reference
71-75	$36,036 ($33,149-$39,175)	.46	$46,552 ($33,368-$64,944)	.60
76-80	$33,098 ($30,327-$36,123)	.03	$41,267 ($29,482-$57,763)	.01
80-90	$27,425 ($25,381-$29,633)	< .0001	$35,705 ($25,570-$49,856)	< .0001
Race				
White	$32,389 ($30,955-$33,889)	Reference	$30,962 ($27,281-$35,140)	Reference
Black	$35,909 ($31,292-$41,207)	.16	$34,762 ($29,019-$41,640)	.11
Other	$39,826 ($34,474-$46,009)	.01	$38,878 ($32,173-$46,979)	.003
Unknown	$95,852 ($28,575-$321,530)	.08	$78,722 ($23,668-$261,838)	.13
Sex[a]				
Female	$32,380 ($30,581-$34,286)	Reference	NA	NA
Male	$34,474 ($32,480-$36,592)	.14	NA	NA
Year of second pleural procedure				
2011	$32,391 ($28,395-$36,949)	Reference	$42,705 ($30,039-$60,711)	Reference
2012	$34,858 ($31,950-$38,031)	.36	$42,957 ($30,835-$59,844)	.94
2013	$34,860 ($31,905-$38,088)	.36	$43,873 ($31,305-$61,487)	.74
2014	$35,998 ($33,119-$39,128)	.18	$46,257 ($33,077-$64,691)	.33
2015	$27,970 ($25,617-$30,539)	.07	$37,694 ($26,985-$52,651)	.13
Marital status[a]				
Married	$34,840 ($32,880-$36,918)	Reference	NA	NA
Not married	$31,682 ($29,782-$33,703)	.03	NA	NA
Unknown	$33,779 ($27,976-$40,785)	.76	NA	NA
Charlson Comorbidity Index score				
0	$37,139 ($34,274-$40,243)	Reference	$51,201 ($36,706-$71,421)	Reference
1	$34,244 ($31,568-$37,146)	.16	$47,091 ($33,697-$65,809)	.15
2	$33,694 ($30,426-$37,313)	.14	$45,648 ($32,528-$64,061)	.08
3	$27,605 ($24,419-$31,207)	< .0001	$38,863 ($27,500-$54,923)	.0002
4	$32,034 ($27,595-$37,188)	.09	$44,731 ($31,315-$63,895)	.12
5+	$33,634 ($29,503-$38,344)	.21	$45,176 ($32,088-$63,602)	.11
Missing	$18,900 ($15,238-$23,444)	< .0001	$29,466 ($19,920-$43,586)	< .0001

(Continued)

TABLE 8] *(Continued)*

Variables	Univariable		Multivariable	
	Unadjusted Mean (95% CI)	*P* Value	Adjusted Mean (95% CI)	*P* Value
Cancer type[a]				
Other	$35,127 ($32,764-$37,760)	Reference	NA	NA
Lung	$32,441 ($30,821-$34,146)	.07	NA	NA
Location of first thoracentesis[a]				
ED	$38,128 ($32,110-$45,273)	Reference	NA	NA
Inpatient	$31,735 ($30,192-$33,357)	.04	NA	NA
Outpatient	$36,686 ($33,831-$39,781)	.69	NA	NA
Cancer stage at primary cancer diagnosis				
0	$38,979 ($24,666-$61,598)	Reference	$48,773 ($28,244-$84,226)	Reference
I	$38,117 ($31,926-$45,509)	.93	$47,128 ($33,108-$67,086)	.89
II	$30,609 ($25,555-$36,664)	.34	$37,496 ($26,291-$53,474)	.29
III	$31,335 ($27,853-$35,251)	.37	$36,705 ($26,601-$50,646)	.23
IV	$33,002 ($31,435-$34,647)	.48	$35,617 ($26,062-$48,674)	.18
Occult	$37,263 ($21,275-$65,265)	.90	$41,345 ($21,952-$77,873)	.65
Unknown	$43,395 ($34,424-$54,703)	.68	$51,839 ($35,384-$75,947)	.81
Not available	$37,152 ($23,510-$58,711)	.88	$44,931 ($26,014-$77,602)	.80
Time from first thoracentesis to second pleural procedure, d[a]				
1-2	$33,468 ($30,746-$36,432)	Reference	NA	NA
3-5	$31,436 ($29,056-$34,011)	.29	NA	NA
6-9	$33,451 ($30,893-$36,221)	.99	NA	NA
10-14	$35,642 ($32,642-$38,917)	.31	NA	NA
Time from cancer diagnosis to first thoracentesis, mo				
≤ 6	$34,129 ($32,525-$35,812)	Reference	$46,640 ($33,539-$64,857)	Reference
6	$31,326 ($28,917-$33,936)	.07	$38,914 ($27,896-$54,284)	.002

We decided a priori to include variables that were associated at the 0.2 level in univariable analysis in the multivariable analysis. For the multivariable model, we used backward selection to retain only variables with a level of significance of $P < .05$. CCI = Charlson comorbidity index; ED = emergency department; IPC = indwelling pleural catheter; MPE = malignant pleural effusion; NA = not applicable.
[a]Variable was excluded from multivariable model based on backward selection criteria ($P > .05$).

this level of cost is not available in the SEER Medicare database. Prospective studies may assess the hypotheses that these analyses generated more accurately. This study is also limited in that the findings may not be generalizable to other countries or to all patients.

Despite these limitations, these study findings may help to identify patients who would most benefit from specific MPE treatments and potentially newer technologies, optimizing MPE outcomes and the associated economic burden of MPE.

Interpretation

Guideline-consistent care, defined as definitive treatment for rapidly recurrent MPE, may result in fewer procedures and complications and in lower costs. Guideline-consistent care improved from 23.9% from 2007 through 2011 to 37.7% from 2011 through 2015, driven by IPC use.

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Additional information: The e-Appendixes, e-Figures, and e-Tables are available online under "Supplementary Data."

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