RESEARCH ARTICLE

Factors influencing malignant mesothelioma survival: a retrospective review of the National Mesothelioma Virtual Bank cohort [version 1; referees: 1 approved, 2 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 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, 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 below the age of 45, female gender, epithelioid histological subtype, stage I, peritoneal occurrence, and had treatment that consisted of combining 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 is associated with improved survival compared to local therapy alone.

Keywords

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

Open Peer Review

Referee Status: ? ? ✓

	Invited Referees 1	2	3
version 1 published 03 Aug 2018	? report	? report	✓ report

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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) disease[3]. 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 disease[4]. 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 exposure[6]. 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].

After the pleura, the peritoneum is the second most frequent site of origin of mesothelioma. The epidemiological studies of peritoneal mesothelioma are complicated by the rarity of this disease, as well as by possible geographic and temporal variations in diagnostic practices[8]. While survival for patients with peritoneal mesothelioma is more favorable, with patients surviving up to 60 months[9,10], limited number of papers explored factors affecting the survival of peritoneal mesothelioma.

However, given the rarity of the disease, few databases have a 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 it includes populations residing in Pennsylvania and New York states (two of the top 5 states for mesothelioma-associated mortality)[11]. Previous SEER (Surveillance, Epidemiology and End Result Program) based studies exploring factors that influence mesothelioma did not include populations residing in Pennsylvania and New York[12].

Previously published research of pleural mesothelioma suggested that histological type (epithelioid) and early stages were associated with improved survival with surgical treatment[13]. 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 better life expectancy as compared to male patients[14].

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 disease[15]. 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 regiments 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 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 both pleural and peritoneal malignant mesothelioma cases. The NMVB database only records general treatment type including cancer directed surgery alone, surgery combined with chemotherapy, as well as surgery combined with chemotherapy and radiation. The specific type of treatment (such as exact surgery type of type of chemotherapy regimen used) is not recorded in the NMVB. NMVB enrolls patients from NMVB collaborative sites (New York University, University of Pennsylvania, University of Maryland, Roswell Park Cancer Institute and University of Pittsburgh Medical Center) in the north east region of country. Thus, there may be a selection bias with patients because there are few patients enrolled from the other regions of the country due to NMVB network coverage. In addition, NMVB has developed to collect mesothelioma biospecimens and data from prospectively consented retrospectively identified patients.

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), presence 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 period. 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 malignant mesothelioma including biphasic, epithelial or epithelioid, and sarcomatoid. The desmoplastic histology subtype is classified as sarcomatoid, and papillary mesothelioma as epithelial or epithelioid[16,17]. For the purpose of this study, the 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 to pleural mesothelioma cases that have surgical resections, there is no formal TNM staging system for peritoneal malignant 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. The metastatic disease status was defined as the tumor spread from the point of origin to the lymph node and other organs in the body.

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

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 prognostic 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 analysis[18].

Results

The majority of patients were European American (97%) and male (77%). Positive history of smoking has been reported by 364 (57 %) patients among n=641 and positive history of asbestos exposure has been reported by 413 cases (78 %) among n= 531. The epithelial or epithelioid histological subtype was the most prevalent histology in this dataset (n = 636), in 71.4% of cases. Cancer directed surgery has been performed in 54 % cases, while surgery and chemotherapy treatment jointly has been 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 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).

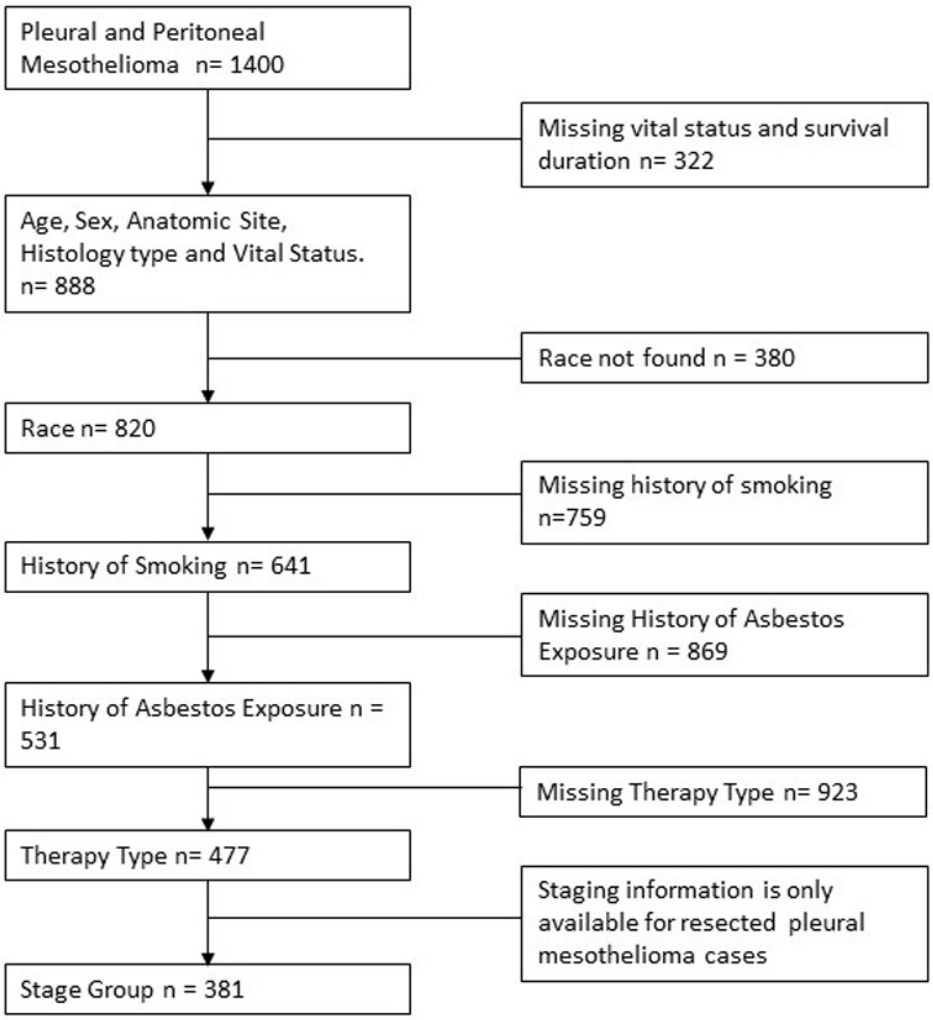

Figure 1. Study workflow and case inclusion and exclusion criteria.

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 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.

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	1.4.0-1.9 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

. 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= 88). We included all the predictive prognostic variables except for stage, because there is no established TNM

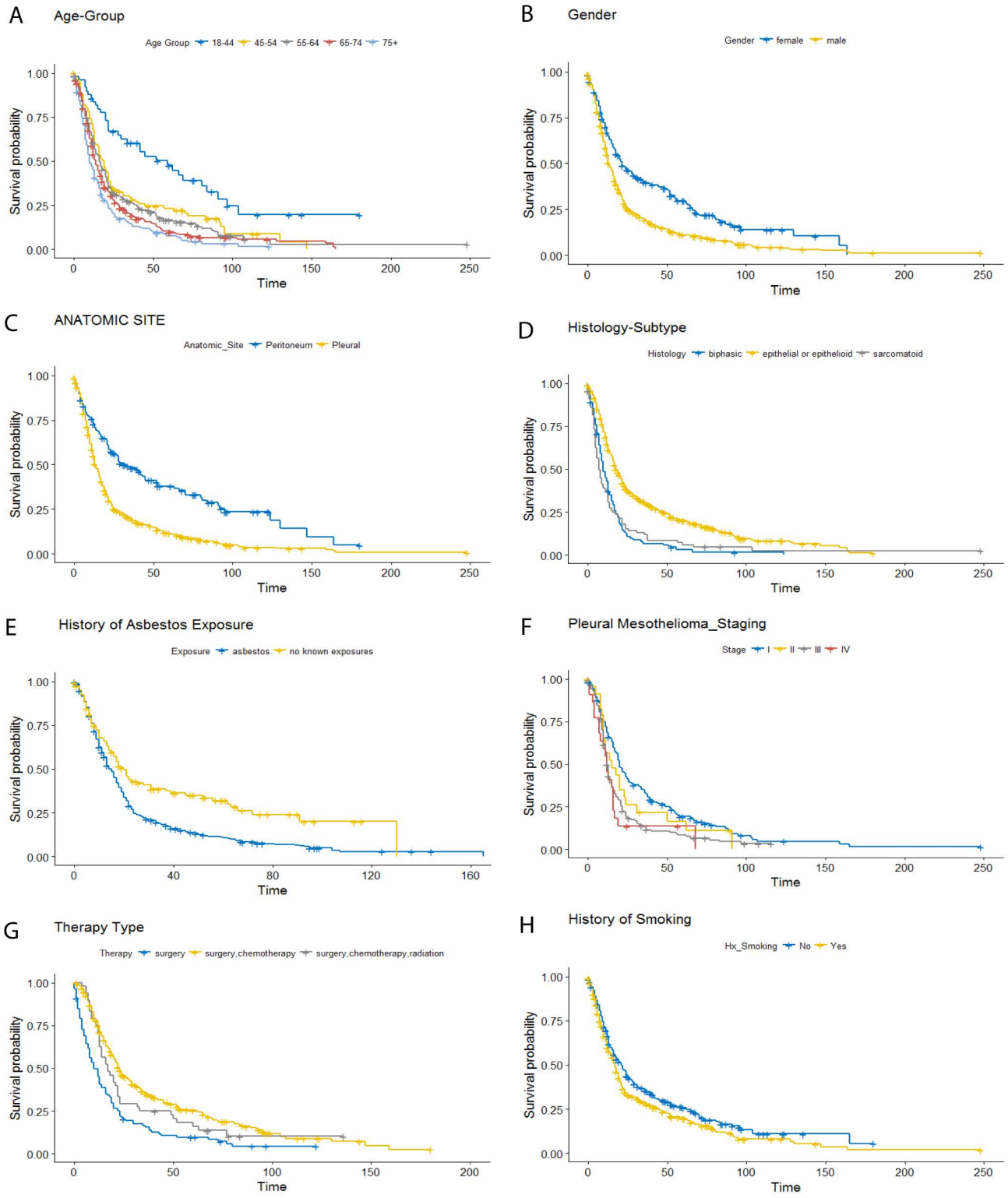

Figure 2. Kaplan Meier Curve analysis performed at age (**a**), gender (**b**), anatomic site (**c**), histology subtype (**d**), history of asbestoses exposure (**e**), staging (pleural mesothelioma) (**f**), therapy type (**g**), and history of smoking (**h**).

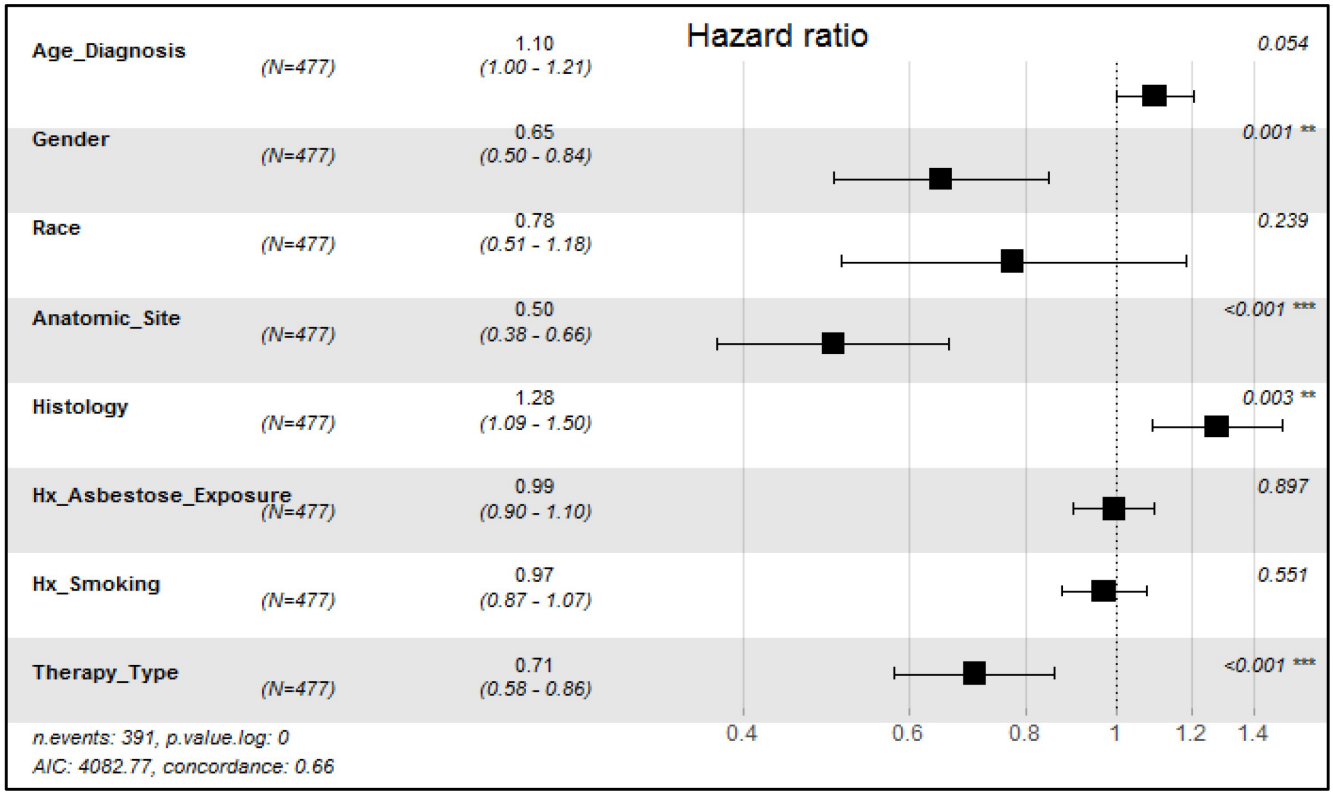

Figure 3. Adjusted Cox Hazard analysis, predictors of mesothelioma survival, multivariable analysis (n=477).

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, a region with an aging population, environmental concerns, history of notable asbestos exposure, and other risk factors associated with mesothelioma development. This region has not been covered by 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 the more prevalent pleural presentation. Survival analysis on the NMVB cohort demonstrated that being aged 44 and under, female gender, epithelioid histological subtype, Stage I of the disease, peritoneum anatomic 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 were all prognostic factors[12]. This study also corroborates previous investigations suggesting that peritoneal presentation, especially among women, is associated with longer survival[19].

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 exposures[14,20–23]. 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 exposure[24]. 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 missing information on specific surgical treatment type in this dataset. 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.

Malignant mesothelioma is a life-threatening condition that has been under investigated and is important to investigate further, considering that its mortality epidemic has not shown signs of improvement in 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 identify and evaluate cases of nonsurgical mesothelioma management because many patients are not good candidates for surgery. An improved understanding of factors associated with

mesothelioma morbidity and mortality may help identify high-risk groups with different occupational exposures who should be further evaluated for responsiveness to preventive and innovative management strategies for mesothelioma. The identification of these factors could help patients at risk for therapy failure who may benefit from novel interventions or avoiding 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 open to all research community and envision that in the future, existing information repositories like NMVB will be harnessed to greater extent to investigate rare diseases like mesothelioma.

Data availability

The investigator can obtain the de-identified data from National Mesothelioma Virtual Bank by submitting the letter of intent (LOI) (https://mesotissue.org/node/26). The NMVB Research Evaluation Panel (REP) is composed of extramural scientists with varied expertise including laboratory science, lung pathology, mesothelioma, and statistics (https://mesotissue.org/rep) reviews scientific merit of requests for NMVB specimens/data and makes recommendation to fulfil the request after the approval of data use agreement (DUA).

Competing interests

No competing interests were disclosed.

Grant information

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Current Referee Status: ? ? ✓

Version 1

Referee Report 19 October 2018

doi:10.5256/f1000research.16914.r39375

✓ **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.

Referee Expertise: Pulmonary Medicine and Thoracic Oncology

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

Referee Report 10 October 2018

doi:10.5256/f1000research.16914.r38743

? **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 al[1]).The lack of information about genetics is a limiting factor that should be acknowledge 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 al[2].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 al[3]. (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 al[4]; Baumann F et al[5]. Moreover, mesotheliomas develops in carriers of germline mutations of BAP1 (Carbone M., Kanodia S., JTO 2016[6], and mutations of BAP1 may increase susceptibility to low doses of asbestos and other mineral fibers (Napolitano A., Pellegrini L., et al[7]). 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 al[8].

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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.

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

I have read this submission. I 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.

Referee Report 29 August 2018

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? **Nico van Zandwijk** [1,2]
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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 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.

Referee Expertise: Thoracic oncology

I have read this submission. I 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, 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-comp . 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