







RESEARCH ARTICLE

REVISED Factors influencing malignant mesothelioma survival: a retrospective review of the National Mesothelioma Virtual Bank cohort [version 3; peer review: 2 approved, 1 approved with reservations]

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Abstract

Background: Malignant mesothelioma (MM) is a rare but deadly malignancy with about 3,000 new cases being diagnosed each year in the US. Very few studies have been performed to analyze factors associated with mesothelioma survival, especially for peritoneal presentation. The overarching aim of this study is to examine survival of the cohort of patients with malignant mesothelioma enrolled in the National Mesothelioma Virtual Bank (NMVB).


Methods: 888 cases of pleural and peritoneal mesothelioma cases were selected from the NMVB database, which houses data and associated biospecimens for over 1400 cases that were diagnosed from 1990 to 2017. Kaplan Meier’s method was performed for survival analysis. The association between prognostic factors and survival was estimated using Cox Hazard Regression method and using R software for analysis.

Results: The median overall survival (OS) rate of all MM patients,

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including pleural and peritoneal mesothelioma cases is 15 months (14 months for pleural and 31 months for peritoneal). Significant prognostic factors associated with improved survival of malignant mesothelioma cases in this NMVB cohort were younger than 45, female gender, epithelioid histological subtype, stage I, peritoneal occurrence, and having combination treatment of surgical therapy with chemotherapy. Combined surgical and chemotherapy treatment was associated with improved survival of 23 months in comparison to single line therapies.

Conclusions: There has not been improvement in the overall survival for patients with malignant mesothelioma over many years with current available treatment options. Our findings show that combined surgical and chemotherapy treatment in peritoneal mesothelioma is associated with improved survival compared to local therapy alone.

Keywords

Mesothelioma, Survival analysis. Cox hazard regression analysis, Biobanking, Risk factor

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REVISED Amendments from Version 2

We have included co-authors in this version who are collaborators of National Mesothelioma Virtual Bank and provide specimens and data to the resource. They have been involved in the design of the work, providing resources, reviewing and edit the manuscript and finally approved the revised version 3.

See referee reports

Introduction

Malignant mesothelioma is a rare and fatal malignancy, associated with occupational and environmental exposure to asbestos. As per [American Cancer Society](#), approximately 3000 new cases are diagnosed per year in the United States. The pleura is the primary site of mesothelioma occurrence, but it also occurs at other sites (pericardium, peritoneum, tunica vaginalis testis)^{1,2}. For pleural mesothelioma, the median overall survival age ranges from 21 months (for Stage I) to 12 month (for Stage IV) disease³. In the 1970s, the incidence of mesothelioma cases started to increase, and it became evident that the occupational and environmental exposures to asbestos (occurring during 1930s–1970s) were associated with the increased incidence of this fatal disease⁴. Despite regulations aimed to ban the industrial use of asbestos by US Occupational Safety and Health Administration (OSHA) in 1970, data do not suggest a decline in the incidence of malignant mesothelioma in the U.S.⁵. However, the impact of these changes are difficult to assess due to the fact that mesothelioma is typically diagnosed decades after the initial asbestos exposure⁶. A recent multisite cohort investigation reported that the median time of diagnosis from the first environmental exposure was 38.4 years (IQR 31.3–45.4 years)⁷. Both genetics and environmental exposure plays a critical role in acquiring malignant mesothelioma. BAP1 is the only gene reported to be in a causal pathway for malignant mesothelioma development in connection with asbestos exposure. BAP1 germ line mutation has been found to be a risk factor for the development of malignant mesothelioma in families where the mutation is found in 50% of members. This mutation has also found to be linked to the development of BAP1 cancer syndrome, characterized by an increased incidence of malignant mesothelioma, uveal and cutaneous melanoma, and melanocytic BAP1-mutated atypical intradermal tumors^{8,9}.

The majority of pleural malignant mesothelioma cases in men and women are linked to exposure to asbestos. Asbestos particle exposure can occur from indoor and outdoor commercial and naturally occurring asbestos. Naturally Occurring Asbestos (NOA) concentration in soil is commonly below the threshold for detection by light microscopy but nevertheless can still cause potential hazardous airborne exposure. Detection of environmental exposure to NOA is much more challenging than detection of commercial exposure to asbestos. Activity based sampling is considered to be very important for health risk assessment and to characterize the environmental exposure^{10,11}. Another approach is to study high risk populations and screen patients with benign pleural disease through radiographic imaging. Previous

research has also explored the differences between the development of malignant mesothelioma in patients that had environmental exposure like NOA, and those that have genetic risk factors in conjunction with occupational exposure (even at a low level). In cases of malignant mesothelioma that have been linked to environmental exposure, BAP1 mutations have mainly been seen in younger population with equal gender and pleural/peritoneal distribution^{12,13}.

After pleura, the peritoneum is the second most frequent site of origin of mesothelioma¹⁴. Epidemiological studies of peritoneal mesothelioma are limited by the rarity of this disease, as well as by possible geographic and temporal variations in diagnostic practice¹⁵. While survival for patients with peritoneal mesothelioma is more favorable, with patients surviving up to 60 months^{16,17}, limited number of studies have explored factors affecting the survival of peritoneal mesothelioma.

However, given the rarity of the disease, few databases have sufficient number of cases and treatment data to make analysis of therapeutic options with statistical significance possible. NMVB is an especially valuable resource for mesothelioma research, as beyond its capability as a biorepository it includes well annotated data for populations residing in Pennsylvania and New York states (two of the top 5 states for mesothelioma-associated mortality)¹⁸. Previous SEER (Surveillance, Epidemiology and End Result Program) based studies exploring factors that influence mesothelioma have not included populations residing in Pennsylvania and New York¹⁹.

Previously published research of pleural mesothelioma suggest that histological type (epithelioid) and early stages are associated with improved survival following surgical treatment²⁰. Other predictive factors explored in previously published literature including gender, advanced age, weight loss, chest pain, poor performance status, as well as low hemoglobin, leukocytosis, and thrombocytosis. It has been suggested that female patients with mesothelioma have a better life expectancy as compared to male patients²¹.

Currently there are few therapeutic options, including surgery, chemotherapy, radiation therapy and a combination of these options that may significantly improve the overall survival from this deadly disease²². Considering the aggressive nature and poor prognosis associated with this disease, improving our existing knowledge regarding the biology of the disease and factors predictive of the efficacy of existing therapeutic options and treatment regimens for malignant mesothelioma is critical.

In this study, we analyzed malignant mesothelioma cases from the [National Mesothelioma Virtual Bank](#) (NMVB) to evaluate the effect of clinical, pathological, and epidemiological factors, and therapeutic options as determinants of overall survival. Thus our study adds geographic breadth to the existing mesothelioma research knowledge. Additionally, our dataset includes cases of peritoneal mesothelioma, which were not the focus of previous studies.

Methods

Ethical considerations

This study is conducted under the Institutional Review Board (IRB) approval (IRB #0608194) of NMVB and its supporting sites, with approval from the principal investigator of NMVB to use the de-identified data from the resource.

Data source

The patient cohort for this study (n=888) is selected from the NMVB resource, which contains data and biospecimens from both pleural and peritoneal malignant mesothelioma cases. The NMVB database records treatment type in general categories of “cancer directed surgery alone, surgery combined with chemotherapy, as well as surgery combined with chemotherapy and radiation”. The specific details of treatment (such as exact surgery type of type of chemotherapy regimen used) are not recorded in the NMVB. The NMVB enrolls patients from NMVB collaborating sites (New York University, University of Pennsylvania, University of Maryland, Roswell Park Cancer Institute and University of Pittsburgh Medical Center), located in the north east region of the USA. This geographic emphasis has the potential for a selection bias as few patients are enrolled from the other regions of the country due to NMVB network coverage. NMVB was developed to collect mesothelioma biospecimens and data from prospectively consented as well as retrospectively identified patients, which allows for capture of both previous and currently treated cases of mesothelioma.

Patient selection

Demographic, treatment, clinical and survival information of histologically confirmed pleural and peritoneal mesothelioma patients diagnosed between 1999 and 2017 were obtained from the NMVB database. Inclusion criteria included the following: confirmed diagnosis of malignant mesothelioma (limited to pleural and peritoneal presentation), availability of complete data on age, gender, race, asbestos exposure, smoking history, history of alcohol use, histological type, site of tumor, disease stage (for pleural presentation), vital status, and survival duration. Exclusion criteria included the following: benign mesothelioma, and tumor site other than pleura and peritoneum. This investigation was limited to the most common histological subtypes of diffuse malignant mesothelioma including biphasic, epithelial or epithelioid, and sarcomatoid. The desmoplastic histology subtype is classified as sarcomatoid, and papillary mesothelioma as epithelial or epithelioid^{23,24}. For the purpose of this study, tumor anatomic site is classified into two main categories: pleura (which includes visceral/parietal pleura and lung, chest wall, ribs) and peritoneum (includes peritoneal cavity and organs involved). This analysis focused on 888 participants that met the inclusion criteria. Patient characteristics are presented in [Table 1](#). Case selection flow is presented in [Figure 1](#).

Definition of staging and metastatic disease

We have performed analysis of staging data for pleural mesothelioma cases that have undergone surgical resection, however used a surrogate staging system for peritoneal mesothelioma as there is no formal TNM staging system for peritoneal malignant

Table 1. Patient characteristics.

Variables	Number of patients
Age	888
18–44	49
45–54	102
55–64	266
65–74	312
75 +	161
Gender	888
Male	683
Female	205
Anatomic Site	888
Pleural	740
Peritoneum	148
Histology	888
Epithelial or epithelioid	636
Biphasic	165
Sarcomatoid	87
Race	820
European American	792
Non-European American	28
History of Smoking	641
Yes	364
No	277
History of Asbestos Exposure	531
Yes	413
No	118
Stage Group (limited to pleural cases)	381
I	178
II	24
III	157
IV	22
Therapy Type	477
Surgery	101
Surgery + Chemo	327
Surgery + Chemo + Radiation	49

mesothelioma. We converted the TNM staging of pleural mesothelioma into stage grouping as per [College of American Pathology \(CAP\) protocol 2017 for pleural malignant mesothelioma](#). Metastatic disease status was defined as the tumor spread from the point of origin to the lymph node and other organs in the body.

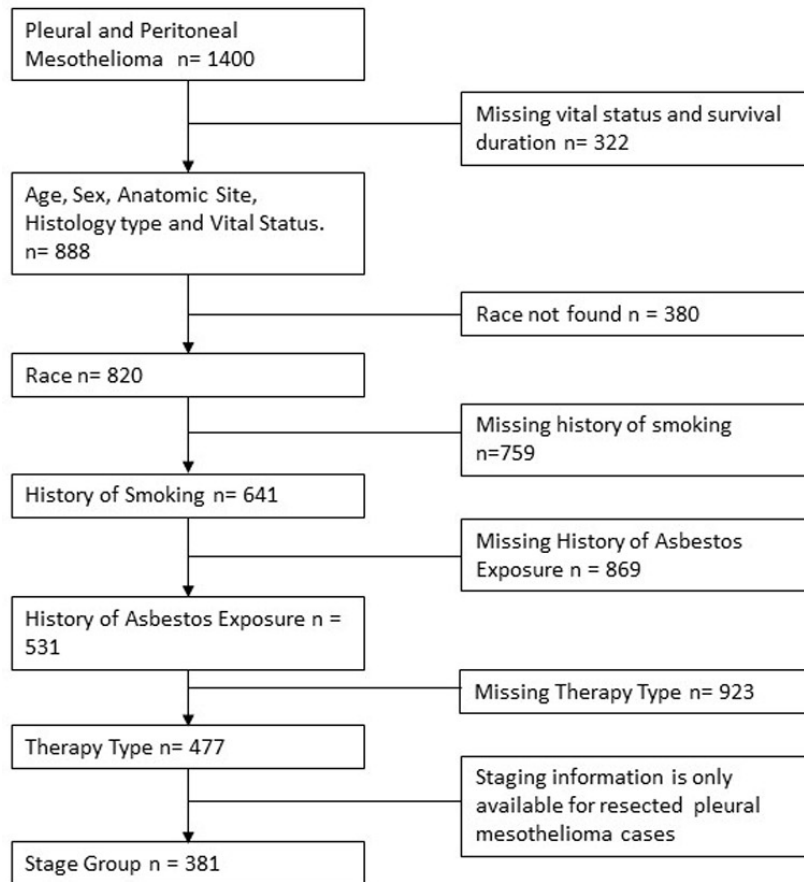


Figure 1. Study workflow and case inclusion and exclusion criteria.

Statistical analyses

We included the following variables in the analysis: age, gender, race, smoking history, history of alcohol, asbestos exposure, site of tumor, histological type, treatment, staging and outcome variables including vital status and survival period. Duration of observation was defined as time (in months) between date of initial diagnosis until death (vital status = expired) or the date of last known contact for each participant. Smoking history was analyzed as a dichotomous variable (yes/no), where current, past and smoking for a brief period of time, were grouped as positive history of smoking (yes). The contribution of the three treatment types on mesothelioma survival rate is evaluated in this study.

We constructed survival curves using the Kaplan-Meier method for the entire dataset, followed by a separate analysis limited to female patients. We also performed a separate Kaplan-Meier analysis for peritoneal cases only. We performed Log-rank test of equality across strata for categorical variables. We analyzed the independent contribution to mesothelioma survival of several prognostics with univariable and multivariable regression methods based on the Cox proportional hazards model. Variables were entered into the model using a forward selection approach, starting with the most significant variable (based on the

unadjusted p-value) and then continuing in order of significance. We analyzed factors contributing to mesothelioma survival separately for cases with complete data and with missing data to rule out any systematic bias associated with cases with missing data. Two-tailed p-values less than 0.05 were considered significant. We used [The R Project](#) (version 3.4.0) for Statistical Computing to perform all analysis²⁵.

Results

The majority of patients were European American (97%) and male (77%). History of smoking was reported by 364 (57 %) patients among n=641 and history of asbestos exposure was reported in 413 cases (78 %) among n= 531. Epithelial or epithelioid histological subtype was the most prevalent histology in 71.4% of cases in this dataset (n = 636). Cancer directed surgery was performed in 54 % cases, while surgery and chemotherapy treatment jointly was administered in 37% of cases. The median overall survival of the cohort was 15 months. [Table 2](#) and [Figure 3](#) demonstrate the results of the univariable and multivariable analysis respectively (Cox proportional hazard regression models).

Overall, the non-parametric univariate Kaplan Meier analysis and log rank tests demonstrated longer survival in younger

Table 2. Unadjusted Cox Hazard Regression Analysis, predictors of mesothelioma survival (n=888). Ref – Reference group.

Variable	Hazard ratio	95% Confidence interval	p value for trend
Age			
18–44	1.00	Ref	
45–54	2.0	1.3-3	P=0.001
55–64	2.3	1.6-3.3	P<0.001
65–74	2.7	1.8-3.9	P<0.001
75+	3.4	2.3-5.1	P<0.001
Gender			
Female	1.0	Ref	
Male	1.6	1.4-1.9	P<0.001
Anatomic site			
Peritoneum	1.0	Ref	
Pleural	2.1	1.7-2.6	P<0.001
Therapy			
Surgery	1.0	Ref	
Surgery, chemo	0.49	0.39-0.62	P<0.001
Surgery, chemo, radiation	0.63	0.44-0.90	P=0.011
Smoking history			
No	1.0	Ref	
Yes	1.2	1-1.5	P=0.022
Stage (pleural cases only)			
I	1.0	Ref	
II	1.3	0.82-2.0	P<0.27
III	1.7	1.31-2.1	P<0.001
IV	2.0	1.24-3.2	P=0.004
Histology			
Biphasic	1.0	Ref	
Epithelial or epithelioid	0.48	0.40-0.57	P<0.001
Sarcomatoid	0.97	0.74-1.26	P=0.797
Race			
Non European American	1.0	Ref	
European American	1.8	1.1-2.8	P<0.012
Asbestos Exposure			
Yes	1.0	Ref	
No	0.61	0.48-0.78	P<0.001

age group (18–44 years), female gender, with no known asbestos exposure history, epithelioid histological type, combined surgical and chemotherapy, Stage I, or peritoneum presentation (Figure 2a–2i).

The median survival for age group 18–44 years was 59 months (95% CI: 34 - 91) but much less favorable for the age group

75 and over, at 10 months (95% CI: 9 – 13). The median survival for females was 22 months (95% CI: 18 - 30) as compared to 14 months for males (95% CI: 13-16). The group with no reported history of asbestos exposure had a median survival rate of 20 months (95% CI: 16 - 31), as compared to median survival of 15 months (95% CI: 13-17) for the group with reported exposure. The epithelioid histological type median had a

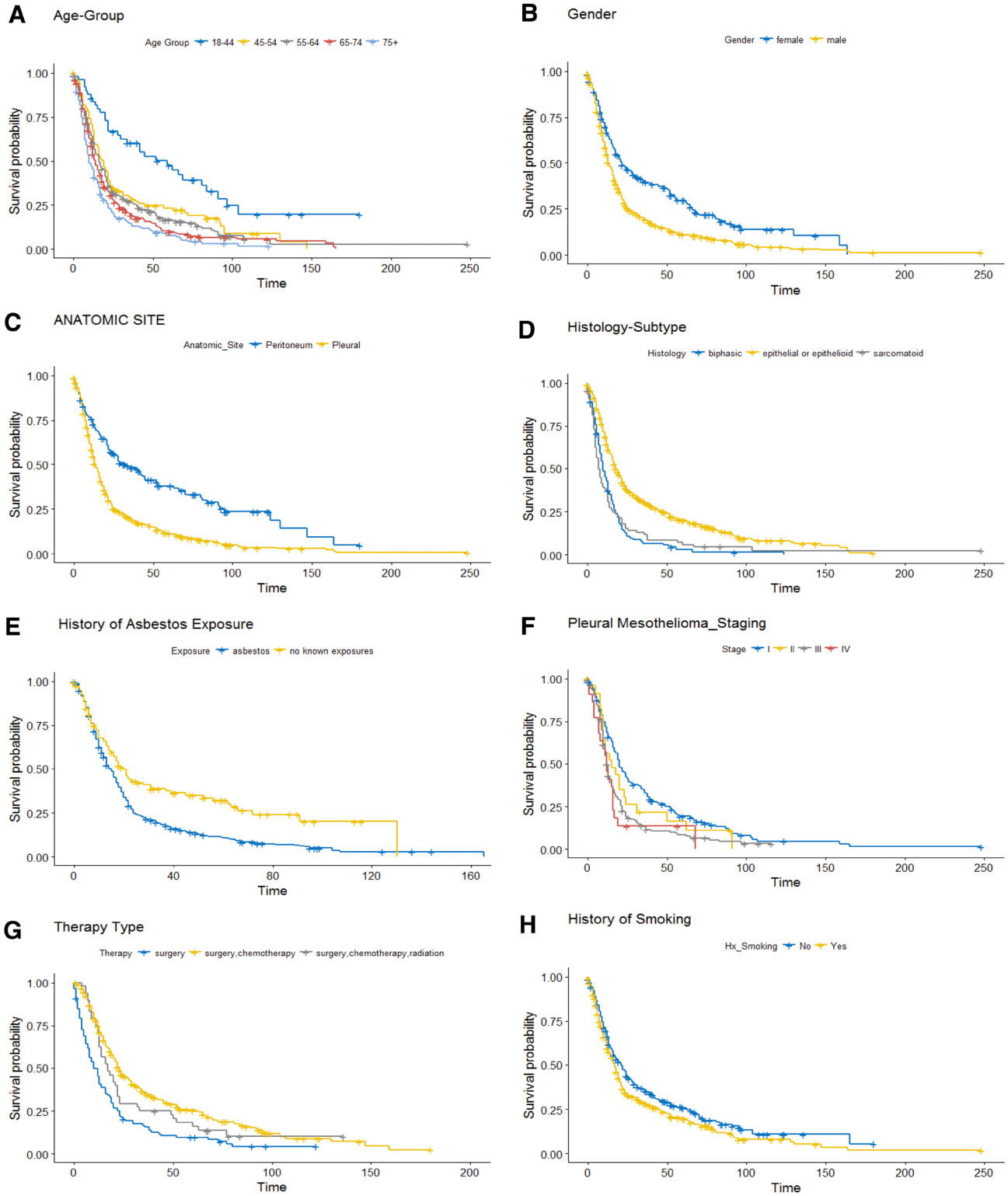


Figure 2. Kaplan Meier Curve analysis performed at age (a), gender (b), anatomic site (c), histology subtype (d), history of asbestoses exposure (e), staging (pleural mesothelioma) (f), therapy type (g), and history of smoking (h).

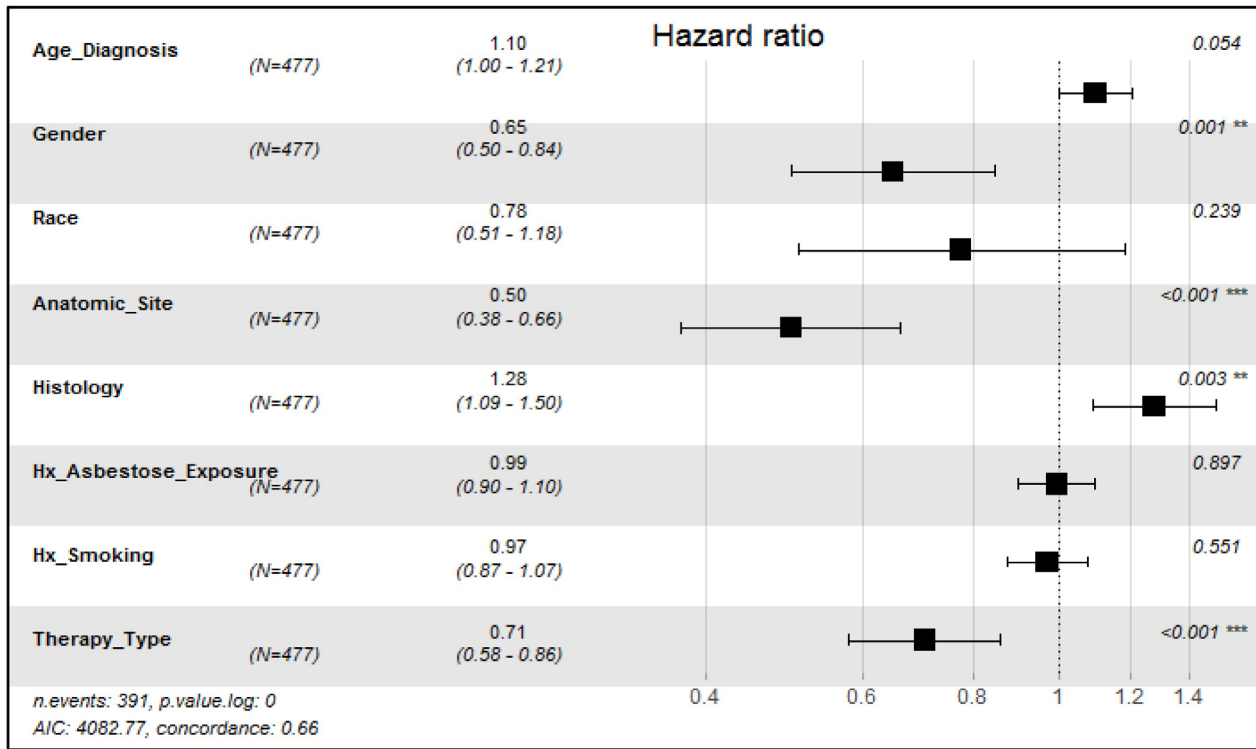


Figure 3. Adjusted Cox Hazard analysis, predictors of mesothelioma survival, multivariable analysis (n=477).

median survival of 18 months (95% CI: 17-21) as compared to 10 months for biphasic (95% CI: 9-13) and 7 months for sarcomatoid subtype (95%CI: 6-11). The European American group had a median survival of 15 months (95% CI: 13 – 16) as compare to median survival of 34 months (95% CI: 21-83) in non-European American population. The analysis suggests patients receiving combined therapies [(surgical and chemotherapy (95% CI: 13-19), surgical plus chemotherapy and radiation therapy (95% CI: 10-21)] had a more favorable median survival period in comparison to those with single line surgical therapy (95% CI: 8-14). Overall, median OS was most favorable (23 months (95% CI 21 to 27 months)) for patients treated with combined surgery and chemotherapy. Adding radiation to chemotherapy did not improve survival.

The median survival period for stage I group (including stages IA and IB) was 20 months (95% CI: 18 – 25) as compared to 12 months for stages III and IV. Presentation in the peritoneum site and no history of smoking was also associated with improved survival (Figure 1). When stratified by anatomic site of tumor, the median survival period among patients with peritoneal mesothelioma, who received surgical and chemotherapy, demonstrated longer survival of 28 months (95% CI: 28 – 45) as compared to 14 months (95% CI: 11 – 17) in patients with pleural mesothelioma.

Overall, multivariable analysis confirmed that younger age groups, female gender, peritoneal anatomic site, combination

of surgery and chemotherapy, no history of smoking, early stage (I and II), and epithelial histology were all predictors of more favorable survival (Table 2).

In addition, we performed multivariable cox hazard proportional analysis on the complete dataset of n= 477 which had no missing record variables that has obtained from the primary dataset (n= 888). We included all the predictive prognostic variables except for stage, because there is no established TNM staging for peritoneal mesothelioma. We presented these results as supplementary analysis in Figure 3.

Discussion and conclusion

The focus of this study has been on the exploration of risk factors affecting mortality in the states of Pennsylvania and New York, which represent a region with an aging population, environmental concerns, well documented history of asbestos exposure, and other risk factors associated with mesothelioma development. This region has not been comprehensively covered in previously reported investigations. In addition to expanding the geographic region in this study, another added value of this study is that we explored factors contributing to survival for peritoneal mesothelioma separately from those for the more prevalent pleural mesothelioma. Survival analysis on the NMVB cohort demonstrated that patient age younger than 45, female gender, epithelioid histological subtype, Stage I of the disease, peritoneum as primary site and surgical therapy combined with chemotherapy were favorable prognostic factors. This

study corroborates the analysis of the SEER data by Taioli *et al.* suggesting that female gender, younger age, early stage, and surgery alone are all good prognostic factors¹⁹. This study also corroborates previous investigations suggesting that peritoneal presentation, especially among women, is associated with longer survival²⁶.

Consistent with the literature, our data suggests that women have longer survival in comparison to men, which may be due to factors like lower levels of smoking amongst females and/or different levels of environmental exposure^{21,27–30}. Specifically, women may be more likely to have para-occupational exposures, which typically refer to an asbestos-exposed worker serving as a vector for the transport of fibers to the household setting and family members. Other terms used in this context include household contact, take-home exposure or domestic exposure³¹. Exact factors explaining survival advantage among women needs to be further investigated in future research.

Strengths of this study include the use of a very large dataset collected utilizing uniform data collection protocol. The weaknesses of this study include lack of detailed data on specific surgical treatment type and also the fact that exposure data is self-reported and not corroborated by radiologic analyses. We also recognize that our population may not be representative of the entire population of mesothelioma patients, as large number of patients in the general population are not good surgical candidates. Additionally, while we attempted to obtain detailed occupational exposure data for asbestos and other substances, participants' ability to recall the duration and details of their exposure is a potential source of bias. In our future investigations, we will also focus on BAP1 mutations. We will also focus our investigation on patients who are not surgical candidates, including from ethnic minorities, and younger patients.

Malignant mesothelioma is a life-threatening condition that has been under-investigated and warrants greater investigation, considering that it is a lethal disease associated with high mortality with short survival and its incidence has not shown signs of improvement over the past several decades. Further studies are needed to evaluate screening, diagnostic, staging and treatment for various subtypes of mesothelioma.

In the future, it would be particularly interesting to include in the cohort cases that do not qualify for surgical management because of advanced disease. An improved understanding of factors associated with mesothelioma morbidity and mortality may help identify high-risk groups based on different occupational exposures. Such groups may be further evaluated for responsiveness to innovative management strategies for mesothelioma. The identification of these factors could help stratify patients at risk for therapy failure who may benefit from novel interventions or could avoid treatments that are not effective or with high mortality risk. We hope our report underscored the significant value of NMVB as a national research resource pairing data and biospecimens which are made available (through an application process) to the entire research community. We envision that in the future, existing information and biospecimen repositories like NMVB will be harnessed to greater extent and foster greater investigation studies into rare diseases like mesothelioma.

Data availability

An investigator can obtain de-identified data from National Mesothelioma Virtual Bank by application process: 1) submit a letter of intent (LOI) (<https://mesotissue.org/node/26>) to the NMVB (email address). The NMVB Research Evaluation Panel (REP), composed of extramural scientists with varied expertise including laboratory science, lung pathology, mesothelioma, and statistics (<https://mesotissue.org/rep>) then reviews requests for scientific merit and provides recommendations for approval. Thereafter once a data (or material in case of request for biospecimen) use agreement (DUA) has been concluded between investigator and NMVB, the data (or biospecimen) can be provided to the applicant.

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I agree with Dr Amin that this a very valuable study, describing 1% of national (USA) mesothelioma cases, that were not part of the SEER database. In the revised version the outcomes of this prognostic factors study have been discussed in detail, while the limitations of the dataset were clearly addressed. The results from previous prognostic factors studies are mostly confirmed. The prognostic data of patients with peritoneal mesothelioma, who received combined modality treatment, are considered especially important and may well assist in drafting guidelines for this selected group of patients.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 19 October 2018

<https://doi.org/10.5256/f1000research.16914.r39375>

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Tobias Peikert

Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA

This manuscript summarizes the data from a large cohort of patients with pleural and peritoneal mesothelioma from the National Mesothelioma Virtual Tissue Bank (NMVB). The cases are from New York and Pennsylvania. The study confirms findings from prior analysis of the SEER database, which did not include patients from these states. Patient survival is dependent on age, gender, disease stage, disease site (pleural versus peritoneal), histological subtype and presence of multi-modality therapy. However there are several limitations.

1. As with most large mesothelioma databases surgically treated patients are over represented. In fact only 10-15% of patients with mesothelioma are candidates for surgery and most patients are treated with systemic chemotherapy. Consequently despite being a large cohort the study population is not representative of the majority of mesothelioma patients. Future studies should include a representative proportion of non-surgical patients.
2. The conclusions about differences in therapy are difficult to interpret since not detailed treatment data (curative versus palliative), R1 versus >R1 resection, type of surgery and type of radiation therapy are not collected. It is also not clear of the patients in fact completed all therapies listed. In addition treatment data was only available in a subset of patients.
3. In regards to the younger age patients BAP1 mutation status would be very helpful to explore. Some of this data should be available since the NMVB data set has been used for multiple correlative studies. It would be interesting to know if molecular analysis or immune staining are available for a subset of patients.
4. The observation of a trend towards improved survival for non-Caucasian Americans is also very interesting and deserves further exploration.

Minor comments:

The text on page 5 regarding the differences between the therapeutic groups should list the mean survival for the groups and not only the CI. (Also, could a single line of surgery been palliative pleurodesis?)

Page 6 the n for the primary data set should be changed from 88 to 888.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pulmonary Medicine and Thoracic Oncology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 13 Dec 2018

Waqas Amin, University of Pittsburgh, Pittsburgh, USA

1. We agree that our large cohort may not be representative of the general population of such patients and we recognize this weakness in the limitations section. NMVB cohort had very small number of cases that were not surgical candidates for their treatment of disease. We have not analyzed them because of insufficient number for meaningful statistical analysis.
2. The specific treatment information has not collected in NMVB database. However, in future studies we will pull the information of specific treatments and include them in the analysis. Again, this limitation is recognized in the paper.
3. We have highlight the issue related to younger age patients BAP1 mutation status in our introduction section paragraph 2. We would like to point out that we do not have such information in our database as of December 2018.
4. There is a significant number of non-European American participants in the NMVB cohort due to geographic location of resource and its participants. We will further explore racial differences in survival in our future papers.

Response to Minor Comments:

Corrected.

Competing Interests: No

Reviewer Report 10 October 2018

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Michele Carbone

Thoracic Oncology Program, University of Hawaii Cancer Center, Honolulu, HI, USA

This is a well done comprehensive report of analyses performed by a distinguished team of investigators who studied mesothelioma survival in the NMVB. The information presented is certainly useful to the scientific community. Most NMVB cases are from the States of New York and Pennsylvania where the Authors note there was significant exposure to asbestos.

Critiques:

1. Mesotheliomas developing in carriers of germline mutations have significant improved survival (see Consensus Report Carbone M., Kanodia S., et al¹). The lack of information about genetics is a limiting factor that should be acknowledged and that likely influences the finding that young age is a predictor of prolonged survival as these mesothelioma characteristically occur in young patients. In short this issue should be discussed.
2. The information about asbestos exposure is based on self-reported history. This information is often unreliable, as patients who think to have been exposed may not have been exposed and vice versa (asbestos is invisible by the naked eye so it is impossible to be certain whether dust contains or does not contain asbestos fibers, unless the dust is studied at the microscope), as shown for example by comparing results of lung content analyses and self-reported history of exposure: see, Carbone M. et al². The lack of corroborating evidence, such as radiological analyses supporting exposure –about 75% of patients exposed to asbestos develop bilateral plaques, should also be acknowledged.
3. Most recent studies report that presently most pleural mesotheliomas occur in asbestos-exposed individuals, and that instead patients with peritoneal mesothelioma rarely report asbestos exposure (for example only 5/64 patients in a recent series by Richard Alexander. Lee M et al³. (What was the proportion of self-reported asbestos exposure among patients with pleural or peritoneal mesothelioma?
4. **Introduction.** Mesothelioma is associated with exposure to professional exposure to asbestos and to environmental exposure to various mineral fibers including asbestos. Clarify this issue, and define what asbestos is. See Baumann F., Buck BJ, et al⁴; Baumann F et al⁵. Moreover, mesotheliomas develop in carriers of germline mutations of BAP1 (Carbone M., Kanodia S., JTO 2016⁶, and mutations of BAP1 may increase susceptibility to low doses of asbestos and other mineral fibers (Napolitano A., Pellegrini L., et al⁷). These issues are important to understand the reasons of the current ongoing mesothelioma epidemic and also given the different prognosis and survival of mesotheliomas occurring in carriers of BAP1 mutations.

Minor:

Abstract conclusion last line.....treatment IN PERITONEAL MESOTHELIOMA is associated with improved survival....

Page 3, introduction, bottom, therapeutic options: ref 15 in the rapidly evolving field of mesothelioma therapy is rather old. Replace or add current reference: the most recent review on this topic is Mutti L., Peikert T., et al⁸.

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Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: I have no competing interests to disclose. Dr. Carbone full disclosure: Dr. Carbone's research is funded by grants from: NCI, DoD, V Foundation, and UH Foundation: "Pathogenesis of malignant mesothelioma", through unrestricted donations. Funders listed above have no influence in the research conducted, publications, etc. In addition, Dr. Carbone has pending patent applications on BAP1, a patent using anti-HMGB1 monoclonal antibody or other HMGB1 antibodies as a novel mesothelioma therapeutic strategy, Patent No.: 9,561,274 issued, and a patent HMGB1 as a biomarker for asbestos exposure and mesothelioma early detection Application No.: 14/123,722 Patent No.: 9,244,074. Dr. Carbone is a board certified Pathologist and provides consultation for mesothelioma expertise and diagnosis, including paid medical-legal consulting.

Reviewer Expertise: mesothelioma and asbestos, environmental carcinogenesis, gene environment interaction, cancer syndromes

I confirm that I have read this submission and believe that I have an appropriate level of

expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 13 Dec 2018

Waqas Amin, University of Pittsburgh, Pittsburgh, USA

1. We have highlighted the importance mesotheliomas developing in carriers of germline mutations have significantly improved survival. In the limitations, we recognize the fact that we do not have genetic information.
 2. We discuss the issue environmental exposure (Natural Occurring Asbestos) and occupational exposure and their association with pleural and peritoneal mesothelioma in introduction section. We recognize that we do not have radiological analysis to support exposure and rely on self-reported data.
 3. In our cohort of analysis, the ratio of pleural mesothelioma with asbestos exposure to malignant peritoneal mesothelioma with asbestos exposure is 23:277.
 4. Information on various exposures and BAP1 has been added to the introduction
- We have updated the citations in the manuscripts and made minor corrections.

Competing Interests: No

Reviewer Report 29 August 2018

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888 cases (out of 1400 cases) enrolled in the NMVB, representing around 1% of all mesothelioma cases (occurring from 1900 till 2107) in the US, are being used for this prognostic factors study.

Comparing the distribution of patients in this study with epidemiological studies suggests that over-representation of surgical and peritoneal cases may be present in the series presented. Multivariate analyses in a skewed population may give rise to the wrong conclusions, and statistical/epidemiological advice is needed to assure that the conclusions from current analysis are valid.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Thoracic oncology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 08 Oct 2018

Waqas Amin, University of Pittsburgh, Pittsburgh, USA

We would like to thank Reviewer 1 for their thoughtful comments. We would like to point out that, while our paper focuses on 1% of national mesothelioma cases, describing this population is extremely valuable as this group of patients is not a part of SEER and has not been captured by previous research. Findings should be considered in the context of related findings from other populations. While the role of aggressive surgery remains controversial for this groups of patients, few epidemiological studies have evaluated treatment patterns of these patients. The significance of these results, consistent with Reviewer's comments, is further motivated by the fact that existing studies are flawed by their limited size and inclusion criteria. In the updated version of this paper, we commented (Discussion section) on selection of patients being a potential bias. We also commented on the fact that the treatment of our patients were consistent with ASCO guidelines. Also in the discussion, we pointed out that our conclusions are based on this particular group of patients and more extensive research needs to be implemented on the national and global level to draw more accurate conclusions.

We also acknowledge regression analysis may be insufficient to control for confounding if groups are not largely overlapping. In the case of single exposures or assessing treatment effectiveness, causal inference methods (e.g. propensity score-based methods) may be more appropriate. One of our co-authors (Landsittel) is very familiar with these methods, having served as a PI of a methods contract on the topic (see <https://www.pcori.org/research-results/2013/guidance-researchers-optimal-methods-conducting-comparative-effectiveness>). However, we did not feel that these methods were entirely applicable since the goals of this project focused on describing a range of risk factor

associations, which was still best accomplished through regression. Future analyses could focus on using such methods for more refined questions about a specific exposure. We have two coauthors, an epidemiologist (Linkov; associate professor of Ob/Gyn and Epidemiology) and a biostatistician (Landsittel; professor of biomedical informatics), who actively participated in the development of this paper, as well as data analysis. Their qualifications, that uniquely correspond to the primary focus of this research, are outlined below. Each has expertise in relevant methods, exposures and disease outcomes, has over 100 publications, and has 15-20 years of experience in research.

Competing Interests: none

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