Original Article

# Management of Malignant Pleural Effusions in U.S. Veterans: A Retrospective Review

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Purpose: To compare malignant pleural effusion (MPE) treatment outcomes and complications among patients receiving indwelling pleural catheter (IPC), talc pleurodesis (TPS), or dual therapy. Outcomes were determined by measuring length of stay (LOS) and post-procedure dyspnea scores. Complications were measured by comparing intervention failures and adverse events.

Methods: The Veterans Affairs' Corporate Data Warehouse was utilized to retrospectively review the charts of 314 MPE subjects. Dyspnea scores were estimated by researchers and LOS was determined by adding the duration of stay for all admissions post procedure. Complications were recorded through chart review.

Results: IPC exhibited higher failure rates than the other approaches 1 year post intervention. Pneumonia/chest infection rate and lung entrapment were also more prevalent. There was no significant difference in dyspnea rates. LOS illustrated a significant difference between groups, with talc patients spending a median of 7 days in the hospital immediately post procedure, while IPC and IPC + TPS patients spent a median of 3 and 2 days, respectively.

Conclusion: Patients receiving IPC or combination treatment spend fewer days in the hospital than TPS patients. However, IPC appears to be associated with more adverse events and higher long-term failure rates than other management strategies.

Keywords: talc pleurodesis, indwelling pleural catheter, malignant pleural effusion

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# Introduction

Malignant pleural effusions (MPEs) affect more than 150,000 patients and account for over 125,000 hospital admissions every year in the United States (US).<sup>1,2)</sup> End-stage metastatic disease, particularly lung carcinoma, typically presents with exudative effusions, which indicate a prognosis of anywhere from 3 to 12 months. Some of these patients remain asymptomatic, while others require intervention to alleviate their dyspnea. Due to the high mortality rate of this diagnosis, management is often palliative and aimed at improving patient quality of life (i.e., reducing dyspnea).

There are several different strategies in managing MPE. The most common include recurrent thoracentesis,

talc pleurodesis (TPS), placement of an indwelling pleural catheter (IPC), or a combination of TPS and IPC.<sup>3)</sup> Thoracentesis remains a viable option for patients and can offer transient relief from dyspnea for those with poor life expectancy.<sup>4)</sup> TPS, IPC, and combination therapy are considered viable long-term management options for MPE and preferred in patients with extended life expectancy.<sup>4)</sup> TPS aims to obliterate the pleural space and prevent the recurrent accumulation of exudate. This can be done surgically via thoracoscopy or through administration via a large bore chest tube. IPC allows for continuous drainage via insertion of a subcutaneously bored catheter into the pleural space.<sup>4)</sup>

Very few studies have compared the efficacy of longterm management strategies for MPE. The Second Therapeutic Intervention in Malignant Effusion (TIME2) and Australasian Malignant Pleural Effusion (AMPLE) trials compared outcomes and adverse events associated with IPC or TPS. Both concluded that IPC and TPS are equally effective at reducing patient dyspnea and that TPS was associated with longer length of stay (LOS) in the hospital.<sup>5,6)</sup> However, the TIME2 trial contradicts the AMPLE trial in concluding that IPC was associated with more adverse events.<sup>5)</sup> Demmy et al. compared the pleurodesis rates of IPC vs TPS in a US population but did not evaluate metrics such as LOS and adverse events.<sup>7)</sup> Another more recent randomized control trial called IPC-Plus compared outcomes of IPC versus the dual treatment. This study found that administration of a talc slurry into a pleural catheter improved symptoms better than IPC alone but did not find any statistically significant differences in LOS or rates of adverse events.<sup>8)</sup>

These trials, while important, were mostly done on United Kingdom (UK) (TIME2 and IPC-Plus) and Australian (AMPLE) populations. A US population may differ from a UK or Australian population in comorbidities and risk factors, such as smoking rates. For example, the current percentage of smokers in the US is 12.5%,<sup>9)</sup> in the UK is 14.7%,<sup>10)</sup> and in Australia is 10.7%.<sup>11)</sup> Smoking is a risk factor for many disease processes and contributes to rates of certain cancers, such as lung carcinoma, which is a key contributor to formation of MPE. Another factor that must be considered when comparing these studies is the sex and ethnicity of the subjects included. The TIME2, AMPLE, and IPC-Plus trials were all able to obtain close to an even distribution between men and women.<sup>5,6,8)</sup> However, they did not include race as a demographic characteristic, so it is impossible to make any assumptions about the heterogeneity of their subjects. These factors are important because certain cancers are more prevalent, or even more deadly, in a specific sex or a specific race. Prostate, lung, and colorectal cancers were most common in men and breast, lung, and colorectal cancers were most common in women in the US in 2020.<sup>12)</sup> African American men and women have the highest death rate for all types of cancer.<sup>13)</sup> A similar situation to that of the US is seen in Australia. Rates of new cancer diagnoses and cancer mortality rates are higher in Indigenous populations compared to non-Indigenous Australians.<sup>14)</sup> However, the opposite is seen in the UK, where non-white population has an overall lower incidence of cancer than the white population.<sup>15)</sup>

The physician and the patient should choose a longterm management strategy for MPE together. This typically involves guidance and education from the physician, and for most, that means following current guidelines. However, these guidelines are not clear on which strategy is superior. The American Thoracic Society guidelines from July 2018 stated that either IPC or TPS is a viable first-line management strategy for these patients.<sup>1)</sup> The European Respiratory Society and the European Association for Cardio-Thoracic Surgery similarly state that IPC is equally efficacious as TPS.<sup>16)</sup> The aim of this study was to provide more clarity for management of MPE for providers, hospital systems, and organizations such as the American Thoracic Society, European Respiratory Society, and European Association for Cardio-Thoracic Surgery when compiling guidelines for patients and physicians.

We used the Veterans Affairs (VA) Health Care System's Corporate Data Warehouse to perform a comprehensive retrospective chart review. The database was searched for all patients who had been coded as having an MPE over a 10-year period. We then filtered this list down to 314 subjects who fit our inclusion criteria. Each individual chart was reviewed, and the data collected.

#### **Materials and Methods**

The study was reviewed and approved by the Institutional Review Board (IRB) of the University of North Dakota and by the IRB of the Fargo VA Medical Center. Informed consent requirements were waived by both IRBs because this was a retrospective database study using the VA's Corporate Data Warehouse. Charts were thoroughly reviewed through the Joint Longitudinal Viewer of MPE patients who underwent one of the following interventions: insertion of an IPC, TPS, or a combination of both procedures between January 1, 2010, and December 31, 2020.

This retrospective study subsequently included 314 patients who fit the criterion for inclusion. The TPS group consisted of 228 patients, the IPC group totaled 48 patients, and the combination group had 38 patients. Demographics were comparable among the groups; most patients were Caucasian males between 66 and 70 years.

Rates of complications associated with each intervention were recorded. Survival rate was measured by calculating the number of days between the date of the procedure and death date. A Cox proportional hazard regression model was used to adjust for likelihood of mortality when patients were chosen for each of the three interventions and adjusted for baseline dyspnea and Eastern Cooperative Oncology Group (ECOG) scores. Dyspnea scores were collected and documented both prior to the procedure and until the end of the study or patient death/loss to follow-up. The chart was first examined for explicit description of dyspnea as mild, moderate, or severe by the examiner or the patient during a clinic visit and was documented as such. If dyspnea level was not specifically notated by the clinician, the researcher would use the context of documented physical activity and subsequent shortness of breath to estimate the score. The criteria used by the researchers were the inability to walk 2 blocks (mild), inability to ambulate around the house or in the community (moderate), and inability to perform activities of daily living (severe). We adapted this method from the one described by Figarska et al., in which they categorized dyspnea based on thematic analysis of patient self-reports and using the Medical Research Council breathlessness scale.<sup>17,18)</sup> Post-procedure dyspnea scores were then averaged over four quarters consisting of 100 days each. An Estimated Marginal Means model for dyspnea scores versus the quarterly interval categories was used to validate these data. LOS was determined by finding the time between hospital admission and discharge for each patient immediately post procedure. The LOS was truncated at 60 days, meaning this was the maximum number of days accounted for in the statistical review per patient.

All variables, with the exception of age, demonstrated a significant distributional departure from normality and thus are represented as median with interquartile range (IQR) in parenthesis. Non-parametric comparison tests with Bonferroni adjustment for multiple comparisons were used for continuous and ordinal variables. Chisquared tests were used for categorical variables. R version 4.0.2 and Stata/MP version 15 were used for statistical calculations.

#### Results

There were 314 subjects who fit the inclusion criteria. **Table 1** shows their demographics. Neither age nor gender differed among the three groups. The average age was 69.2 years and 92.7% were men. Lung cancer was the most common underlying malignancy in the cohort (54.5%). Other cancers (22.6%) and mesothelioma (18.8%) were the next most common. Classification as non-smokers, former smokers, current smokers, or smokeless tobacco users was available for 150 of the subjects. Of those 150, 32.7% were smokers and 18.7% were non-smokers.

Figure 1 depicts the likelihood of survival over a period of 365 days. The downward trends for all three intervention groups were nearly identical after adjusting for baseline ECOG and dyspnea scores (p between all groups is nonsignificant). Figure 2 illustrates the baseline pre-procedure average dyspnea scores for patients as well as the quarterly average dyspnea scores post intervention. While dyspnea improved after each procedure, post-procedural improvement among the groups did not differ significantly. These findings were analyzed using an Estimated Marginal Means model. This statistical analysis showed that progressively altering dyspnea scores for up to 30% of subjects led to no difference in dyspnea severity (p >0.33). Figure 3 displays the total number of days spent in the hospital for each test group. The IPC and the IPC + TPS groups exhibited a relatively similar LOS at 3 and 2 days, respectively. The TPS group (median and IQR: 7 ad 12.8) spent substantially longer in the hospital over the ensuing year than the IPC (median, IQR 3,14) or IPC + TPS patients (median, IQR (2,9) (p < 0.05). Patients with extended post-procedure hospital stays were considered outliers, and their LOS was truncated at 60 days and subsequently configured into the median score of their respective group.

The prevalence of complications is summarized in **Table 2**. Pneumonia/chest infections occurred in 31.3% of the IPC group vs. 15.4% in TPS patients, and 21.1% in patients receiving dual therapy (p < 0.05). Lung entrapment was also more frequent in the IPC group (14.6% versus 4.4% in TPS patients and 5.3% in dual therapy patients, p < 0.05). Differences in the rates of intervention failure became statistically significant at 1 year. IPC failed in 37.5% of patients at this mark, while TPS had a failure rate of only 21.1% and the dual therapy group had

Characteristics	Intervention					
		Overall	IPC	TPS	IPC + TPS	p <sup>j</sup>
	Number in group	314	50	228	36	
	N (available)					Overall
Age <sup>a</sup>	313	69.2 (9.7)	70.1 (9.7)	66.7 (8.8)	69.4 (9.8)	0.18
Male (%) <sup>b</sup>	313	92.7	94	83.3	93.8	0.07
Race (%) <sup>c</sup>	300					0.37
White		73.6	73.3	70.3	74.3	
Black or African-American		19.7	17.8	24.3	19.3	
Other <sup>d</sup>		6.7	8.9	5.4	6.4	
Hispanic (%) <sup>e</sup>	300	3.7	2.2	4.1	2.7	0.52
ECOG baseline <sup>f</sup>		1.0 (1.0)	1.0 (1.0)	1.0 (1.0)	1.0 (1.0)	0.72
Cancer treatment (%)						
Chemotherapy	314	65.9	77.1	68.4	63.2	0.17
Radiotherapy	314	35	33.3	28.9	36.4	0.65
Death (%) <sup>g</sup>	313	92.7	90	91.7	93.4	0.69
Tumor histopathology (%)	314					0.42
Lung		54.5	60.4	60.5	52.2	
Mesothelioma		18.8	10.4	10.5	21.9	
Hematological/Lymphoma		4.1	6.2	5.3	3.5	
Other		22.6	22.9	23.7	22.4	
Smoker (%) <sup>h</sup>	150					0.19
Non-smoker		18.7	28.6	33.3	16.1	
Former smoker		19.3	7.1	25	9.7	
Smoker		32.7	35.7	41.7	31.5	
Smokeless tobacco <sup>i</sup>		29.3	28.6	0	42.7	

Table 1 Baseline demographic data for 314 subjects with MPE

<sup>a</sup>Data on age of the subjects were only available in 313 of the 314 included charts.

<sup>b</sup>Data on the sex of the subjects were only available in 313 of the 314 included charts.

<sup>c</sup>Data on the race of the subjects were only available in 300 of the 314 included charts.

<sup>d</sup>The subheading "other" under "race" includes American Indian; Alaska Native, Asian, and Native Hawaiian, or Other Pacific Islander. <sup>e</sup>Data on ethnicity were only available in 300 of the 314 included charts.

<sup>f</sup>ECOG stands for Eastern Cooperative Oncology Group and is a measure of a patient's ability to care for himself/herself, his/her amount of daily activity, and his/her physical ability.

<sup>g</sup>Mortality data were only available in 313 of the 314 included charts.

<sup>h</sup>Smoking data were only available in 150 of the 314 included charts.

<sup>i</sup>Our study defined smokeless tobacco as things such as chewing tobacco and e-cigarettes.

<sup>j</sup>Non-parametric comparison tests with Bonferroni adjustment for multiple comparisons were used for continuous and ordinal variables, while chi-squared tests were used for categorical variables.

MPE: malignant pleural effusion; IPC: indwelling pleural catheter; TPS: talc pleurodesis

a failure rate of 18.4% (p <0.05). Rates of extrapulmonary complications such as medication adverse events, non-pulmonary infections, arrhythmia, or chest tube dislodgement or inadvertent removal did not differ among the three intervention groups.

#### Discussion

The prognosis is poor for patients who develop an MPE. Treatment should be aimed at reducing their symptoms as well as maximizing their quality of life and time out of the hospital. IPC, TPS, or a combination therapy has been the mainstay of treatment. However, studies aimed at determining the superior long-term management strategy have been contradictory and mainly done in non-US populations. This study shows that TPS is associated with longer hospital stays, at 7 days, compared to the other management strategies in an American veteran population. Despite the longer LOS, all techniques appear to be equally efficacious in reducing dyspnea after the procedure. Although

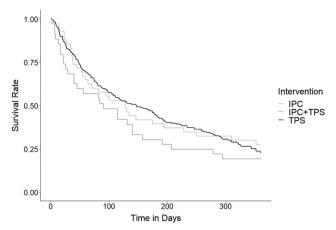


Fig. 1 Survival rate of MPE patients separated into their respective groups of IPC, IPC + TPS, and TPS up to 365 days following treatment. This was completed by using a Cox regression model and adjusting for intervention type, baseline ECOG, and dyspnea scores. The black line represents the TPS group, dark gray is the combination group, and light gray corresponds to the IPC group. There was no statistically significant difference in survival among the groups. MPE: malignant pleural effusion; IPC: indwelling pleural catheter; TPS: talc pleurodesis; ECOG: Eastern Cooperative Oncology Group

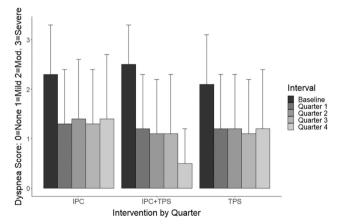
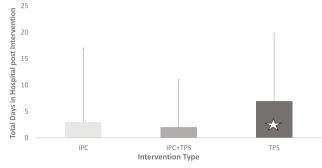
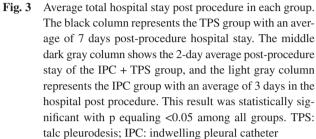


Fig. 2 Changes in dyspnea score among the treatment groups both at baseline and then following intervention in quartiles. The black column corresponds to baseline, while each gray column indicates a quartile following intervention with darkest gray being Q1 and the lightest gray being Q4. The baseline score was determined by the dyspnea score closest to procedure date. Quartiles were made up of 100 days. Improvement in dyspnea was noted in each group following their respective treatment, as expected. However, there was neither statistically significant nor clinically relevant difference in dyspnea improvement when the three groups were compared.





TPS may be associated with longer cumulative LOS and subsequent hospital financial burden, IPC resulted in higher failure rates 1 year after intervention as well as higher rates of pneumonia and lung entrapment.

The efficacy of an MPE management strategy can be defined by many factors, but intervention failure rates (i.e., need for repeat interventions) is a principal component in choosing between IPC, TPS, or the dual therapy. A meta-analysis of five studies found that subjects undergoing TPS required repeat intervention 33% more often than those in the IPC arm.<sup>19)</sup> The AMPLE trial was included in this meta-analysis, and it found that TPS is associated with higher rates of repeat drainage compared to IPC at the 1-year mark.<sup>6)</sup> The TIME2 trial did not record intervention failure rates and cannot be compared to our cohort for this metric. Our study found that IPC had a significantly higher rate of intervention failure at the 1-year mark compared to the other two management strategies. Several factors could have contributed to differences between our finding and that of the AMPLE study. For example, the sex of AMPLE subjects was more evenly distributed, with men making up 53% of the IPC group and 60% of the TPS group,<sup>6)</sup> while our cohort was 92.7% male overall. In addition to our study being predominately male, the group was also largely composed of white subjects (73.6%). It becomes more difficult to compare this characteristic to the other studies that have been published on MPE management because AMPLE, TIME2, and IPC-Plus failed to report ethnicity.5,6,8) Although AMPLE was a randomized trial, while

Complications (%)	Intervention				
	IPC (n = 48)	TPS (n = 228)	IPC + TPS (n = 38)	p <sup>e</sup>	
Med/chemo adverse events	43.8	36.4	36.8	0.63	
Non-pulmonary infections	16.7	12.7	10.5	0.67	
Cardiac arrhythmia	6.2	7	0	0.24	
Chest tube dislodgement <sup>a</sup>	2.1	1.3	0	0.69	
Chest tube inadvertent removal <sup>b</sup>	4.2	1.8	0	0.35	
Pneumonia/Chest infection	31.3	15.4	21.1	< 0.05	
Other complications <sup>c</sup>	22.9	13.2	7.9	0.12	
Lung infarction	4.2	2.6	7.9	0.19	
Lung entrapment <sup>d</sup>	14.6	4.4	5.3	< 0.05	
Intervention failure (days)					
7	2.1	2.2	2.6	1	
30	10.4	8.8	10.5	0.86	
90	16.7	14.5	13.2	0.87	
365	37.5	21.1	18.4	< 0.05	

#### Table 2 Rates of complications

<sup>a</sup>Chest tube dislodgement was defined as the chest tube leaving the pleural space, but not the chest cavity.

<sup>b</sup>Chest tube inadvertent removal was defined as accidental removal of the chest tube/catheter from the chest cavity.

<sup>c</sup>Other complications included pneumothorax, intubation, clogged chest tube, and other miscellaneous complications.

<sup>d</sup>Lung entrapment was defined as a non-expandable lung due to active pleural inflammation, malignancy, or hemothorax.

<sup>e</sup>The p values were calculated using non-parametric comparison tests with Bonferroni adjustment for multiple comparisons.

IPC: indwelling pleural catheter; TPS: talc pleurodesis

our study was retrospective, the sample size in AMPLE was less than half of our study (146 for AMPLE<sup>6)</sup> vs. 314). This larger sample size may lead to greater generalizability than the smaller AMPLE group. Smoking rates may also factor into this difference. As stated before, the smoking rate in Australia is 10.7%.<sup>11)</sup> This is in contrast with the 32.7% smoking rate in our study population. While smoking data were only available for 150 of the 314 subjects included, Journal of Military, Veteran and Family Health endorses a tobacco usage rate of 30% in veterans.<sup>20)</sup> Smoking is a key risk factor in the development of chronic disease and death from cancer.<sup>20,21)</sup> Although difference in failure rates at the 1-year mark might seem irrelevant when the average survival for these patients is 3-12 months,<sup>3,4)</sup> 25.6% of our subjects survived beyond 1 year. This means that a considerable number of patients diagnosed with MPE will require effective, long-term symptom relief. This survival rate is in keeping with the findings of AMPLE and TIME2.<sup>5,6)</sup> Due to the palliative nature of MPE management, some patients might prioritize an intervention strategy that only requires one procedure to improve quality of life.

The rate of complications is another crucial factor that practitioners, hospitals, and patients must consider in choosing an MPE management strategy. Our study found

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that IPC was associated with higher rates of pulmonary infections and lung entrapment than other management strategies. These findings are consistent with those of the TIME2 trial that found higher rates of pleural infections in IPC patients compared to patients managed via TPS.<sup>5)</sup> The AMPLE study reported no difference in total number of adverse events, but it found that 22 subjects accounted for the 30 adverse events in the IPC group, but only 13 subjects accounted for the 23 adverse events in the TPS group.<sup>6)</sup> While the way they interpreted the data showed a non-significant relationship, more subjects contributed to the total number of adverse events in the IPC group than the TPS group. When the focus is shifted to the number of subjects affected by an adverse event, the AMPLE study begins to align with the findings from TIME2 and our study. One can hypothesize that as the sample size increases, this trend may begin to show statistical significance. The risk of infection carries heavy clinical significance. Empyema is associated with a mortality rate of 6%-24%<sup>22)</sup> and biofilm formation can culminate in refractory infections<sup>23)</sup> that require removal of the indwelling catheter and repeat drainage operations. The increased rate of lung entrapment may be artificially elevated because IPC is typically preferred in patients without complete lung expansion.<sup>5)</sup> According to a Cochrane meta-analysis, there is little evidence regarding the most effective management of these patients, but they are typically excluded from MPE trials due to decreased efficacy of pleurodesis.<sup>24)</sup> This may contribute to patients with worse prognosis being preferentially treated via IPC. However, we found that these subjects did not differ in their dyspnea or survival rates. Neither our study nor TIME2 or AMPLE found differences in non-pulmonary complications among the three groups.<sup>5,6)</sup>

LOS is a variable that can also be important to patients so that they can spend more time at home before their condition declines further. This is also important for administrators as longer hospitalization is costly. The AMPLE trial found that IPC patients spent 2 days less (median 10 days vs 12 days) in the hospital compared to pleurodesis patients.<sup>6)</sup> Our results align with theirs, but with an even more significant difference of 3 vs 7 days. This could be a population-dependent variable or could reflect the increasing trend to move patients out of the hospital as rapidly as possible. Differences in healthcare systems could also contribute to differences in the average LOS for these patients. The US typically relies on third party insurance companies or patient self-pay to cover medical expenses, while the Australian system relies on universal public health care financed by tax revenues.<sup>25)</sup> This means that there may be less pressure on physicians to decrease inpatient stays in the US. However, our cohort was different than the average US population in that they all received care from the VA healthcare system. The VA provides free medical services to veterans with conditions related to military service, a disability rating of at least 50%, or for those who cannot afford to pay for care.<sup>26)</sup> Thus, pressure to decrease LOS may be less prevalent in this cohort compared to the average US hospital system.

In our study, the goal of reducing dyspnea was achieved analogously with either of the three possible interventions. No significant difference was found between the groups post procedure at each of the four quarterly periods of 100 days. Comparably, both the AMPLE trial and TIME2 trial note significant improvement of dyspnea from baseline, with both studies using the visual analog scale (VAS) that is validated for patients with MPE.<sup>5,6)</sup> The AMPLE trial measured dyspnea up to 12 months post procedure as a secondary outcome, and no significant difference was observed with dyspnea improvement among the IPC or TPS groups.<sup>6)</sup> The TIME2 trial reported dyspnea as the primary outcome and found no significant difference in dyspnea with IPC

or TPS until 6 months; at which point, the IPC group indicated a significant reduction in dyspnea compared to the TPS group at 6 months post procedure (-14.0 mm; 95% CI, -25.2 to -2.8 mm; P=0.01).<sup>5</sup> However, the TIME2 trial cautions interpretation of the significant difference at 6 months because this study was not powered to clearly address that outcome at 6 months as less than half of patients enrolled actually survived to 6 months to report their level of dyspnea; furthermore, the TIME2 trial did not report the specific quantitative difference in VAS scores among the two groups, making it impossible to interpret if there was a clinically significant difference.<sup>5)</sup> Therefore, a patient deciding between procedures to undergo with the primary factor based only on the amount of relief of dyspnea can be assured in either choice as the palliative goal to significantly reduce dyspnea following either procedure has been shown to be successful in our study with either therapeutic option of IPC, TPS, or both, and is supported by the AMPLE and TIME2 trials.

A limitation of this study is the sample demographics. Our patient population consisted largely of US white males over the age of 60 receiving care in the VA system. Thus, extrapolation to more gender-balanced US population receiving care in a different healthcare system requires further study. Sample size is also a limitation in our study. TPS was a much more prominent procedure among our population when compared to IPC and IPC + TPS. The current sample sizes are associated with about a 50% power to detect a statistical difference in 1 year mortality between interventions. A larger sample size for IPC or combination treatment groups could have altered the results.

A second limitation of this study is the categorization of the dyspnea scores, as they were estimated by the researchers reviewing patient charts. The determined level of dyspnea could be seen as unreliable given the subjectivity of the reports from patients, physicians, and researchers. Using a valid and reliable dyspnea score could increase the reliability of the levels of dyspnea reported and provide better insight at how each intervention affects post-procedure dyspnea. One study by Figarska et al. prospectively evaluated dyspnea severity levels based upon the subject's reported type of physical activity, finding that the severity of these subjectively assigned dyspnea scores was positively associated with mortality.<sup>17)</sup> These subjects were asked whether they felt short of breath under a diverse range of circumstances. Their answers were then used to define the severity of their dyspnea.<sup>17)</sup> Given the nature of our retrospective

study, subjective patient reporting was unable to be attained as these patients were not assessed during their clinic appointments. The researchers were also unable to provide a validated dyspnea scoring system to the deidentified patients as current systems, such as VAS, involve subjective patient reporting of their level of dyspnea. We were, however, able to use a similar approach to Figarska et al., utilizing subjective physical activity levels from the patient's chart to assign dyspnea severity. Employing an Estimated Marginal Means analysis, we were able to prove that this method was statistically valid; the analysis showed that progressively altering dyspnea scores up to 30% resulted in no significant difference (p > 0.33). Another consideration is that current validated scoring systems, while the gold standard, are not always reliable. A large majority of MPE patients are receiving palliative care near the end of life, and it has been found that 54% of these patients are unable to adequately report their dyspnea level.<sup>27)</sup> This means that even scoring systems such as VAS may not always provide consistent insight into a patient's level of dyspnea. It can also be difficult to obtain longitudinal dyspnea scores from MPE patients as nearly half die within the first 100 days after diagnosis. However, as one of the primary complaints among patients diagnosed with MPE is dyspnea, there is significant importance to investigating differences in the reduction of shortness of breath following each intervention option.

# Conclusion

There are many different strategies for managing patients with MPE. While thoracentesis is preferable in some instances, many of these patients need more permanent solutions such as IPC, TPS, or a combination of both. Our study found that these three interventions were equally efficacious in reducing postoperative dyspnea scores. There were, however, limitations to each management strategy. We found that TPS was associated with longer hospital LOS and that IPC was associated with more postoperative complications and higher rates of intervention failure at the 1-year mark.

These findings can help guide physicians and their patients in choosing a management strategy that most closely fits their treatment goals, as well as hospital systems as they look to decrease overhead costs following MPE interventions. Further research with a larger sample should be completed to decipher the differences in postoperative complications, LOS, and dyspnea reduction, and to better guide patients and physicians in the management of this condition.

### **Disclosure Statement**

The authors report no conflicts of interest. This material is the result of work supported with resources and the use of facilities at the Fargo VA Health Care System. The contents do not represent the views of the US Department of Veterans Affairs or the US Government.

#### References

- Feller-Kopman DJ, Reddy CB, DeCamp MM, et al. Management of malignant pleural effusions. An official ATS/STS/STR clinical practice guideline. Am J Respir Crit Care Med 2018; **198**: 839–49.
- Maskell NA. Treatment options for malignant pleural effusions: patient preference does matter. JAMA 2012; 307: 2432–3.
- Akram MJ, Khalid U, Ashraf MB, et al. Predicting the survival in patients with malignant pleural effusion undergoing indwelling pleural catheter insertion. Ann Thorac Med 2020; 15: 223–9.
- Psallidas I, Kalomenidis I, Porcel JM, et al. Malignant pleural effusion: from bench to bedside. Eur Respir Rev 2016; 25: 189–98.
- 5) Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. JAMA 2012; **307**: 2383–9.
- 6) Thomas R, Fysh ETH, Smith NA, et al. Effect of an indwelling pleural catheter vs talc pleurodesis on hospitalization days in patients with malignant pleural effusion: the AMPLE randomized clinical trial. JAMA 2017; **318**: 1903–12.
- Demmy TL, Gu L, Burkhalter JE, et al. Optimal management of malignant pleural effusions (results of CALGB 30102). J Natl Compr Canc Netw 2012; 10: 975–82.
- Bhatnagar R, Keenan EK, Morley AJ, et al. Outpatient talc administration by indwelling pleural catheter for malignant effusion. N Engl J Med 2018; 378: 1313–22.
- 9) Centers for Disease Control and Prevention (US). Current cigarette smoking among adults in the United States. Atlanta, GA. Available from: https://www. cdc.gov/tobacco/data\_statistics/fact\_sheets/adult\_data/ cig\_smoking/index.htm#:~:text=In%202020%2C%20 nearly%2013%20of,with%20a%20smoking%2Drelated%20disease. Accessed Apr 13, 2022.
- Action on Smoking and Health (GB). Smoking Statistics. London, GB. Available from: https://ash.org.uk/ wp-content/uploads/2019/10/SmokingStatistics.pdf. Accessed Apr 13, 2022.

- 11) Cancer Council Victoria (AU). Trends in the Prevalence of Smoking. Melbourne, AU. Available from: https://www.tobaccoinaustralia.org.au/chapter-1-prevalence/1-3-prevalence-of-smoking-adults#:~:text= According%20to%20the%20Australian%20Bureau,aged%2015%20years%20and%20over. Accessed Apr 13, 2022.
- 12) National Cancer Institute (US). Cancer Statistics. Bethesda, MD. Available from: https://www.cancer. gov/about-cancer/understanding/statistics#:~:text=Prostate%2C%20lung%2C%20and%20colorectal%20cancers,diagnoses%20in%20women%20 in%202020. Accessed May 31, 2022.
- 13) National Cancer Institute (US). Cancer Stat Facts: Cancer Disparities. Bethesda, MD. Available from: https://seer.cancer.gov/statfacts/html/disparities.html. Accessed May 31, 2022.
- Australian Institute of Health and Welfare & Cancer Australia 2013. Cancer in Aboriginal and Torres Strait Islander peoples of Australia: an overview. 2013.
- 15) Delon C, Brown KF, Payne NWS, et al. Differences in cancer incidence by broad ethnic group in England, 2013–2017. Br J Cancer [Internet]. 2022; Available from: https://www.nature.com/articles/s41416-022-01718-5. Accessed May 31, 2022.
- 16) Bibby AC, Dorn P, Psallidas I, et al. ERS/EACTS statement on the management of malignant pleural effusions. Eur Respir J 2018; **52**: 1800349.
- 17) Figarska SM, Boezen HM, Vonk JM. Dyspnea severity, changes in dyspnea status and mortality in the general population: the Vlagtwedde/Vlaardingen study. Eur J Epidemiol 2012; **27**: 867–76.
- Stenton C. The MRC breathlessness scale. Occup Med (Lond) 2008; 58: 226–7.

- 19) Iyer NP, Reddy CB, Wahidi MM, et al. Indwelling pleural catheter versus pleurodesis for malignant pleural effusions. a systematic review and meta-analysis. Ann Am Thorac Soc 2019; **16**: 124–31.
- Mshigeni SK, Moore C, Arkadie NL. The prevalence rate of smoking among Veterans: a forgotten epidemic. J Mil Veteran Fam Health 2021; 7: 16–25.
- 21) National Institute of Health (US). Smoking and your heart. Bethesda, MD. Available from: https://www.nhlbi.nih.gov/health-topics/smoking-and-your-heart. Accessed Jun 7, 2022.
- 22) Ahmed AEH, Yacoub TE. Empyema thoracis. Clin Med Insights Circ Respir Pulm Med 2010; **4**.
- 23) Zhang L, Li J, Liang J, et al. The effect of Cyclicdi-GMP on biofilm formation by *Pseudomonas aeruginosa* in a novel empyema model. Ann Transl Med 2020; **8**: 1146.
- 24) Clive AO, Jones HE, Bhatnagar R, et al. Interventions for the management of malignant pleural effusions: a network meta-analysis. Cochrane Database Syst Rev 2016; **2016**: CD010529.
- 25) The Commonwealth Fund (US). International Health Care Systems Profiles: Australia. New York, NY. Available from: https://www.commonwealthfund.org/ international-health-policy-center/countries/australia. Accessed May 31, 2022.
- 26) United States Department of Veterans Affairs (US). Your health care costs. Washington, DC. Available from: https://www.va.gov/health-care/about-va-healthbenefits/cost-of-care/#:~:text=We're%20committed%20to%20providing,afford%20to%20pay%20 for%20care. Accessed May 31, 2022.
- Campbell ML, Templin T, Walch J. Patients who are near death are frequently unable to self-report dyspnea. J Palliat Med 2009; 12: 881–4.