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DOI: https://doi.org/10.1016/j.jtho.2023.08.005

ORIGINAL ARTICLE

The International Association for the Study of Lung Cancer Pleural Mesothelioma Staging Project: Updated Modeling of Prognostic Factors in Pleural Mesothelioma

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Received 25 April 2023; revised 2 August 2023; accepted 4 August 2023
Available online - 9 August 2023

ABSTRACT

Introduction: The International Association for the Study of Lung Cancer developed an international pleural mesothelioma database to improve staging. Data entered from 1995 to 2009 (training data set) were analyzed previously to evaluate supplemental prognostic factors. We evaluated these factors with new clinical data to determine whether the previous models could be improved.

Methods: Patients entered into the database from 2009 to 2019 (validation cohort) were assessed for the association between previous prognosticators and overall survival using Cox proportional hazards regression with bidirectional stepwise selection. Additional variables were analyzed and models were compared using Harrell's C-index.

Results: The training data set included 3101 patients and the validation cohort, 1733 patients. For the multivariable pathologic staging model applied to the training cohort, C-index was 0.68 (95% confidence interval [CI]: 0.656–0.705). For the validation data set (n = 497), C-index was 0.650 (95% CI: 0.614–0.685), and pathologic stage, histologic diagnosis, sex, adjuvant therapy, and platelet count were independently associated with survival. Adding anemia to the model increased the C-index to 0.652 (95% CI: 0.618–0.686). A basic presentation model including all parameters before staging yielded a C-index of 0.668 (95% CI: 0.641–0.695). In comparison, the European Organization for Research and Treatment of Cancer model yielded C-indices

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Disclosure: Dr. Rusch receives institutional clinical trial funding from Genentech; funds for meeting preparation and travel reimbursement from the National Institutes of Health/National Cancer Institute (NIH/NCI) Thoracic Malignancy Steering Committee; and is an unpaid member of the Data Safety Monitoring Committee, Mesothelioma and Radical Surgery 2 trial (Cancer Research United Kingdom). Dr. Opitz reports receiving an institutional grant and participates in the speakers bureau for Roche; participates in the advisory board and speakers bureau for AstraZeneca; participates in an advisory board for Merck Sharp & Dohme and Bristol-Myers Squibb; receives institutional grant from Medtronic; and conducts proctorship for Intuitive. The remaining authors declare no conflict of interest.

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ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2023.08.005

of 0.550 (95% CI: 0.511–0.589) and 0.577 (95% CI: 0.550–0.604) for pathologic staging and presentation models, respectively.

Conclusions: Although significant predictors differed slightly, the International Association for the Study of Lung Cancer training model performed well in the validation set and better than the model of the European Organization for Research and Treatment of Cancer. International collaboration is critical to improve outcomes in this rare disease.

Keywords: Mesothelioma; Pleurectomy/decortication; Extrapleural pneumonectomy; Prognostic factors; Staging

Introduction

Diffuse pleural mesothelioma (PM) represents a challenge with regard to staging and prognostication, owing largely to the rarity of the disease, heterogeneity in patient presentation, and lack of standardization of management and therapy. The goal of an effective staging system is to stratify patients into cohorts on the basis of anatomical factors that differentiate the survival of each group.[1–3] The Mesothelioma Domain (MD) of the International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee (IASLC SPFC) developed an international database in a concerted effort to update the staging system.[4–6] On this basis, the MD analyzed supplemental variables and published models aimed to improve the accuracy of prognosis in PM to facilitate patient selection for treatment protocols.[7] Supplementary prognostic variables collected as part of the IASLC seventh edition were evaluated in three different scenarios in which patients might present: (1) all core clinicodemographic variables, including pathologic stage, available; (2) all core variables but clinical, and not pathologic, stage available; and (3) only certain baseline clinical features (age, sex, histology, and laboratory values) obtained on presentation before staging available.

Despite refinements in staging, modeling, and understanding of PM, there has been little improvement in the ability to select which patients will do well and in whom more aggressive therapy might be considered since 1998 when the European Organization for Research and Treatment of Cancer (EORTC) Lung Cancer Cooperative Group published an analysis of covariates from a series of phase 2 trials.[8] Models on the basis of data entered from January 1995 to August 2009 (training data set) generated updates in a more modern cohort, but with contributions from centers with high proportions of surgical patients, the results may not be generalizable to nonsurgical populations. As many patients with PM present with unresectable or otherwise advanced disease, there is a critical need to evaluate patients on the basis of features available without surgery, including baseline demographics, and clinical variables such as biopsy and laboratory data.

Using new data not included in the training data set, submitted to the Cancer Research And Biostatistics from 2009 to 2019 (validation cohort), we sought to validate the previous IASLC supplemental prognostic model and to refine it further on the basis of the addition of relevant variables. These models were then compared with the previously accepted standard of the EORTC model.[8]

Materials and Methods

Database Populations

The training data set included patient data contributed to the IASLC PM database between 1995 and 2009, with PM diagnosis date no earlier than 1995, and with follow-up data for overall survival (OS) available, as detailed by Pass et al.[1] The median date of pathologic diagnosis for this cohort was March 30, 2004.

The validation data set included patients entered into the IASLC PM database from September 2009 to February 2019 who met all screening criteria and had follow-up for survival. This validation population had pathologic diagnosis dates ranging from June 30, 1997 to January 10, 2019, with a median diagnosis on September 7, 2011. Patients from the validation data set were not included in previous analyses of supplemental prognostic factors.

Definitions for Prognostic Variables

The 2014 analysis identified key prognostic factors, including age (≥50 versus younger), sex (male versus female), histology (epithelioid versus other), platelets (≥400×10^9 cells/liter versus lower), white blood cells (WBCs) (≥ 15.5×10^9 cells/liter versus lower), type of surgical procedure (palliative versus curative-intent, with curative-intent including extrapleural pneumonectomy or pleurectomy/decortication), use of adjuvant therapy (yes versus no, with adjuvant therapy defined as chemotherapy or radiotherapy at any time), and hemoglobin (≥14.6 g/dL versus lower).[7]

For this study, we first established the function of the previous model for the original cohort used to establish the 2014 prognostic indices using the American Joint Committee on Cancer (AJCC) International Union Against Cancer (UICC) eighth edition staging system for mesothelioma to compare the performance of any updates to the model using a single staging system.[9] Pathologic

stage was dichotomized into stage I and II and stage III and IV. Additional models were developed to evaluate the association between survival and anemia (a binary variable defined by hemoglobin levels) and the influence of serum mesothelin on prognosis. The 2014 analysis featured hemoglobin using a binary classifier (high or low with 14.6 g/dL as the cutoff). The updated analysis incorporated a more biologically relevant consideration of anemia as defined by separate hemoglobin cut-points for male (<13.5 g/dL) and female (<11.5 g/dL) patients. As serum mesothelin was collected for a portion of patients in the IASLC PM validation cohort, the distribution of serum mesothelin values was investigated and an optimal cut-point with respect to OS was identified statistically to obtain a binary classification for patients by serum mesothelin level to be used in the newly-developed multivariable models.

The EORTC model was calculated using the five variables found to be independently associated with survival in Curran's analysis of outcomes for PM patients enrolled in five consecutive EORTC phase 2 chemotherapy clinical trials from 1984 to 1993: performance status, WBC, certainty of diagnosis of mesothelioma, sex, and histology.[8]

Statistical Methods

OS was defined as the time from the date of pathologic diagnosis to the date of death attributable to any cause, with patients censored at the date of last contact. Survival distributions were estimated using the Kaplan–Meier method. The optimal cut-point for the continuous variable of mesothelin was identified using the running log-rank method. The performance of the 2014 model in the original and validation data sets was assessed using Harrell's C-index. Harrell's C-index measures the probability that the predicted survival times for two randomly selected patients have the same relative order as the observed survival times in each model. In the validation set, observed survival times were regressed on their predicted survival times as calculated from the 2014 model in log scale. The performance of the EORTC model was assessed in the same way. The association of covariates of interest with OS was assessed by multivariable Cox proportional hazards modeling using bidirectional stepwise selection, with covariates of interest modeled categorically as previously described, and with covariates meeting the criterion of a univariate p value for association with OS of less than or equal to 0.1 used as candidate variables for selection into multivariable models. Harrell's C-index was used to assess the performance of the various multivariable models considered. Cox modeling and Harrell's C-index statistics were generated using the PROC PHREG package within Statistical Analysis System 9.4 for Windows (SAS Institute Inc., Cary, NC). Optimal cut-point analyses were performed through the R version 3.6.1 RLSPLIT package (R Core Team, Vienna, Austria).

Results

The 2014 training data set featured 3101 patients, 906 of whom had available data for histologic diagnosis, sex, age, platelets, and WBC. Of these 906 patients, 757 had sufficient data for modeling featuring the pathologic stage by the eighth edition criteria, and 609 had sufficient for modeling featuring the clinical stage by the eighth edition criteria.

The validation cohort consisted of 1733 patients (Table 1), with various data sets produced depending on what data was missing. For the pathologic stage, 497 had data for all features included in the model developed on the basis of the 2014 IASLC database. Of these, 496 had available data to assess anemia, and 381 also had available mesothelin data. For the clinical stage, 674 patients had data for all features in the 2014 model, 673 of whom had data for anemia, and 540 also had mesothelin. For the model of patient presentation, 905 patients had data for all features in the 2014 model, 903 of whom had data for anemia, and 747 also had mesothelin.

For the comparison of a pathologic staging model to the EORTC model, 457 out of the 497 patients had sufficient data for evaluation by the EORTC model. For the comparison of a presentation model including the clinical stage to the EORTC model, 877 of the 905 patients had sufficient data for evaluation by the EORTC model.

Analysis of 2014 Training Data Set Pathologic Staging Model Using the AJCC/UICC Eighth (Instead of Seventh) Edition Staging System

For the multivariable pathologic staging model applied to the 2014 IASLC training data set population (n = 757), all variables other than curative-intent of surgical procedure remained statistically significant in the multivariable model with AJCC/UICC eighth edition staging system, resulting in a final model that included classifiers for staging, histology, age, sex, use of adjuvant therapy, platelets, and WBC. The C-index for this model was 0.68 (95% confidence interval [CI]: 0.656–0.705), indicating good model performance and comparable performance to the full AJCC/UICC seventh edition staging system model applied to the same population (C-index = 0.679, 95% CI: 0.655–0.702).

Validation of 2014 Pathologic Staging Model

For the multivariable pathologic staging model applied to the validation data set population with sufficient data for all variables (n = 497), pathologic stage, histology, sex, adjuvant therapy, and platelet count were independently

Table 1. Clinical and Demographic Features for Validation Data set (N = 1733)

Variables	n/N (%), Median (Interquartile Range)	Missing Data n/N (%)
Age (y)	67.1 (60.3-73.4)	4/1733 (0.2)
Male sex	1350/1733 (77.9)	4/1733 (0.2)
Epithelial histology (vs. other)	1247/1733 (72)	162/1733 (9.3)
Platelets ($\times 10^9$/liter)	288 (225-372)	596/1733 (34.4)
WBC count ($\times 10^9$/liter)	8 (6.5-10.1)	452/1733 (26.1)
Hemoglobin		
Hemoglobin in men	13.1 (11.6-14.3)	445/1350 (33)
Hemoglobin in women	12.1 (10.8-13.2)	147/379 (38.8)
Serum mesothelin (nmol/liter)	7.8 (6.3-9.6)	646/1733 (37.3)
Clinical stage AJCC/UICC eighth edition		
Stage I	820/1733 (47.3)	317/1733 (18.3)
Stage II	169/1733 (9.8)	
Stage III	326/1733 (18.8)	
Stage IV	101/1733 (5.8)	
Surgical treatment (vs. no surgery)	820/1733 (47.3)	77/1733 (4.4)
Curative-intent surgery among surgical patients (vs. palliative, 2014 match)	389/820 (47.4)	81/820 (9.9)
Pathologic stage		
Stage I	232/820 (28.3)	240/820 (29.3)
Stage II	67/820 (8.2)	
Stage III	273/820 (33.3)	
Stage IV	8/820 (1)	
Adjuvant therapy in surgical patients (vs. no)	653/820 (79.6)	0/820 (0)

AJCC, American Joint Committee on Cancer; UICC, International Union Against Cancer; WBC, white blood cells.

associated with survival (Table 2). The C-index for this model was 0.650 (95% CI: 0.614–0.685), suggesting good model performance; however, age, treatment intent, and white blood cell count, which were significant independent predictors of survival in the original data set, were not associated with survival in the validation data set.

Additional Prognostic Factors: Anemia and Mesothelin

Using the running log-rank method, the optimal cut-point for mesothelin in this data set was found to be 6.7 nmol/liter. On univariate analysis, both anemia (as sex-defined above) and mesothelin greater than or equal to 6.7 nmol/liter were associated with worse survival (Fig. 1*A* and *B*).

Improving the Model

Adding anemia to the updated model including pathologic stage, histology, sex, adjuvant treatment, and platelet count using stepwise regression for the population with available data (n = 496) resulted in slight improvement of the model (C-index of the model with anemia = 0.652, 95% CI: 0.618–0.686). Anemia was an independent predictor of worse survival and sex was not significant when applying the stepwise model after the

Table 2. Results of a Multivariable Model for Overall Survival Featuring 2014 Variables Using Validation Data Set With Sufficient Data for All Model Features (N = 497)

		Overall Survival	
Variable	n/N (%)	HR (95% CI)	*p* Value
Pathologic stage III and IV (versus I and II)	261/497 (53)	1.49 (1.18-1.89)	0.0010
Histology: other (vs. epithelioid)	75/497 (15)	1.61 (1.19-2.17)	0.0018
Male	380/497 (76)	1.39 (1.05-1.84)	0.0202
Age ≥50	440/497 (89)	1.07 (0.74-1.55)	0.7084
Palliative (versus curative)	182/497 (37)	1.18 (0.93-1.50)	0.1687
No adjuvant treatment	67/497 (13)	1.69 (1.25-2.28)	0.0007
Platelets >400 $\times 10^9$/liter	87/497 (18)	1.66 (1.26-2.20)	0.0003
WBC count >15.5 $\times 10^9$/liter	40/497 (8)	1.10 (0.74-1.62)	0.6434

Note: p Value from score chi-square test in Cox regression.
95% CI, 95% confidence interval; HR, hazard ratio; WBC, white blood cells.

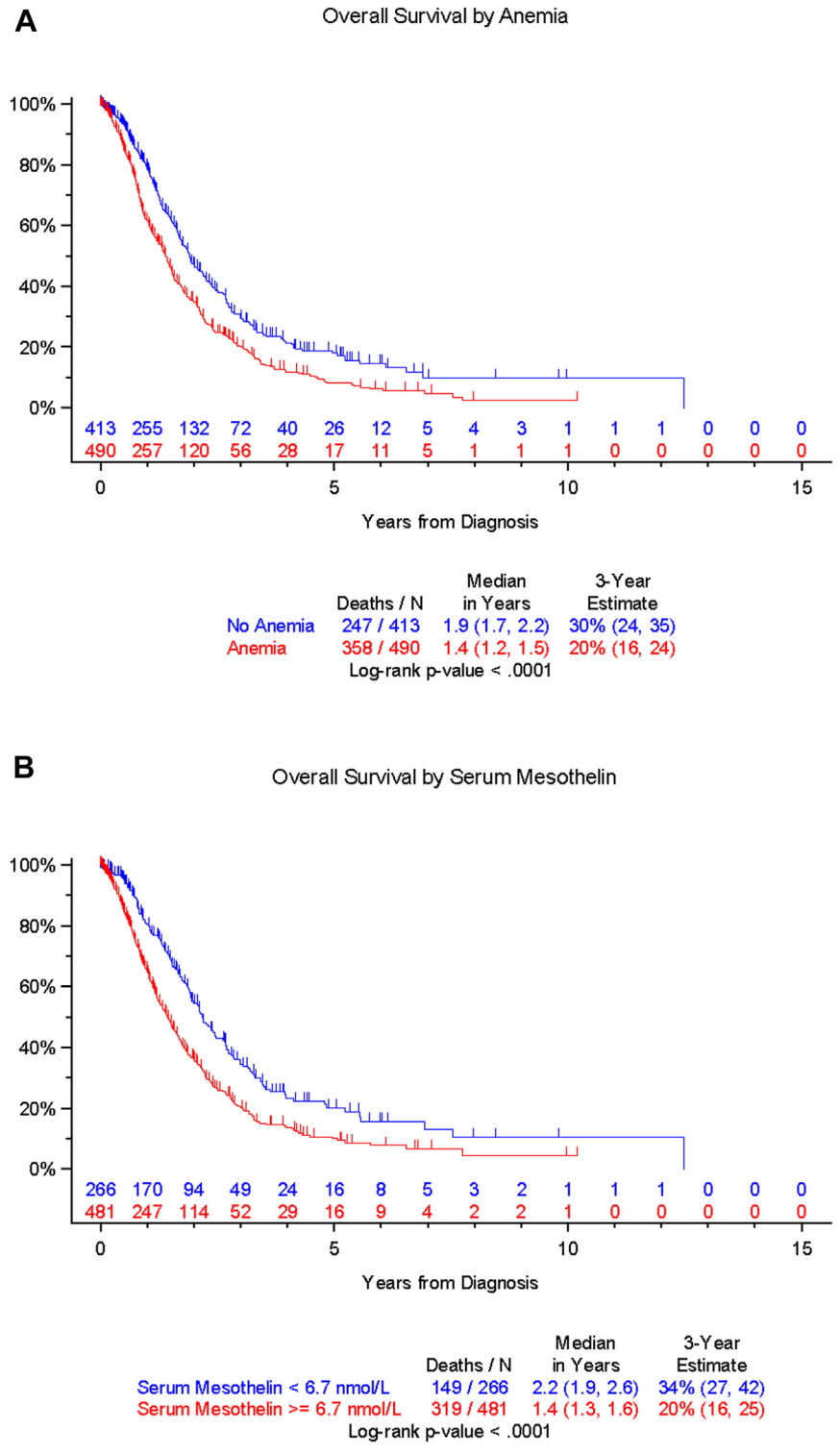

Figure 1. Univariate results featuring variables from the 2014 model using a validation data set with sufficient data for the clinical stage and additional model features of interest. (*A*) Overall survival by anemia (<13.5 g/dL for men and <11.5 g/dL for women) (n = 903). (*B*) Overall survival by mesothelin at a cut-point of 6.7 nmol/liter (n = 747).

inclusion of anemia (Table 3). Using the statistically-derived cut-point of 6.7 nmol/liter, mesothelin was not independently associated with survival in the context of this model.

Modeling for Patients on Presentation

In an effort to estimate the prognosis for patients on presentation, before the availability of information from resection or administration of adjuvant therapy,

Table 3. Results of a Multivariable Bidirectional Stepwise Model Featuring 2014 Prognostic Factors With Anemia Added Using Validation Data Set (N = 496)

		Overall Survival	
Variables	n/N (%)	HR (95% CI)	*p* value
No adjuvant treatment	67/496 (14)	1.63 (1.21-2.21)	0.0014
Platelets >400 × 10^9/liter	87/496 (18)	1.71 (1.30-2.26)	0.0001
Anemia	291/496 (59)	1.62 (1.28-2.05)	<0.0001
Histology: other (vs. epithelioid)	75/496 (15)	1.70 (1.27-2.29)	0.0004
Pathologic stage III/IV (vs. I/II)	260/496 (52)	1.52 (1.20-1.91)	0.0004

Note: p Value from score chi-square test in Cox regression.
95% CI, 95% confidence interval; HR, hazard ratio.

presentation models with and without clinical staging were created.

Using the presentation model of the patient before staging, the model performed well using the validation data set (n = 995) with a C-index of 0.631 (95% CI: 0.608–0.655). The final model included histology, anemia, platelet count, and age (Table 4). White blood cell count was not selected by the stepwise model after the inclusion of anemia. A subsequent model was built by adding mesothelin to the list of covariates considered for multivariate models. Of the 995 patients with complete data for the model with anemia, 838 also had available mesothelin data. The final model featured mesothelin along with histology, anemia, platelet count, and age. This model revealed evidence of improved performance with a C-index of 0.651 (95% CI: 0.626–0.677) (Table 5).

Using the presentation model of a patient with AJCC/UICC eighth edition clinical stage (before surgical resection that would provide surgical staging), the model performed well using the validation data set (n = 903) with a C-index of 0.639 (95% CI: 0.614–0.663). The final model included histology, anemia, platelet count, age, and clinical stage (Supplementary Table 1). White blood cell count was not selected by the stepwise model after the inclusion of anemia. A subsequent model was built by adding mesothelin to the list of covariates considered for multivariate models. Of the 903 patients with complete data for the model with anemia, 747 also had available mesothelin data. The final model featured mesothelin along with histology, anemia, clinical stage, platelet count, and age. This model revealed evidence of improved performance with a C-index of 0.661 (95% CI: 0.634–0.688) (Supplementary Table 2).

We then compared the models with clinical staging to those with pathologic staging, using homogenous data sets with both clinical and pathologic staging data available and data for the additional predictors used in multivariate modeling. The C-index for the clinical staging model with histology, anemia, platelets, clinical stage, and age (n = 470) is 0.610 (95% CI: 0.574–0.645). Adding mesothelin (n = 356) improved the performance of the model, with a C-index of 0.636 (95% CI: 0.592–0.681). For comparison, in the pathologic staging model with histology, anemia, platelets, pathologic staging, and adjuvant therapy in the same data set (n = 470), age did not reach significance and the C-index was 0.646. When mesothelin was evaluated with the pathologic staging model (n = 356), histology, anemia, platelets, pathologic staging, and adjuvant therapy were significantly associated with survival, whereas both age and mesothelin were not selected into the multivariate stepwise model. The C-index for the latter was 0.672 (95% CI: 0.629–0.715).

Table 4. Results for Multivariable Bidirectional Stepwise Model Featuring Variables From 2014 Prognostic Factors With Validation Data Set Presentation Model Plus Anemia

		Overall Survival	
Variables	n/N (%)	HR (95% CI)	*p* value
Histology: other (vs. epithelioid)	212/995 (21)	1.94 (1.62-2.32)	<0.0001
Anemia	538/995 (54)	1.49 (1.27-1.76)	<0.0001
Platelets >400 × 10^9/liter	201/995 (20)	1.68 (1.39-2.03)	<0.0001
Age ≥50	917/995 (92)	1.61 (1.18-2.21)	0.0028

Note: Data set: validation cohort with clinical stage, sufficient data for all candidate model features (N = 995). *p* Value from score chi-square test in Cox regression.
95% CI, 95% confidence interval; HR, hazard ratio.

Table 5. Results for Multivariable Bidirectional Stepwise Model Featuring Variables From 2014 Prognostic Factors Validation Data Set With AJCC/UICC Eighth Edition Clinical Stage With Anemia and Mesothelin Added

		Overall Survival	
Variable	n/N (%)	HR (95% CI)	*p* Value
Histology: other (vs. epithelioid)	185/838 (22)	1.96 (1.60-2.39)	<0.0001
Anemia	424/838 (51)	1.51 (1.27-1.80)	<0.0001
Mesothelin >6.7 nmol/liter	540/838 (64)	1.43 (1.18-1.73)	0.0003
Platelets >400 × 10^9/liter	175/838 (21)	1.53 (1.24-1.90)	<0.0001
Age ≥50	773/838 (92)	1.59 (1.11-2.26)	0.0111

Note: Data set: validation cohort with clinical stage, sufficient data for all candidate model features (n = 838). *p* Value from score chi-square test in Cox regression.
95% CI, 95% confidence interval; AJCC, American Joint Committee on Cancer; UICC, International Union Against Cancer; HR, hazard ratio.

Model Performance Compared With Historic Standard

When comparing the pathologic staging model on the basis of the updated data set (n = 877) to the EORTC model, the C-index of the 2021 model was 0.631 (95% CI: 0.594–0.668), which suggests stronger performance than the EORTC model in this data set, which had a C-index of 0.550 (95% CI: 0.511–0.589). For a simple presentation model (even before clinical staging), a basic presentation model with histology, sex, age, platelets, and white blood cell count was created, as was originally done in the 2014 analysis. The C-index for this model in the current data set was 0.587 (95% CI: 0.561–0.614). Adding anemia resulted in a model with a C-index of 0.643 (95% CI: 0.618–0.667), whereas adding anemia and mesothelin resulted in a C-index of 0.668 (95% CI: 0.641–0.695). For comparison, the C-index for the EORTC model in the population within this data set with data available for comparison was 0.577 (95% CI: 0.550–0.604).

Discussion

Prognostic factors inform about the likelihood of a clinical event, such as disease progression or mortality, independent of treatment received. Whereas prognostic factors may guide treatment decisions, they differ from predictive factors, which indicate whether a specific treatment is likely to be effective on the basis of patient-specific biology. As treatment options expand to include checkpoint inhibition, other immunomodulation, and antiangiogenic agents, understanding the relationships between prognostic factors, predictive factors, and outcomes is critical to proportionately more patients.[10] The inclusion of a larger proportion of nonsurgical patients in our data set increases the generalizability of our results to many nonsurgical patients presenting in the modern era.

The large data set included in the current study included patients treated from 1997 to 2019. Whereas treatment has evolved to some extent, the prognostic factors assessed in this study remain relevant today. Treatment in PM has only recently included expanded options. Chemotherapy has involved the same two drugs since a 2003 publication detailed improved survival with the addition of pemetrexed to cisplatin.[11] Other than a shift from extrapleural pneumonectomy toward proportionately more extended pleurectomy/decortication after work by Flores et al.[12] reported improved survival with the latter,[13] surgery has not changed. Immunotherapy now has a role in the treatment of PM. The CHECKMATE-743 clinical trial, published in 2021, found a significantly improved OS of 18.1 months (95% CI: 16.8–21.4) for the combination of the immune checkpoint inhibitors nivolumab and ipilimumab, compared with 14.1 months (95% CI: 12.4–16.2) for the chemotherapy control arm ($p = 0.002$).[14] Although the MAPS study reported a median survival of 18.8 months (95% CI: 15.9–22.6) for patients treated with the angiogenesis inhibitor bevacizumab with cisplatin-pemetrexed, compared with 16.1 months (95% CI: 14.0–17.9) with chemotherapy alone ($p = 0.0167$), this regimen has not been consistently used worldwide.[15] There is no published clinical trial yet comparing checkpoint inhibitors to a regimen including bevacizumab. Given the timing of these advances and the period over which this data set was collected, it is likely that few participants received these regimens. Clinical trial results are most useful in understanding predictive, rather than prognostic, factors for survival.

Despite advances in proteomics, imaging, and other technology, no single nomogram has been developed to stratify patients with PM well into distinct groups with differing survival on the basis of prognostic factors. This, in turn, contributes to a lack of standardization in patient selection for various treatment protocols. The IASLC SPFC MD's creation of a multinational multicenter registry and an electronic data capture for prospective data collection represents the largest coordinated international effort to improve staging in PM. The IASLC

SPFC MD previously analyzed the seventh edition data set to explore whether the addition of other clinicodemographic features improved prognostication among surgically managed patients, resulting in a final model in which pathologic stage, histology, age, intent of treatment, adjuvant treatment, platelet count, and WBC count were significant predictors of survival. The current study aimed to validate this model in a modern data set that included more patients who were not treated with surgery. Generally, the model performed better for the validation data set than historic comparative models such as EORTC, but several variables were not significant in this updated series.

When the AJCC/UICC eighth edition staging system was applied to patients analyzed in the previous series, the model performance was equivalent (C-index 0.68 versus 0.679 for the original analysis). Notably, however, the variable reflecting the intent of treatment (curative versus palliative) was not significant in the multivariable model (whereas it was in the original version). It is possible that applying the updated staging system placed more emphasis on the strength of pathologic staging in predicting survival and, in this patient population, which included mostly patients who were treated surgically, the number of patients treated with only palliative intent was too small to identify significant effect for that covariate.

On attempting to validate the final model from the previous analysis with the updated data set, the model performed generally well on the basis of C-index (C-index 0.65 versus 0.679), but several covariates that had been significant in the first analysis were not associated with survival in this data set: age, treatment intent, and WBC count. Whereas multiple studies have reported age is an independent predictor of survival in PM,[7,16–18] others have not.[8,19–21] In an analysis of 636 patients undergoing extrapleural pneumonectomy, age was associated with survival for 117 patients who survived 3 years or more, but when stratified by sex, this association was only seen for women.[22] It is possible that an interaction between age and sex and differing populations in these studies may explain differences in the finding of age as a predictor of survival. A sensitivity analysis evaluating survival for patients stratified by age (dichotomized at 50 y) and sex, reported the best survival for young women (Supplementary Fig. 1), but differences in pairwise survival between young men and women and between young and older women were not significant, possibly because of the small number of patients age younger than 50 years in this data set.

Developing accurate prognostic models is critical to guide clinicians in evaluating patients with a rare disease such as PM, but this remains a major knowledge gap in thoracic oncology. Other investigators have used machine learning to generate best-performing multivariable models, including a group analyzing 269 patients treated in Scotland between 2008 and 2014.[23] Age, WBC, and albumin were prognostic and—depending on whether OS less than 6 months or OS greater than 12 months were used as the primary outcome—histology and platelet count (6 mo) or histology and c-reactive protein (12 mo) were also significant. The C-index for these models was greater than 0.73 in all data sets using these end points, suggesting good model performance but many questions regarding their study remain, particularly how patients were treated in these cohorts. In a more recent analysis applying the classification and regression tree model previously described by the authors[24] to 289 patients treated with cytoreductive surgery in Japan and Australia between 1991 and 2016, investigators found that weight loss, hemoglobin, performance status, albumin, and histology were significant predictors of survival.[25] The authors' application of the model to a highly selected surgical population resulted in a C-index of 0.62 (95% CI: 0.57–0.66), similar, or lower to that of the model applied to the investigators' original data set, which was 0.68 (95% CI: 0.60–0.75) and that of the current study (0.65 as described above). Notably, the classification and regression tree model found albumin to have a significant independent association with survival; although we did not evaluate the effect of albumin in the current model because of missingness for 47% of the patients.

Given the limitations of our model's performance, we sought to evaluate additional parameters available for the study cohort that might improve it. Anemia has been found to be a strong independent predictor of lower survival in PM,[25] particularly for patients with epithelial disease.[26,27] When added to the original model in the current study, anemia was predictive of worse survival in both the pathologic stage model and the presentation models. This finding contrasts with that of the previous study, which reported no independent effect of hemoglobin—the laboratory parameter on which the definition of anemia is based. This is likely because, in the 2014 analysis, hemoglobin was treated as a single variable, dichotomized around the value of 14.6, which is the reference used for anemia for men in most laboratories. Given the strong association between female sex and survival,[7,27,28] we hypothesized that the negative impact of low hemoglobin on survival was being offset by most of the patients with low hemoglobin being women. We, therefore, treated this information as anemia, with clinical definitions on the basis of sex. Indeed, anemia, as defined appropriately, was predictive of worse survival in the current series.

The diagnostic and prognostic utility of serum mesothelin are areas of ongoing research.[10,29–31] In a

multicenter study with blinded centralized measurement of biomarkers, plasma mesothelin was an independent predictor of survival with higher values associated with worse survival; also, mesothelin improved the predictive ability of both the EORTC and Cancer and Leukemia Group B prognostic indices.[10] For this study, serum mesothelin was predictive of survival and improved the performance of the presentation models. When assessed in the context of the pathologic staging model; however, mesothelin was not independently associated with survival. Serum mesothelin may represent a marker for increased tumor volume,[32] and when full pathologic staging is available, the collinearity between mesothelin, and stage results in a lack of significance for mesothelin as a covariate in the final model.

Other clinicodemographic and molecular data might improve the model further. Multiple groups have reported an independent association between increased tumor volume and worse survival.[26,33,34] In their attempt to validate a multimodality therapy–based prognostic index that included tumor volume and c-reactive protein before chemotherapy, histologic diagnosis, and progression after chemotherapy, Greb et al.[35] found that the addition of albumin to their model improved the C-index at 6 and 12 months, although not at 24 months, with an overall C-index of 0.608 for the expanded model. In an analysis stratified by type of curative-intent surgery for patients treated between 2007 and 2014, Yeap et al.[36] added molecular data to clinicodemographic variables to create separate optimal models for patients treated with extrapleural pneumonectomy (n = 191) and pleurectomy/decortication (n = 193). The pneumonectomy cohort model included the group's previously described molecular prognostic test,[37] claudin-15–to–vimentin ratio-based molecular subtype, neutrophil-to-lymphocyte ratio, and tumor volume, and yielded a C-index of 0.644. The pleurectomy cohort model included these parameters and performance status and albumin, yielding a C-index of 0.641.[36] Nguyen et al.[38] added immunophenotyping and developed models on the basis of the following: (1) gene alterations, (2) tumor microenvironment, and (3) clinical features, yielding C-indices of 0.632, 0.591 and 0.596, respectively. When combined, the gene expression and tumor microenvironment model resulted in a C-index of 0.649, and when clinical features were added, 0.646, suggesting that gene expression most strongly predicted survival in their samples.[38]

Another potential prognostic factor that could not be assessed with the current data set was germline *BAP1* mutation status.[39] Pathogenic germline *BAP1* mutations have been reported in 7% to 10% of all patients with PM, with frequencies highest for younger patients and those with a family history of mesothelioma.[40,41] This is clinically relevant because of the increasing body of evidence supporting a more favorable prognosis for *BAP1*-associated PM, with a median survival of 5 to 7 years, and some patients surviving 10 to 20 years or longer.[39,41,42] The current study population included only 11% of patients under age 50 and the presence of germline *BAP1* mutation or family history of PM was unknown as the population predominantly predated widespread germline testing. However, *BAP1* and other hereditary cancer syndromes are relevant for future studies of prognostic factors.

The MD's previous work assessed a model on the basis of the patient's clinical presentation given the lack of staging to simulate the situation in which a PM patient first presents for evaluation.[7] In this updated analysis of prognostic factors, we evaluated presentation models with and without staging, but clinical staging did not seem to alter the performance of the models. Without clinical staging, the C-index of the model with anemia was 0.631 (95% CI: 0.608–0.655) and with anemia and mesothelin was 0.651 (95% CI: 0.626–0.677). With clinical staging, the same models resulted in C-indices of 0.639 (95% CI: 0.614–0.663) and 0.661 (95% CI: 0.634–0.688), respectively. It is possible that the lack of accuracy of clinical staging in PM and the strong association between other prognosticators (such as histology, sex, and anemia) and survival reduced the usefulness of the clinical stage as a predictor of survival. On diagnosis of PM, the availability of clinical and demographic features such as age, histology, and laboratories provide a useful tool to predict outcomes to some extent on presentation and reserve higher risk or more aggressive therapy for those with better prognosis.

In conclusion, although several predictors were no longer associated with survival, the IASLC 2014 model performed well and better than the EORTC model in the newest IASLC validation data set. Updates in the model using supplemental prognostic factors improved the model relative to the EORTC, but there is still room for better performance. In particular, faced with the basic presentation model before resection and full pathologic staging, it is difficult to predict who will do well. Still, we have enhanced the prognostication relative to historic models and this can, in turn, improve patient selection, the key to individualizing treatment. This is especially true as we try to expand global health capabilities and can use more readily available data such as basic presentation features to evaluate and manage patients in less developed countries.

The real challenge with identifying prognosticators is that not all high-volume mesothelioma centers track the same variables for all patients. Standardizing the way

data are collected and reported will enable analyses to improve prognostication and ultimately facilitate better treatment planning.

CRediT Authorship Contribution Statement

Andrea S. Wolf: Conceptualization, Methodology, Validation, Writing–original draft, Writing–review and editing, Visualization.

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Dorothy J. Giroux: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing–original draft, Writing–review and editing, Visualization, Supervision, Project administration, Funding acquisition.

Anna K. Nowak: Investigation, Resources, Data curation, Writing–review and editing.

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Acknowledgments

This project is supported through a grant from AstraZeneca. The authors thank the International Association for the Study of Lung Cancer (IASLC) employees of Cancer Research And Biostatistics for their support as statistical consultants and for attending the IASLC World Conference on Lung Cancer for the Staging Project. Dr. Rusch was supported by the National Institutes of Health/National Cancer Institute (Cancer Center Support Grant P30 CA008748). The co-authors and members of the IASLC Staging and Prognostic Factors Committee (SPFC) also thank Patricia Vigues, SPFC Project Coordinator for providing administrative support for the project, and the SPFC as a whole.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at 10.1016/j.jtho.2023.08.005.

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Appendix 2. Chairpersons and Members of the Subcommittees of the Malignant Pleural Mesothelioma Domain of the IASLC Staging and Prognostic Factors Committee

IASLC Staging and Prognostic Factors Committee Chair: Hisao Asamura.

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Appendix 3. Participating Institutions in the Mesothelioma Staging Project Database

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