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Determinants of Mortality Among US Patients Diagnosed With Malignant Pleural Mesothelioma Over the Past Decade

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Abstract

Background: Malignant Pleural Mesothelioma (MPM) is a primary pleural tumor with scarce prognostic data estimates given its rarity. This study aims to explore the epidemiologic and survival predictors amongst patients with MPM, extending from the largest and most recent study conducted between 1973 and 2009.

Methods: 3384 patients diagnosed with MPM between 2010 and 2017 were enrolled from the Surveillance, Epidemiology, and End Results (SEER) database. Demographics, clinical characteristics, overall mortality (OM), and cancer-specific mortality (CSM) estimates were analyzed. Multivariate Cox model was used to identify independent prognostic factors, where a hazard ratio (HR) greater than 1 denotes adverse prognostic factors.

Results: Our cohort revealed a male predominance (77.16%), with over 80% diagnosed after age 59, peaking between 60 and 79 years old (60.17%). Epithelioid mesothelioma (41.78%), non-Hispanic whites (78.13%), and diagnosis at distant stage (71.60%) were the most common subgroups in their respective categories. 365 patients (10.79%) lacked pleural effusion at diagnosis. In multivariate analyses, higher overall mortality (OM) was associated with male gender (HR = 1.24, 95% CI 1.14–1.37, $p < 0.01$), age >80 years (HR = 2.17, 95% CI 1.41–3.35, $p < 0.01$), fibrous mesothelioma (HR = 2.21, 95% CI 1.95–2.51, $p < 0.01$), and distant stage (HR = 1.55, 95% CI 1.34–1.81, $p < 0.01$). Higher cancer-specific mortality (CSM) was associated with male gender (HR = 1.25, 95% CI 1.13–1.38, $p < 0.01$), age >80 years (HR = 2.02, 95% CI 1.29–3.15, $p < 0.01$), fibrous mesothelioma (HR = 2.24, 95% CI 1.97–2.55, $p < 0.01$), and distant stage (HR = 1.59, 95% CI 1.36–1.87, $p < 0.01$). Lower OM and CSM was observed in patients who underwent any type of treatment. Nonmalignant pleural effusion, based on histology, was associated with higher CSM (HR = 1.22, 95% CI 1.05–1.4, $p < 0.05$).

Conclusion: Fibrous mesothelioma, older age, and distant disease were associated with increased mortality. All intervention strategies were associated with improved survival outcomes. Earlier diagnosis may improve outcomes, as available interventions are associated with lower mortality when feasible at diagnosis. The study paves the way for further prospective and retrospective studies to focus on the identification of patient subsets that may benefit from early mesothelioma screening.

Keywords: Malignant pleural mesothelioma, Uncommon cancers, Tumor epidemiology, Rare malignancies, Rare oncology

1. Introduction

Mesothelioma, primarily arising from the pleural cavity, is linked to asbestos exposure

in about two-thirds of cases.^{1,2} Other implicated factors include ionizing radiation to supra-diaphragmatic fields,³ carbon nanotube exposure, Simian virus 40 (SV40), and BAP1 somatic

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mutations.^{4–7} Symptoms include chest pain, cough, hoarseness, etc.⁸ and disease progression can lead to complications like superior vena cava syndrome, bowel obstruction from mass effect through the diaphragm, arrhythmias, and neurologic deficits with spinal cord compression.⁹ Initial diagnosis involves contrast-enhanced chest CT, pleural effusion analysis, and biopsy. Treatment typically involves platinum-based chemotherapy with pemetrexed, with or without tumor resection.¹⁰ Despite a comprehensive study from 1973 to 2009, gaps exist in understanding baseline epidemiology and independent prognostic factors and determinants of survival in the past decade. To address this, using a large US population-based dataset, we aimed to assess clinical characteristics and independent prognostic factors among MPM patients.

2. Methods

2.1. Study design

A population-based retrospective cohort study utilized the SEER research data, specifically the Nov 2020 submission database (<http://www.seer.cancer.gov>), from 17 registries, sponsored by the United States National Cancer Institute (US NCI). The SEER Program is a leading source of cancer-related data in the United States, comprising 18 population-based cancer registries, collecting cancer incidence, clinicopathological features, and survival data, for about 28% of the U.S. population.¹² The SEER database is a publicly available dataset providing de-identified patient data. Thus, the need for an IRB approval was waived.

2.2. Data selection

2.2.1. Inclusion criteria

All patients with MPM diagnosed from 2010 to 2017 were selected from the SEER database based on (1) Primary site [c38.4] and (2) histological type [ICD-O-3: 9050, 9051, 9052, 9053].

2.2.2. Exclusion criteria

The study excluded patients with unknown age at diagnosis, race, or stage of MPM.

2.3. Study variables

2.3.1. Main exposure

All the variables included in this cohort except the year of diagnosis were used as main predictors of prognosis.

2.3.2. Outcomes

Overall mortality due to any cause at the end of the study was categorized as “yes”, and patients who survived were classified as “no”.

Cancer-specific mortality, referring to patients who died of MPM at the end of the study, was categorized as “yes”, and patients dying of other causes were classified as “no”.

2.3.3. Survival months

Survival time for overall mortality was calculated from diagnosis to death or the last follow-up date (December 31, 2017), as reported in the SEER registry. Similarly, for cancer-specific mortality, survival time was calculated from diagnosis to MPM-related death or the last follow-up date, as recorded in the SEER registry.

2.3.4. Sociodemographic and tumor characteristics

Extracted variables include age at diagnosis, gender, race (White, Black, and others), origin (Non-Hispanic and Hispanic), stage at diagnosis (localized, regional, and distant), geographic residential area, yearly income, marital status, year of diagnosis, surgery, and radiation.

2.4. Statistical analysis

The Cox proportional hazard regression model assumes proportional hazard rates over time. Variables with a p-value <0.1 in the univariate Cox regression model were included in the multivariate Cox proportional analyses to identify independent prognostic factors for overall mortality (OM) and cancer-specific mortality (CSM), where a hazard ratio (HR) greater than 1 indicates adverse prognostic factors. All tests were two-sided, with a 95% confidence interval, and a p-value <0.05 was considered statistically significant. The statistical analysis was conducted using STATA 18.0 software.

3. Results

Patients in our study, as detailed in [Table 1](#), were predominantly male (77.16%), with most diagnoses occurring between 60 and 79 years of age (60.17%). Epithelioid MPM (41.78%) was the prevalent histological group, while biphasic MPM was the least common (9.81%). The majority of patients were married (66.4%) and had distant metastasis at the time of diagnosis (71.6%). Non-Hispanic Whites constituted the majority (78.13%), with a prevalent annual income of \$75,000+ (38.03%) and residence in metropolitan areas (60.02%). Feasible surgical resection of the primary tumor was observed in up

Table 1. Demographic and Clinicopathologic characteristics of US patients diagnosed with Malignant Pleural mesothelioma between 2010 and 2017.

Characteristics	N=	%
Total	3384	100
Gender		
Female	773	22.84
Male	2611	77.16
Age at diagnosis, y.o		
0–39	29	0.86
40–59	368	10.87
60–79	2036	60.17
80+	951	28.10
Histologic subtype		
Epithelioid mesothelioma	1414	41.78
Fibrous mesothelioma	384	11.35
Malignant mesothelioma, NOS	1254	37.06
Biphasic mesothelioma	332	9.81
Marital status		
Married	2248	66.43
Single	357	10.55
Divorced/separated	278	8.22
Widowed	501	14.80
Tumor stage		
Localized	339	10.02
Regional by direct extension only	354	10.46
Regional lymph nodes involved only	101	2.98
Regional by both direct extension and lymph node involvement	167	4.93
Distant	2423	71.60
Race		
Non-Hispanic white	2644	78.13
Non-Hispanic black	163	4.82
Hispanic	418	12.35
Other	159	4.70
Living area		
Counties in metropolitan areas of 1 million persons	2031	60.02
Counties in metropolitan areas of 250,000 to 1 million persons	720	21.28
Counties in metropolitan areas of 250,000 persons	250	7.39
Nonmetropolitan counties adjacent to a metropolitan area	237	7.00
Nonmetropolitan counties not adjacent to a metropolitan area	146	4.31
Income per year		
\$< \$55,000	551	16.28
\$55,000–64,999	639	18.88
\$65,000–74,999	907	26.80
\$75,000+	1287	38.03
Radiation		
No	2993	88.45
Yes	391	11.55
Chemotherapy		
No	1616	47.75
Yes	1768	52.25
Surgery ± radiation		
No	3154	93.20
Yes	230	6.80
Surgery		
No	2492	73.64
Yes	892	26.36

(continued on next page)

Table 1. (continued)

Characteristics	N=	%
Pleural effusion		
None	365	10.79
Benign	726	21.45
Malignant	1308	38.65
Pleural effusion, NOS	985	29.11
Year of diagnosis		
2010	430	12.71
2011	458	13.53
2012	431	12.74
2013	431	12.74
2014	394	11.64
2015	437	12.91
2016	401	11.85
2017	402	11.88

to a third of patients (26.36%), and approximately half underwent chemotherapy (52.25%). A combination of surgery and radiation was administered to 230 patients (6.80%), and 391 patients (11.55%) underwent radiation. Pleural effusion was absent in up to 10% of patients (see Table 1).

Table 2 illustrates the univariate analysis of factors influencing overall mortality (OM) and cancer-specific mortality (CSM). Higher OM was associated with male gender (HR = 1.29, 95% CI 1.19–1.41, $p < 0.01$), age >80 years (HR = 2.88, 95% CI 1.89–4.41, $p < 0.01$), age group 60–79 years (HR = 2.01, 95% CI 1.32–3.06, $p < 0.01$), fibrous epithelioma (HR = 2.39, 95% CI 2.12–2.70, $p < 0.01$), widowed patients (HR = 1.19, 95% CI 1.07–1.32, $p < 0.01$), distant metastasis (HR = 1.30, 95% CI 1.15–1.47, $p < 0.01$), and residence in nonmetropolitan counties not adjacent to a metropolitan area. The aforementioned covariates were associated with higher CSM. Improved OM and CSM was associated with surgical resection of the primary tumor (HR = 0.59, 95% CI 0.54–0.64, $p < 0.01$), chemotherapy (HR = 0.67, 95% CI 0.62–0.72, $p < 0.01$), radiation therapy (HR = 0.73, 95% CI 0.66–0.82, $p < 0.01$), a combination of surgery and radiation (HR = 0.55, 95% CI 0.47–0.63, $p < 0.01$), and an annual income of \$75,000+ (HR = 0.86, 95% CI 0.78–0.96, $p < 0.01$).

Multivariate regression analyses, adjusting for covariates in Table 3, revealed higher OM in male patients (HR = 1.24, 95% CI 1.14–1.37, $p < 0.01$), elderly patients aged >80 years (HR = 2.17, 95% CI 1.41–3.35, $p < 0.01$), fibrous mesothelioma (HR = 2.21, 95% CI 1.95–2.51, $p < 0.01$), and patients with distant metastasis (HR = 1.55, 95% CI 1.34–1.81, $p < 0.01$). CSM mortality was also higher in these groups and amongst patients with pleural effusion with negative cytology (HR = 1.22, 95% CI 1.05–1.4, $p < 0.05$). Lower OM and CSM were

Table 2. Crude analysis of factors associated with all-cause mortality and MPM related mortality among US patients between 2010 and 2017.

Characteristics	Overall mortality Crude hazard ratio (95% confidence interval)	MPM-specific mortality Crude hazard ratio (95% confidence interval)
Gender		
Female	1 (reference)	1 (reference)
Male	1.29 (1.19–1.41) **	1.31 (1.19–1.43) **
Age at diagnosis, y.o		
0–39	1 (reference)	1 (reference)
40–59	1.37 (0.89–2.11)	1.35 (0.87–2.10)
60–79	2.01 (1.32–3.06) **	1.92 (1.25–2.96) **
80+	2.88 (1.89–4.41) **	2.72 (1.76–4.19) **
Histologic subtype		
Epithelioid mesothelioma	1 (reference)	1 (reference)
Fibrous mesothelioma	2.39 (2.12–2.70) **	2.42 (2.14–2.74) **
Malignant mesothelioma, NOS	1.47 (1.35–1.59) **	1.41 (1.29–1.54) **
Biphasic mesothelioma	1.45 (1.28–1.65) **	1.46 (1.28–1.67) **
Marital status		
Married	1 (reference)	1 (reference)
Single	1.03 (0.92–1.17)	1.02 (0.90–1.16)
Divorced/separated	1.05 (0.92–1.19)	1.03 (0.89–1.19)
Widowed	1.19 (1.07–1.32) **	1.16 (1.04–1.29) **
Tumor stage		
Localized	1 (reference)	1 (reference)
Regional by direct extension only	0.97 (0.83–1.14)	1.01 (0.85–1.19) *
Regional lymph nodes involved only	1.25 (0.98–1.59)	1.22 (0.94–1.58)
Regional by both direct extension and lymph node involvement	1.09 (0.89–1.33)	1.17 (0.96–1.44)
Distant	1.30 (1.15–1.47) **	1.34 (1.18–1.53) **
Race		
Non-Hispanic white	1 (reference)	1 (reference)
Non-Hispanic black	1.03 (0.87–1.22)	1.01 (0.85–1.21)
Hispanic	1.03 (0.92–1.15)	0.96 (0.86–1.08)
Other	0.99 (0.84–1.19)	0.95 (0.79–1.14)
Living area		
Counties in metropolitan areas of 1 million persons	1 (reference)	1 (reference)
Counties in metropolitan areas of 250,000 to 1 million persons	0.99 (0.90–1.08)	0.99 (0.90–1.09)
Counties in metropolitan areas of 250,000 persons	1.05 (0.91–1.21)	1.05 (0.91–1.22)
Nonmetropolitan counties adjacent to a metropolitan area	1.14 (0.98–1.31)	1.18 (1.02–1.37) *
Nonmetropolitan counties not adjacent to a metropolitan area	1.23 (1.03–1.47) *	1.28 (1.07–1.53) **
Income per year		
\$< \$55,000	1 (reference)	1 (reference)
\$55,000–64,999	0.95 (0.84–1.07)	0.95 (0.84–1.08)
\$65,000–74,999	0.92 (0.82–1.03)	0.9 (0.80–1.01)
\$75,000+	0.86 (0.78–0.96) **	0.86 (0.77–0.97) *
Surgery ± radiation		
No	1 (reference)	1 (reference)
Yes	0.55 (0.47–0.63) **	0.55 (0.48–0.64) **
Chemotherapy		
No	1 (reference)	1 (reference)
Yes	0.67 (0.62–0.72) **	0.69 (0.64–0.74) **
Radiation		
No	1 (reference)	1 (reference)
Yes	0.73 (0.66–0.82) **	0.75 (0.67–0.84) **
Surgery		
No	1 (reference)	1 (reference)
Yes	0.59 (0.54–0.64) **	0.58 (0.54–0.64) **
Pleural effusion		
None	1 (reference)	1 (reference)
Benign	1.09 (0.96–1.26)	1.15 (0.99–1.33)
Malignant	1.16 (1.02–1.32) *	1.21 (1.06–1.38) **
Pleural effusion, NOS	1.14 (1.01–1.31) *	1.19 (1.03–1.36) *

**p < 0.01, *p < 0.05.

Table 3. Multivariate cox proportional hazard regression analyses of factors affecting all-cause mortality and MPM related mortality among US patients between 2010 and 2017.

Characteristics	Overall mortality Crude hazard ratio (95% confidence interval)	MPM-specific mortality Crude hazard ratio (95% confidence interval)
Gender		
Female	1 (reference)	1 (reference)
Male	1.24 (1.14–1.37) **	1.25 (1.13–1.38) **
Age at diagnosis, y.o		
0–39	1 (reference)	1 (reference)
40–59	1.31 (0.84–2.02)	1.28 (0.82–2.01)
60–79	1.78 (1.17–2.74) **	1.68 (1.08–2.59) *
80+	2.17 (1.41–3.35) **	2.02 (1.29–3.15) **
Histologic subtype		
Epithelioid mesothelioma	1 (reference)	1 (reference)
Fibrous mesothelioma	2.21 (1.95–2.51) **	2.24 (1.97–2.55) **
Malignant mesothelioma, NOS	1.24 (1.14–1.35) **	1.19 (1.09–1.30) **
Biphasic mesothelioma	1.58 (1.39–1.79) **	1.58 (1.39–1.81) **
Marital status		
Married	1 (reference)	1 (reference)
Single	1.13 (0.99–1.27)	1.12 (0.98–1.27)
Divorced/separated	1.13 (0.99–1.29)	1.11 (0.97–1.28)
Widowed	1.09 (0.98–1.23)	1.09 (0.97–1.23)
Tumor stage		
Localized	1 (reference)	1 (reference)
Regional by direct extension only	1.06 (0.9–1.25)	1.09 (0.92–1.29)
Regional lymph nodes involved only	1.28 (0.99–1.64)	1.26 (0.97–1.64)
Regional by both direct extension and lymph node involvement	1.39 (1.14–1.71) **	1.50 (1.22–1.85) **
Distant	1.55 (1.34–1.81) **	1.59 (1.36–1.87) **
Race		
Non-Hispanic white	1 (reference)	1 (reference)
Non-Hispanic black	1.08 (0.91–1.28)	1.06 (0.89–1.28)
Hispanic	1.11 (0.99–1.24)	1.03 (0.91–1.16)
Other	1.09 (0.91–1.29)	1.02 (0.85–1.23)
Living area		
Counties in metropolitan areas of 1 million persons	1 (reference)	1 (reference)
Counties in metropolitan areas of 250,000 to 1 million persons	0.99 (0.9–1.09)	0.99 (0.90–1.09)
Counties in metropolitan areas of 250,000 persons	1.05 (0.89–1.24)	1.05 (0.89–1.24)
Nonmetropolitan counties adjacent to a metropolitan area	1.02 (0.86–1.21)	1.07 (0.89–1.28)
Nonmetropolitan counties not adjacent to a metropolitan area	1.1 (0.89–1.36)	1.15 (0.93–1.42)
Income per year		
\$< \$55,000	1 (reference)	1 (reference)
\$55,000–64,999	0.97 (0.85–1.11)	0.99 (0.87–1.15)
\$65,000–74,999	0.97 (0.84–1.12)	0.97 (0.84–1.13)
\$75,000+	0.96 (0.84–1.11)	0.99 (0.85–1.15)
Surgery ± radiation		
No	1 (reference)	1 (reference)
Yes	0.68 (0.54–0.86) **	0.68 (0.53–0.86) **
Chemotherapy		
No	1 (reference)	1 (reference)
Yes	0.74 (0.69–0.80) **	0.77 (0.71–0.83) **
Radiation		
No	1 (reference)	1 (reference)
Yes	1.09 (0.93–1.29)	1.13 (0.96–1.35)
Surgery		
No	1 (reference)	1 (reference)
Yes	0.76 (0.69–0.84) **	0.73 (0.66–0.81) **
Pleural effusion		
None	1 (reference)	1 (reference)
Benign	1.15 (0.99–1.32)	1.22 (1.05–1.4) *
Malignant	0.97 (0.83–1.13)	1.02 (0.87–1.21)
Pleural effusion, NOS	0.95 (0.81–1.10)	0.98 (0.84–1.16)

**p < 0.01, *p < 0.05.

associated with available interventions, such as a combination of surgery and radiation, chemotherapy, and radiation alone.

4. Discussion

In this US-based study on malignant pleural mesothelioma (MPM), we observed a male and non-Hispanic White predominance, consistent with existing literature. Over half of our cohort (52.25%) underwent chemotherapy, highlighting its prevalent use. Our findings identified key determinants of mortality, encompassing tumor stage, age, gender, histologic subtype, and pleural fluid cytology.

The observed male and White predominance aligns with existing literature.¹¹ Consistent with prior studies, epithelioid MPM emerged as the predominant histologic subtype, constituting two-thirds of cases (41.78%).¹³ While pleural effusion typically accompanies the diagnosis, our study revealed a slight deviation, with up to 10% of our cohort lacking pleural effusion at the time of diagnosis.¹⁴

Analysis of socioeconomic and demographic factors unveiled that the majority of MPM patients resided in metropolitan areas, with an annual income exceeding \$75,000 (38.03%). This association underscores the challenging and delayed diagnosis of MPM, a process necessitating extensive testing that individuals with higher income and those residing in metropolitan areas are more likely to afford and access.^{15–18}

Survival trends aligned with the findings of Taioli's previous research, showcasing improved outcomes in younger patients, females, and those diagnosed at an early stage.¹¹ This trend was noted in univariate analysis. Multivariate analysis further revealed enhanced survival amongst female patients, those with earlier disease stages, and younger patients. Similar to Taioli's study, our analysis demonstrated that all available interventions were associated with lower mortality. Despite these positive associations, the overall prognosis for MPM remains bleak, with overall survival ranging from 9 to 17 months post-diagnosis due to late diagnosis.^{19–21} Our investigation emphasizes the critical need to identify patient subsets that could benefit from early MPM screening, given the statistically significant association between early diagnosis and improved outcomes for this malignancy characterized by an otherwise dismal prognosis.

Concerning pleural effusion, our study deviates from historical prognostic patterns. While malignant pleural effusion has been associated with aggressive disease in various malignancies,²² our data reveals that over the past decade, pleural

effusion did not impact overall mortality. However, patients with pleural effusion and negative cytology exhibited a higher CSM in various cancers^{23,24} and no effect on OM, indicating complications of MPM, rather than the disease itself as a driving factor. Notably, advanced MPM can lead to heart failure, and parapneumonic effusion, further complicating the clinical picture.²⁵

4.1. Strengths and limitations

This study's strength lies in its reliance on the largest cancer database in the USA that enabled enrolment of an adequate sample size for such a rare pathologic entity. Despite the valuable insights provided by our study, several limitations exist that can be addressed by further research. Absence of data on immunotherapy and comorbidities coupled with incomplete estimates on chemotherapy in the SEER database are notable shortcomings. Further research looking at these variables can yield important therapeutic and prognostic information.

5. Conclusions

This study assessing the epidemiologic and mortality outcomes amongst MPM patients over the past decade yielded important prognostic information. Treatment improves overall and cancer-specific mortality statistics, but most cases are intercepted at advanced stages, thereby resulting in a dismal prognosis. Pleural effusion as a complication worsens prognosis. Further studies to determine the efficacy of comprehensive monitoring protocols and early intervention strategies could help optimize survival outcomes in these patients.

Statement of ethics

The SEER Dataset was a public-use dataset, of which the informed consent was waived.

Funding sources

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Data availability statement

The data used and/or analyzed in this study are available in the Surveillance, Epidemiology, and End Results (SEER) Database of the National Cancer Institute (<http://seer.cancer.gov>).

Conflict of interest statement

No potential conflict of interest was reported by the authors.

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