Original Article

Quantitation and predictors of short-term mortality following extrapleural pneumonectomy, pleurectomy/decortication, and nonoperative management for malignant pleural mesothelioma

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Background: For malignant pleural mesothelioma (MPM), the benefit of resection, as well as the optimal surgical technique, remain controversial. In efforts to better refine patient selection, this retrospective observational cohort study queried the National Cancer Database in an effort to quantify and evaluate predictors of 30- and 90-day mortality between extrapleural pneumonectomy (EPP) and pleurectomy/decortication (P/D), as well as nonoperative management.

Methods: After applying selection criteria, cumulative incidences of mortality by treatment paradigm were graphed for the unadjusted and propensity-matched populations, as well as for six *a priori* age-based intervals (≤60, 61–65, 66–70, 71–75, 76–80, and ≥81 years). The interaction between age and hazard ratio (HR) for mortality between treatment paradigms was also graphed. Cox multivariable analysis ascertained factors independently associated with 30- and 90-day mortality.

Results: Of 10,723 patients, 2,125 (19.8%) received resection (n=438 EPP, n=1,687 P/D) and 8,598 (80.2%) underwent nonoperative management. The unadjusted 30/90-day mortality for EPP, P/D, and all operated cases was 3.0%/8.0%, 5.4%/14.1%, and 4.9%/12.8%, respectively. There were no short-term mortality differences between EPP and P/D following propensity-matching, within each age interval, or between age subgroups on interaction testing (P>0.05 for all). Nonoperative patients had a crude 30- and 90-day mortality of 9.9% and 24.6%, respectively. Several variables were identified as predictors of short-term mortality, notably patient age (HR 1.022, P<0.001), Charlson-Deyo comorbidity index (HR 1.882, P<0.001), receipt of

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treatment at high-volume centers (HR 0.834, P=0.032) and induction chemotherapy (HR 1.735, P=0.025), among others. The patient (yearly) incremental increase in age conferred 2.0% (30 day) and 2.2% (90 day) increased risk of mortality (P<0.001).

Conclusions: Quantitative estimates of age-associated 30- and 90-day mortality of EPP and P/D should be considered when potentially operable patients are counseled regarding the risks and benefits of resection.

Keywords: Mesothelioma; pleural; surgery; extrapleural pneumonectomy (EPP); pleurectomy; mortality

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Introduction

A relatively uncommon but highly aggressive neoplasm, malignant pleural mesothelioma (MPM) poses major challenges to multidisciplinary management (1). While guidelines endorse the use of first-line cytotoxic chemotherapy and adjuvant radiation therapy in surgical patients, the routine use of chemotherapy and radiation therapy have both been questioned by phase III trials (2,3). Surgical therapy in the form of extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/D) is considered the cornerstone of therapy for operable patients (1), but it is also not supported by high-level evidence from randomized clinical trials (4).

However, extrapolation of the aforementioned trials to clinical practice remains difficult, largely owing to noteworthy limitations. The SAKK study of radiotherapy was underpowered (2,5), and the MS01 investigation utilized a regimen that is no longer the standard of care (3,6). Most strikingly, the MARS trial demonstrated an infeasibility to conduct a surgical randomized trial and documented a high perioperative mortality rate (12.5%) in the surgical (EPP) arm, which could have dampened the possible outcome advantages offered by surgery (7).

The chief lesson from MARS was that because resection is a morbid procedure, patients must be carefully selected pre-operatively in order to minimize post-operative morbidities and mortality, the presence of which can reduce the degree of surgical benefits. Careful patient selection and improvements in technical experience and postoperative care have led to reductions in mortality rates (8). For example, patient-related factors, including age (≥65 years), male sex, forced expiratory volume in 1 second (FEV1) (<60% of predicted), and lower preoperative hemoglobin level, convey a higher risk for perioperative mortality (9). The presence of patient comorbidities, such as peripheral vascular disease, cerebrovascular disease, congestive heart failure and benign lung disease, are also independently associated with poor perioperative outcomes. In addition to patient characteristics, several treatment-related factors, including the operation type (EPP) and surgical center volume (<5 procedures per year), have been shown to predict for increased perioperative mortality (10). While EPP carries 30-day mortality rates of 4–7% (2,11,12), the lung-sparing P/D procedure has been increasingly utilized in contemporary periods and has been demonstrated to have fewer complications and equivalent or superior survival as compared to EPP (11,13-18). However, although the MARS 2 trial (NCT02040272) continues to accrue, an analogous study to MARS has not been completed utilizing P/D; hence, the role of resection remains in flux, and both techniques are endorsed by the National Comprehensive Cancer Network (NCCN) (1).

In order to refine pre-operative patient selection, as well as to address the controversy regarding surgical approaches (EPP *vs.* P/D), it is imperative to better quantify and evaluate predictors of short-term (30- and 90-day) mortality with EPP versus P/D, as well as with nonoperative management. This investigation, therefore, aimed to address this knowledge gap by examining the large, contemporary National Cancer Database (NCDB). We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-1779).

Methods

The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society that consists of information

regarding tumor characteristics, patient demographics, and patient survival for approximately 70% of the United States population (19). The American College of Surgeons and the CoC have not verified and are neither responsible for the analytic or statistical methodology employed nor the conclusions drawn from these data. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). As all patient information in the NCDB is de-identified, this study was exempt from institutional review board evaluation. The NCDB Participant User File corresponding to mesothelioma [2004–2013] was utilized for this study.

Methodological analysis of this study mirrored recent studies of other neoplasms, including testing the hypothesis that postoperative mortality was related to age (20,21). As a result, short-term (30- and 90-day postoperative) mortality was compared between EPP and P/D (previously reported NCDB codes identifying each surgical procedure) (18,22,23) using *a priori* age-based intervals (≤60, 61–65, 66–70, 71–75, 76–80, and ≥81 years). Because this comparison required technical resectability and proper documentation of surgical technique, subjects with T4 (unresectable) disease as well as those who underwent nondefinitive/palliative or ambiguous/unknown surgery were excluded. Of note, there was no exclusion based on nodal status, because (I) there are a multitude of data showing that well-selected cases can attain appropriate survival with low short-term mortality, and (II) resection is an option in NCCN guidelines for well-selected node-positive patients (1,4,24-26). Other exclusion criteria were lack of a coded vital status, primary mesothelioma location in a non-intrathoracic site, and/or metastatic (or unknown) disease.

Additionally, because is important to quantify the short-term mortality risk in the unresected population as well, a nonoperative cohort was also separately analyzed (having received chemotherapy, radiotherapy, chemoradiotherapy, or supportive care). For this cohort, 30- and 90-day mortality was defined from the time of initial diagnosis. No comparisons of mortality between the surgical and nonsurgical cohorts was made, owing to a multitude of uncontrolled retrospective selection biases and fundamental discrepancies in defining the 30- and 90-day windows.

Statistical analysis

In accordance with the variables in NCDB files, information collected on each patient broadly included demographic, clinical, and treatment data. Statistical analysis was performed with STATA version 14 (College Station, TX, USA). Tests were two-sided, with a threshold of $P<0.05$ for statistical significance. First, clinical characteristics of the overall cohort were tabulated. Second, cumulative incidences of mortality by treatment paradigm were then tabulated and graphed for each age interval as well as the whole population. Propensity matching was utilized to better balance groups (27-29). Propensity scores were calculated using a multivariable logistic regression model, with the dependent variable being the particular treatment technique and the independent variables being those that were statistically significant for correlation with mortality on multivariable analysis. Patients were matched 1:1 without replacement to avoid potential bias from many-to-one matching. Standardized differences were assessed to ensure balance between each of the variables included in calculating the propensity score to the matched cohorts, with a value <0.1 signifying an inconsequential imbalance (*Table 1*) (30). Third, interaction testing was utilized to create forest plots aiming to evaluate the interaction between age and hazard ratio (HR) for mortality between treatment paradigms. Lastly, Cox multivariable analysis was performed to ascertain factors independently associated with 30- and 90-day mortality. We present the following article in accordance with the STROBE reporting checklist (31).

Results

A patient selection diagram is illustrated in *Figure 1*. Overall, 10,723 patients met study criteria (*Table 2*). Of these, 2,125 (19.8%) received resection (n=438 EPP, n=1,687 P/D) and 8,598 (80.2%) underwent nonoperative management. Of note, a plurality of patients were node-negative and treated at facilities in the upper quartile of case volume (defined by the total number of cases over the NCDB study period). Chemotherapy was delivered to 303 (69.2%) subjects in the EPP group (n=122 induction chemotherapy), 928 (55.0%) in the P/D cohort (n=194 induction), and 3,656 (42.5%) of the nonoperative cases.

The 30-day mortality was 3.0% and 5.4% for EPP and P/D, respectively; corresponding 90-day mortality figures were 8.0% and 14.1% (*Table 3*). When aggregated, the overall unadjusted 30- and 90-day mortality rates for resected patients were 4.9% and 12.8%, respectively. *Figure 2* displays cumulative incidences of short-term mortality by receipt of EPP versus P/D, displaying no differences within each age group (P=0.222, 0.647, 0.547, 0.155, 0.635, and 0.447, respectively, for ages ≤60, 61–65, 66–70, 71–75, 76–80, and ≥81 years). Although there was a statistical difference when

Table 1 Standardized mean differences of each parameter utilized for propensity score matching

Parameter	Standardized differences
Age	
≤60 years	0.066
61–65 years	0.034
66–70 years	0.062
71–75 years	0.044
76–80 years	0.006
≥81 years	0.076
Charlson-Deyo comorbidity index	
0	0.011
1	0.029
2+	0.030
Insurance type	
Private	0.080
Medicaid	0.055
Medicare	0.054
Other	0.016
Uninsured	0.072
Patient residence	
Metro	0.031
Urban	0.044
Rural	0.000
Unknown	0.011
Facility type	
Academic	0.067
Community	0.063
Unknown	0.023
Case volume (quartile)	
1–4	0.000
5–9	0.068
10–19	0.011
20+	0.054
Clinical T classification	
T1	0.006
T2	0.017
T3	0.028
TX	0.039
Clinical N classification	
N0	0.000
N1	0.028
N2	0.095
N3	0.030
NX	0.054
Histology	
Epithelioid	0.005
Biphasic	0.022
Sarcomatoid	0.008
Unknown	0.016
Chemotherapy	
No	0.000
Yes	0.000
Unknown	0.000
Induction chemotherapy	
No	0.000
Yes	0.000
Unknown	0.000

evaluating all subjects (P=0.001), this difference did not persist following propensity matching (P=0.193).

Additionally, despite the lack of differences between EPP and P/D within each age-based subgroup, interaction testing was performed to further evaluate HRs for mortality between age-related (unadjusted) groups. Forest plots are shown in *Figure 3*, demonstrating that the effect size was not significantly different between the six age-based cohorts at 30 (P=0.958) or 90 (P=0.955) days.

Figure 4 illustrates short-term mortality of the nonoperated cohort. For these high risk patients, the crude 30- and 90-day mortality was 9.9% and 24.6%, respectively (*Table 3*).

Following univariable evaluation (*Table 4*), multivariable Cox analysis was performed to assess factors predicting for 30- and 90-day mortality (*Table 5*). Variables associated with both outcomes included comorbidities, insurance, case volume, histology, and chemotherapy. Of note, surgical patients having received induction chemotherapy were associated with higher 30- and 90-day mortality (P=0.025),

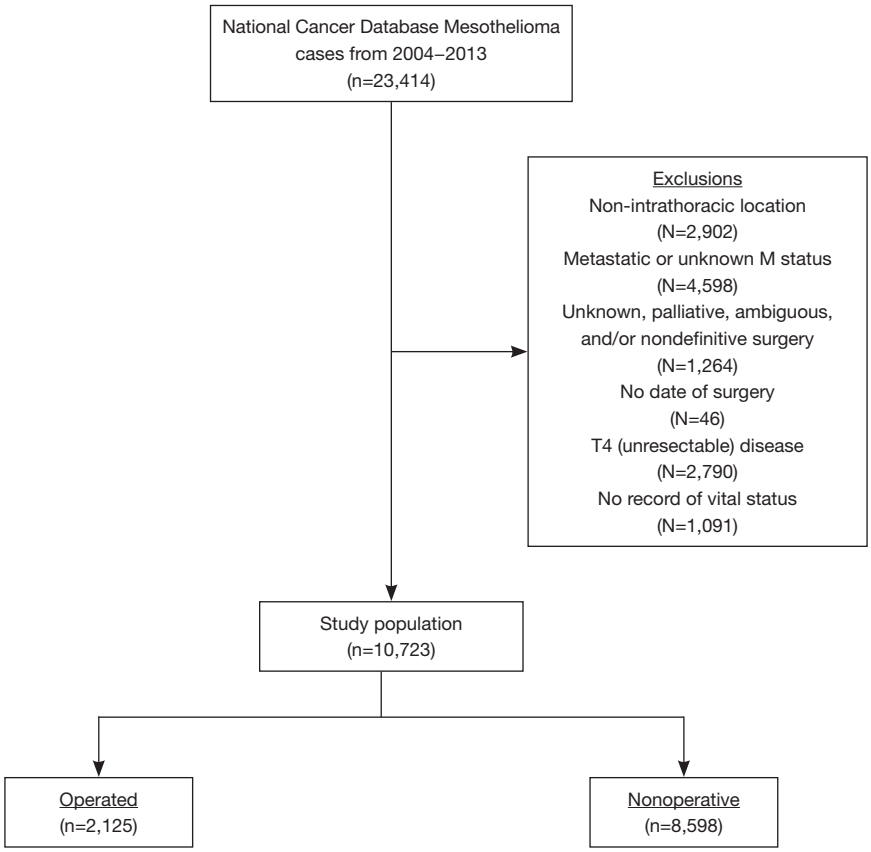

Figure 1 Patient selection diagram for this study.

whereas treatment at high-volume centers was associated with less mortality (P=0.032). Age was also significantly associated with both 30- and 90-day mortality (P<0.001); each yearly incremental increase in age (at diagnosis) conferred a 2.0% increased risk of 30-day mortality and 2.2% increased risk of 90-day mortality.

Discussion

MPM management continues to be debated; the decision to resect, as well as the optimal technique thereof, remain controversial. A quantitative understanding of mortality risk (and predictors thereof) for several approaches is thus critical to better refine patient selection. The largest such study of its kind, this investigation of a large, contemporary national database quantitates age-associated 30- and 90-day mortality of EPP and P/D, which should be considered when potentially operable patients are counseled regarding the risks and benefits of resection.

The reader is strongly cautioned when interpreting these data, largely owing to confounding by operability status in NCDB studies, which results in well-selected surgical patients and the vast majority of nonoperative patients being unresectable/inoperable. As a result, if a potentially operable patient is weighing resection versus lack thereof, the clinician can obtain a quantifiable estimate of that patient's estimated 30- and 90-day postoperative mortality based on age and the proposed surgical technique (*Table 3*). However, short-term mortality risks in potentially operable patients declining resection cannot be ascertained from this study because they are not synonymous with the nonoperative group herein.

These data also imply that nonoperative (largely unresectable and/or inoperable) patients have a high baseline mortality, a notion that has been under-studied from a quantitative perspective (*Table 3*). Given the high rate of short-term mortality in certain subsets (e.g., older patients with greater comorbidities), these data may question whether nonoperative candidates should receive aggressive therapies (i.e., systemic therapy and/

Table 2 Clinical characteristics of the study population

Parameter	EPP (N=438)	P/D (N=1,687)	Nonoperative (N=8,598)
Age			
≤60 years	140 (32%)	340 (20%)	851 (10%)
61–65 years	98 (22%)	253 (15%)	789 (9%)
66–70 years	102 (23%)	314 (19%)	1,182 (14%)
71–75 years	50 (11%)	299 (18%)	1,477 (17%)
76–80 years	36 (8%)	291 (17%)	1,732 (20%)
≥81 years	12 (3%)	190 (11%)	2,567 (30%)
Gender			
Male	337 (77%)	1,357 (80%)	6,738 (78%)
Female	101 (23%)	330 (20%)	1,860 (22%)
Race			
White	423 (97%)	1,569 (93%)	7,984 (93%)
Black	8 (2%)	68 (4%)	385 (5%)
Other	7 (2%)	50 (3%)	229 (3%)
Charlson-Deyo comorbidity index			
0	336 (77%)	1,211 (72%)	5,747 (67%)
1	88 (20%)	373 (22%)	2,039 (24%)
2+	14 (3%)	103 (6%)	812 (9%)
Insurance type			
Private	231 (53%)	615 (37%)	1,791 (21%)
Medicaid	10 (2%)	29 (2%)	157 (2%)
Medicare	180 (41%)	985 (58%)	6,219 (72%)
Other	12 (3%)	41 (2%)	284 (3%)
Uninsured	5 (1%)	17 (1%)	147 (2%)
Income (US dollars/year)			
<$63,000	221 (51%)	973 (58%)	5,535 (64%)
≥$63,000	199 (45%)	662 (39%)	2,770 (32%)
Unknown	18 (4%)	52 (3%)	293 (3%)
Patient residence			
Metro	367 (84%)	1,373 (81%)	6,863 (80%)
Urban	43 (10%)	207 (12%)	1,141 (13%)
Rural	8 (2%)	22 (1%)	147 (2%)
Unknown	20 (5%)	85 (5%)	447 (5%)

Table 2 (*continued*)

Table 2 (*continued*)

Parameter	EPP (N=438)	P/D (N=1,687)	Nonoperative (N=8,598)
Facility type			
Academic	275 (63%)	800 (47%)	2,611 (30%)
Community	152 (35%)	868 (52%)	5,958 (69%)
Unknown	11 (3%)	19 (1%)	29 (0%)
Case volume (quartile)			
1–4	11 (3%)	82 (5%)	558 (7%)
5–9	31 (7%)	191 (11%)	1,341 (16%)
10–19	76 (17%)	416 (25%)	2,634 (31%)
20+	320 (73%)	998 (59%)	4,065 (47%)
Years of diagnosis			
2004–2005	111 (25%)	378 (22%)	1,990 (23%)
2006–2007	89 (20%)	370 (22%)	2,080 (24%)
2008–2009	84 (19%)	402 (24%)	2,002 (23%)
2010–2011	102 (23%)	342 (20%)	1,666 (19%)
2012–2013	52 (12%)	195 (12%)	860 (10%)
Clinical T classification			
T1	66 (15%)	332 (20%)	2,595 (30%)
T2	99 (23%)	379 (23%)	1,768 (21%)
T3	85 (19%)	236 (14%)	1,029 (12%)
TX	188 (43%)	740 (44%)	3,206 (37%)
Clinical N classification			
N0	194 (44%)	822 (49%)	4,099 (48%)
N1	18 (4%)	51 (3%)	244 (3%)
N2	48 (11%)	116 (7%)	911 (11%)
N3	5 (1%)	11 (1%)	105 (1%)
NX	173 (39%)	687 (41%)	3,239 (38%)
Histology			
Epithelioid	279 (64%)	834 (49%)	2,979 (35%)
Biphasic	73 (17%)	204 (12%)	505 (6%)
Sarcomatoid	24 (6%)	191 (11%)	1,031 (12%)
Unknown	62 (14%)	458 (27%)	4,083 (47%)

Percentages may not add to 100% because of rounding. EPP, extrapleural pneumonectomy; P/D, pleurectomy/decortication.

Table 3 Crude rates of 30- and 90-day mortality in the unadjusted population

Age group	EPP		P/D		All operated		Nonoperative	
	Dead/total patients	Mortality	Dead/total patients	Mortality	Dead/total patients	Mortality	Dead/total patients	Mortality
30-day mortality								
≤60 years	3/140	2.1%	7/340	2.1%	10/480	2.1%	56/851	6.6%
61–65 years	3/98	3.1%	10/253	4.0%	13/351	3.7%	44/789	5.6%
66–70 years	4/102	3.9%	19/314	6.1%	23/416	5.5%	65/1,182	5.5%
71–75 years	0/50	0.0%	19/299	6.4%	19/349	5.4%	103/1,477	7.0%
76–80 years	2/36	5.6%	21/291	7.2%	23/327	7.0%	180/1,732	10.4%
≥81 years	1/12	8.3%	20/190	10.5%	21/202	10.4%	406/2,567	15.8%
All patients	13/438	3.0%	96/1,783	5.4%	109/2,221	4.9%	854/8,598	9.9%
90-day mortality								
≤60 years	9/140	6.4%	34/340	10.0%	43/480	9.0%	132/851	15.5%
61–65 years	6/98	6.1%	19/253	7.5%	25/351	7.1%	115/789	14.6%
66–70 years	9/102	8.8%	34/314	10.8%	43/416	10.3%	186/1,182	15.7%
71–75 years	3/50	6.0%	40/299	13.4%	43/349	12.3%	311/1,477	21.1%
76–80 years	6/36	16.7%	59/291	20.3%	65/327	19.9%	458/1,732	26.4%
≥81 years	2/12	16.7%	52/190	27.4%	54/202	26.7%	912/2,567	35.5%
All patients	35/438	8.0%	238/1,687	14.1%	273/2,125	12.8%	2,114/8,598	24.6%

EPP, extrapleural pneumonectomy; P/D, pleurectomy/decortication.

or radiotherapy) near the end of life (32), a notion that has been promulgated from randomized trials (3) and retrospective data (29).

This investigation additionally sheds light into potentially modifiable factors of short-term mortality, such as therapy at high-volume facilities (33) and lack of induction chemotherapy (34). These should be integrated with a thorough pre-operative assessment if surgery is being planned. This assessment should comprise of several important factors not coded in the NCDB, including performance status, cardiopulmonary function, volume and location of disease, and mental/emotional tolerance of the proposed therapy. Additional factors such as age, nodal status, and histology can be added to create a "complete clinical picture" on which the decision to operate is made.

The mortality figures herein are roughly comparable to existing data (2,10-17). They are, however, considerably lower than the MARS data, which documented a 30-day mortality (11%) numerically similar to operated patients ≥81 years of age in this study (10.4%) (7). However, the median age of the MARS population was 62, which is difficult to extrapolate to a more "general" MPM population whose median age at diagnosis is nearly a decade older (1).

There are several noteworthy shortcomings of any retrospective NCDB study, in addition to the lack of important information not coded in the NCDB mentioned above (34,35). First, the goal of this investigation was not to evaluate overall mortality (examined elsewhere) (10,13-18); although examining short-term mortality attenuates many biases associated with assessment of overall mortality, lead-time and immortal time bias can never be eliminated. It also cannot be ascertained whether "short-term mortality" in this paper equated to "treatment-related mortality," since specific complications and/or causes of mortality are not given in the NCDB. This likely explains the discrepancy between the lack of postoperative mortality differences between EPP and P/D herein, as compared to other studies showing fewer complications with P/D (10,12-17). Importantly, comparisons made between patients treated with surgery and nonoperative management is subject to significant clinical heterogeneity, including but not limited to differences in patient surgical fitness or tolerability.

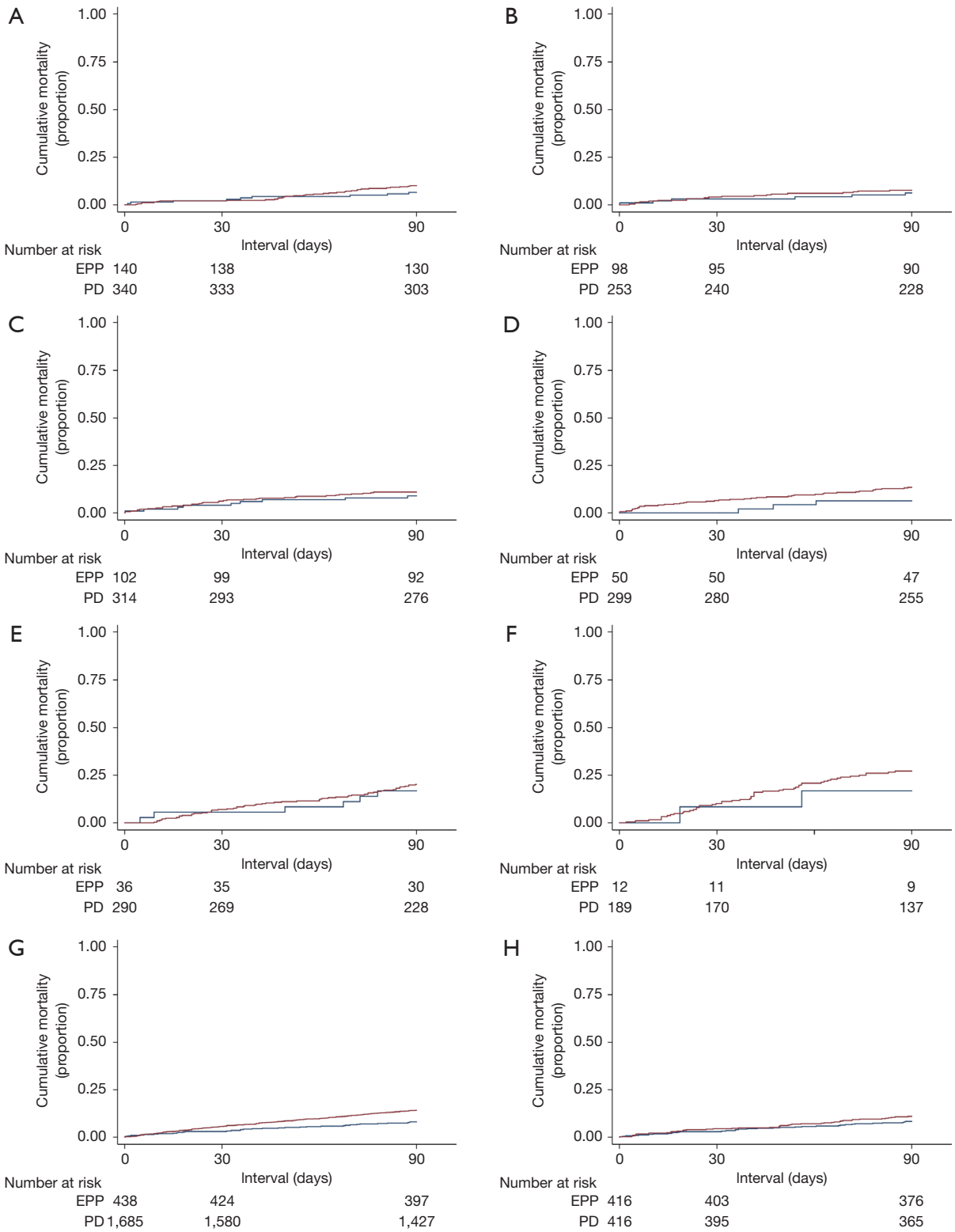

Figure 2 Cumulative incidence of short-term mortality in patients having received extrapleural pneumonectomy (EPP, blue) and pleurectomy/decortication (P/D, red) in patients aged ≤60 (A), 61–65 (B), 66–70 (C), 71–75 (D), 76–80 (E), ≥81 years (F), all patients (G), and following propensity matching (H).

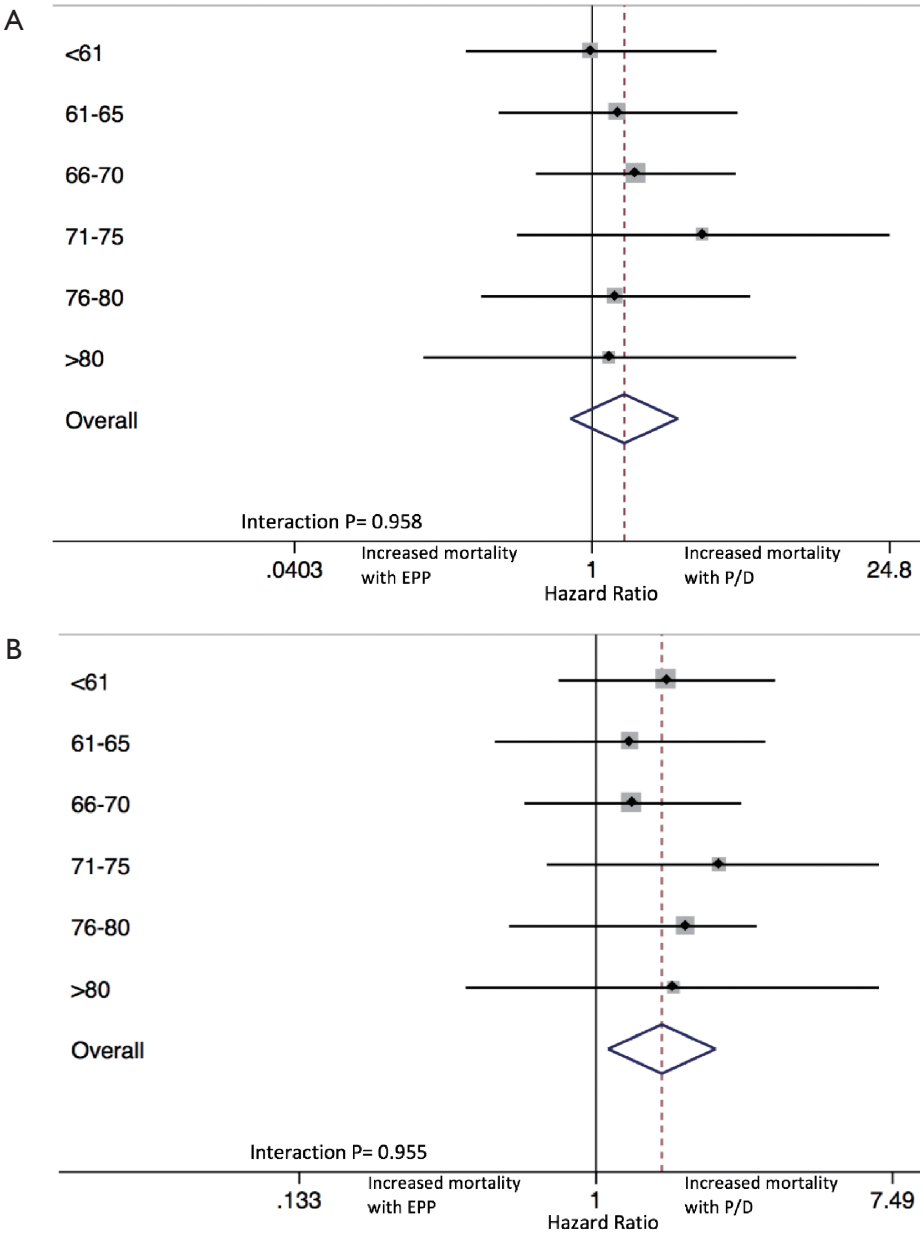

Figure 3 Forest plots of interaction testing in the unadjusted cohort at 30 (A) and 90 days (B) between the six age-based subgroups as part of the comparison between extrapleural pneumonectomy (EPP) and pleurectomy/decortication (P/D).

MPM conveys a poor short-term prognosis irrespective of surgical versus nonoperative management. Herein, we sought to corroborate that the short-term mortality conveyed by EPP or P/D was not associated with increases in baseline short-term mortality compared to nonoperative management. Additionally, a major limitation of including both induction and postoperative chemotherapy (cycles and agents of which are not given in the NCDB) is that every operated patient who received induction chemotherapy remained alive until resection; in other words, those who died following induction were likely a part of the nonoperative group. Next, it is acknowledged that the nonoperative subjects, who have known gender biases (36), were a notably heterogeneous population, comprising of those who were "fit" enough to tolerate chemotherapy (likely resulting in the significant association with 30- and

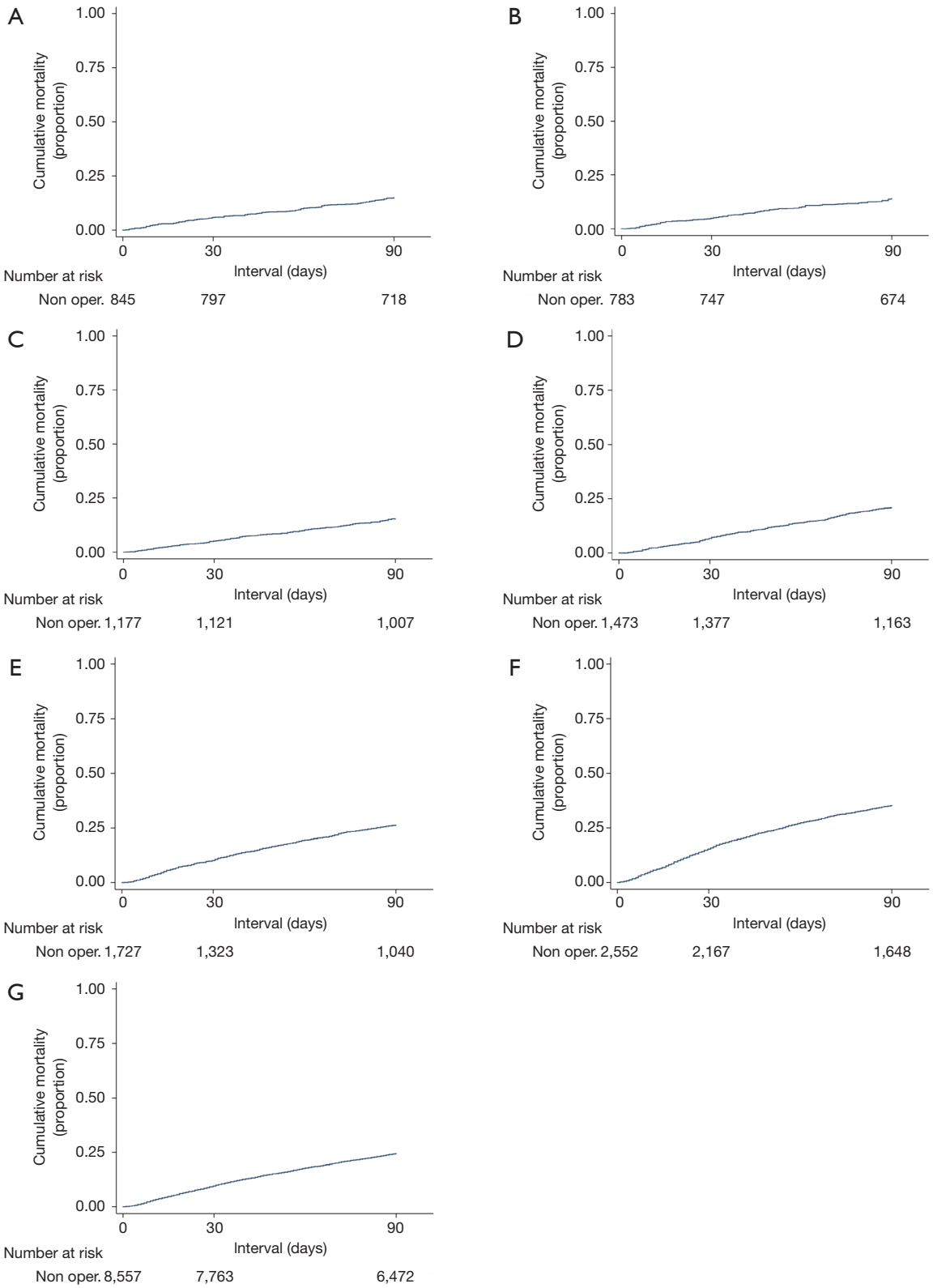

Figure 4 Cumulative incidence of short-term mortality in the nonoperative patients aged ≤60 (A), 61–65 (B), 66–70 (C), 71–75 (D), 76–80 (E), ≥81 years (F), and all patients (G).

Table 4 Univariable Cox proportional hazards model for 30- and 90-day mortality

Parameter	30-day mortality		90-day mortality	
	HR (95% CI)	P value	HR (95% CI)	P value
Age				
Continuous variable	1.056 (1.048–1.064)	<0.001*	1.050 (1.045–1.055)	<0.001*
Gender				
Male	REF	REF	REF	REF
Female	0.993 (0.848–1.162)	0.926	0.985 (0.892–1.087)	0.761
Race				
White	REF	REF	REF	REF
Black	1.126 (0.832–1.525)	0.441	1.057 (0.869–1.286)	0.577
Other	0.864 (0.560–1.332)	0.509	0.847 (0.645–1.112)	0.232
Charlson-Deyo comorbidity index				
0	REF	REF	REF	REF
1	1.659 (1.431–1.923)	<0.001*	1.460 (1.329–1.604)	<0.001*
2+	2.574 (2.147–3.085)	<0.001*	2.287 (2.032–2.574)	<0.001*
Insurance type				
Private	REF	REF	REF	REF
Medicaid	2.987 (1.956–4.562)	<0.001*	1.604 (1.166–2.207)	0.004*
Medicare	2.204 (1.819–2.669)	<0.001*	1.839 (1.646–2.054)	<0.001*
Other	1.710 (1.120–2.612)	0.013*	1.309 (0.999–1.716)	0.050*
Uninsured	1.297 (0.681–2.472)	0.429	1.472 (1.042–2.082)	0.029*
Income (US dollars/year)				
<$63,000	REF	REF	REF	REF
≥$63,000	0.811 (0.703–0.936)	0.004*	0.766 (0.699–0.838)	<0.001*
Unknown	1.100 (0.786–1.540)	0.578	0.976 (0.782–1.219)	0.831
Patient residence				
Metro	REF	REF	REF	REF
Urban	1.222 (1.019–1.465)	0.031*	1.194 (1.064–1.340)	0.003*
Rural	1.313 (0.832–2.070)	0.242	1.135 (0.836–1.541)	0.417
Unknown	1.079 (0.808–1.441)	0.608	1.088 (0.908–1.305)	0.359
Facility type				
Academic	REF	REF	REF	REF
Community	1.655 (1.424–1.923)	<0.001*	1.569 (1.431–1.721)	<0.001*
Unknown	1.129 (0.420–3.033)	0.810	1.025 (0.549–1.914)	0.939
Case volume (quartile)				
1–4	REF	REF	REF	REF
5–9	0.981 (0.748–1.288)	0.895	0.952 (0.796–1.138)	0.586

Table 4 (*continued*)

Table 4 (*continued*)

Parameter	30-day mortality		90-day mortality	
	HR (95% CI)	P value	HR (95% CI)	P value
10–19	0.830 (0.643–1.070)	0.150	0.862 (0.730–1.018)	0.080
20+	0.591 (0.461–0.759)	<0.001*	0.691 (0.588–0.812)	<0.001*
Years of diagnosis				
2004–2005	REF	REF	REF	REF
2006–2007	1.028 (0.852–1.241)	0.774	0.927 (0.825–1.041)	0.201
2008–2009	0.991 (0.820–1.199)	0.929	0.919 (0.818–1.033)	0.159
2010–2011	0.922 (0.753–1.290)	0.432	0.827 (0.729–0.938)	0.003
2012–2013	1.144 (0.907–1.444)	0.256	0.962 (0.829–1.116)	0.609
Clinical T classification				
T1	REF	REF	REF	REF
T2	0.913 (0.745–1.120)	0.384	0.942 (0.833–1.065)	0.338
T3+	0.809 (0.629–1.041)	0.099	0.927 (0.801–1.072)	0.306
TX	1.496 (1.276–1.755)	<0.001*	1.292 (1.169–1.428)	<0.001*
Clinical N classification				
N0	REF	REF	REF	REF
N1	0.884 (0.570–1.372)	0.583	0.919 (0.703–1.200)	0.533
N2	0.941 (0.737–1.202)	0.629	1.070 (0.926–1.237)	0.357
N3	0.645 (0.288–1.444)	0.286	0.864 (0.561–1.331)	0.507
NX	1.496 (1.276–1.755)	<0.001*	1.358 (1.245–1.481)	<0.001*
Histology				
Epithelioid	0.440 (0.358–0.540)	<0.001*	0.310 (0.274–0.350)	<0.001*
Biphasic	0.659 (0.492–0.883)	0.005*	0.491 (0.410–0.587)	<0.001*
Sarcomatoid	REF	REF	REF	REF
Unknown	0.847 (0.705–1.016)	0.074	1.088 (0.908–1.305)	<0.001*
Surgical technique				
Nonoperative	REF	REF	REF	REF
Extrapleural pneumonectomy	0.580 (0.468–0.718)	<0.001*	0.549 (0.480–0.628)	<0.001*
Pleurectomy/decortication	0.305 (0.177–0.583)	<0.001*	0.303 (0.217–0.424)	<0.001*
Chemotherapy				
No	REF	REF	REF	REF
Yes	0.056 (0.042–0.075)	<0.001*	0.168 (0.150–0.188)	<0.001*
Unknown	0.277 (0.171–0.448)	<0.001*	0.448 (0.351–0.572)	<0.001*
Induction chemotherapy				
No	REF	REF	REF	REF
Yes	0.344 (0.184–0.642)	0.001*	0.249 (0.158–0.391)	<0.001*
Unknown	0.955 (0.820–1.111)	0.548	1.066 (0.972–1.169)	0.175

*, statistically significant P values. Only items in the final multivariable model are shown. HR, hazard ratio; CI, confidence interval.

Table 5 Multivariable Cox proportional hazards model for 30- and 90-day mortality

Parameter	30-day mortality		90-day mortality	
	HR (95% CI)	P value	HR (95% CI)	P value
Age				
Continuous variable	1.020 (1.012–1.029)	<0.001*	1.022 (1.017–1.027)	<0.001*
Charlson-Deyo comorbidity index				
0	REF	REF	REF	REF
1	1.435 (1.236–1.664)	<0.001*	1.315 (1.196–1.444)	<0.001*
2+	1.882 (1.567–2.261)	<0.001*	1.766 (1.567–1.990)	<0.001*
Insurance type				
Private	REF	REF	REF	REF
Medicaid	2.737 (1.783–4.203)	<0.001*	1.644 (1.191–2.268)	0.002*
Medicare	1.577 (1.283–1.945)	0.018*	1.110 (0.984–1.252)	0.090
Other	1.249 (0.814–1.915)	0.308	0.945 (0.719–1.241)	0.684
Uninsured	1.387 (0.724–2.654)	0.324	1.507 (1.062–2.138)	0.021*
Income (US dollars/year)				
<$63,000	REF	REF	REF	REF
≥$63,000	0.952 (0.820–1.106)	0.520	0.861 (0.784–0.946)	0.002*
Unknown	1.717 (0.963–3.062)	0.067	1.094 (0.771–1.554)	0.614
Patient residence				
Metro	REF	REF	REF	REF
Urban	1.194 (0.988–1.444)	0.067	1.163 (1.031–1.312)	0.014*
Rural	1.159 (0.731–1.837)	0.531	0.991 (0.728–1.350)	0.956
Unknown	0.756 (0.460–1.242)	0.269	0.990 (0.744–1.317)	0.946
Facility type				
Academic	REF	REF	REF	REF
Community	1.069 (0.910–1.256)	0.415	1.107 (1.004–1.222)	0.042*
Unknown	2.236 (0.811–6.164)	0.120	2.563 (1.352–4.861)	0.004*
Case volume (quartile)				
1–4	REF	REF	REF	REF
5–9	0.977 (0.743–1.285)	0.870	0.948 (0.792–1.136)	0.564
10–19	0.878 (0.679–1.135)	0.320	0.895 (0.757–1.058)	0.193
20+	0.731 (0.565–0.945)	0.017*	0.834 (0.707–0.984)	0.032*
Years of diagnosis				
2004–2005			REF	REF
2006–2007			0.918 (0.817–1.032)	0.151

Table 5 (*continued*)

Table 5 (*continued*)

Parameter	30-day mortality		90-day mortality	
	HR (95% CI)	P value	HR (95% CI)	P value
2008–2009			0.954 (0.847–1.074)	0.435
2010–2011			1.001 (0.876–1.142)	0.992
2012–2013			1.097 (0.939–1.282)	0.242
Clinical T classification				
T1	REF	REF	REF	REF
T2	1.091 (0.888–1.340)	0.409	1.093 (0.965–1.238)	0.161
T3	1.031 (0.799–1.330)	0.815	1.120 (0.967–1.299)	0.131
TX	1.367 (1.109–1.684)	0.003*	1.097 (0.962–1.250)	0.167
Clinical N classification				
N0	REF	REF	REF	REF
N1	1.295 (0.833–1.014)	0.251	1.289 (0.986–1.687)	0.064
N2	1.196 (0.935–1.530)	0.154	1.323 (1.143–1.531)	<0.001*
N3	0.880 (0.392–1.975)	0.756	1.142 (0.740–1.762)	0.549
NX	1.034 (0.853–1.253)	0.733	1.107 (1.066–1.367)	0.003*
Histology				
Epithelioid	0.560 (0.455–0.690)	<0.001*	0.363 (0.320–0.411)	<0.001*
Biphasic	0.941 (0.701–1.263)	0.684	0.650 (0.543–0.779)	<0.001*
Sarcomatoid	REF	REF	REF	REF
Unknown	0.784 (0.652–0.943)	0.010*	0.568 (0.509–0.633)	<0.001*
Surgical technique				
Nonoperative	REF	REF	REF	REF
Extrapleural pneumonectomy	0.815 (0.651–1.020)	0.074	0.772 (0.672–0.886)	<0.001*
Pleurectomy/decortication	0.597 (0.335–1.063)	0.080	0.630 (0.448–0.885)	0.008*
Chemotherapy				
No	REF	REF	REF	REF
Yes	0.061 (0.043–0.085)	<0.001*	0.212 (0.189–0.239)	<0.001*
Unknown	0.342 (0.211–0.555)	<0.001*	0.544 (0.426–0.695)	<0.001*
Induction chemotherapy				
No	REF	REF	REF	REF
Yes	4.241 (2.105–8.545)	<0.001*	1.735 (1.071–2.811)	0.025*
Unknown	0.936 (0.804–1.090)	0.395	1.082 (0.703–1.664)	0.722

*, statistically significant P values. Only items in the final multivariable model are shown. HR, hazard ratio; CI, confidence interval.

90-day mortality on Cox modeling) as well as those too frail to receive any oncologic therapy. These disparate patients were deliberately merged similar to an intention-to-treat analysis, where patients are analyzed together regardless of whether they were able to receive the intervention. It also allowed for a more "real-world" viewpoint of expected mortality rates (rather than artificial inflation if the supportive care subjects were removed, for instance). Furthermore, specific selection criteria influencing the surgical approach, including patient characteristics and surgeon's preferences, are not made available via the NCDB and represents an additional limitation of this study. Lastly, although the NCDB includes data for 70% of the United States population, only CoC-accredited facilities contribute data; as such, these findings may not necessarily be representative of the entire United States population.

Conclusions

As MPM management remains controversial, a quantitative understanding of mortality risk (and predictors thereof) for several treatment approaches is thus critical to better refine patient selection. The largest such study of its kind, this investigation of a large, contemporary national database quantitates age-associated 30- and 90-day mortality of EPP and P/D, which should be considered when potentially operable patients are counseled regarding the risks and benefits of resection.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). As all patient information in the NCDB is de-identified, this study was exempt from institutional review board evaluation. The NCDB Participant User File corresponding to mesothelioma [2004–2013] was utilized for this study.

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