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Nomogram for Estimating Overall Survival in Patients With Metastatic Pancreatic Cancer

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Objectives: This analysis investigated nomogram use to evaluate metastatic pancreatic cancer prognosis.

Methods: Thirty-four baseline factors were examined in the Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) (*nab*-paclitaxel plus gemcitabine vs gemcitabine) data set. Factors significantly ($P < 0.1$) associated with overall survival (OS) in a univariable model or with known clinical relevance were tested further. In a multivariable model, factors associated with OS ($P < 0.1$) were selected to generate the primary nomogram, which was internally validated using bootstrapping, a concordance index, and calibration plots.

Results: Using data from 861 patients, 6 factors were retained (multivariable analysis): neutrophil-lymphocyte ratio, albumin level, Karnofsky performance status, sum of longest diameter of target lesions, presence of liver metastases, and previous Whipple procedure. The nomogram distinguished low-, medium-, and high-risk groups (concordance index, 0.67; 95% confidence interval, 0.65–0.69; median OS, 11.7, 8.0, and 3.3 months, respectively).

Conclusions: This nomogram may guide estimates of the range of OS outcomes and contribute to patient stratification in future prospective metastatic pancreatic cancer trials; however, external validation is required to improve estimate reliability and applicability to a general patient population. Caution should be exercised in interpreting these results for treatment decisions: patient characteristics could differ from those included in the nomogram development.

Key Words: clinical variables, metastatic pancreatic cancer, *nab*-paclitaxel plus gemcitabine, nomogram, prognosis

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Metastatic pancreatic cancer (MPC) is an aggressive disease in which chemotherapy is the main treatment option,[1] but outcomes in chemotherapy-treated patients can vary substantially.[2] Clinical assessment of patient prognosis is based on various patient and disease factors, including performance status, presence of liver metastases, age, number of metastatic sites, carbohydrate antigen 19-9 (CA 19-9), and weight, among others.[3–5] However, the extensive variability in patient profiles and the qualitative nature of known prognostic markers create challenges in treatment selection and patient counseling.[6]

Efforts to improve the individualization of prediction of specific outcomes have led to the use of nomograms. A nomogram is a graphical representation of a multivariable predictive model used to derive a numerical probability of an outcome of interest.[7] Its primary strength is the ability to consider multiple prognostic factors simultaneously.[8,9] Nomograms have been used in various cancers, including ovarian,[10] breast,[11] prostate,[12] and gastrointestinal,[13] but the use of nomograms has been limited in MPC, a disease with a very poor prognosis. Developing such a nomogram may be valuable to inform stratification parameters in future clinical trials and may provide a guide to individual survival outcomes for patients with MPC.

The phase 3 Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) (N = 861), one of the largest published clinical trials in MPC, provides a robust data set for the development of a nomogram to predict overall survival (OS) in patients with MPC treated with chemotherapy.[14] In MPACT, patients were randomized to receive either *nab*-paclitaxel plus gemcitabine or

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TABLE 1. Univariable Analyses of Potential Prognostic Factors and Multivariable Cox Proportional Hazards Model to Predict Survival

	Univariable Analysis		Multivariable Analysis†	
Baseline Factors*	**HR (95% CI)**	***P****	**HR (95% CI)**	***P***
Clinical factors				
Neutrophil-lymphocyte ratio	1.07 (1.06–1.09)	<0.001	1.05 (1.04–1.07)	<0.001
Albumin level, g/L	0.93 (0.92–0.94)	<0.001	0.94 (0.93–0.96)	<0.001
Karnofsky performance status	0.97 (0.96–0.97)	<0.001	0.98 (0.97–0.99)	<0.001
Presence of liver metastasis	1.67 (1.37–2.05)	<0.001	1.44 (1.17–1.77)	<0.001
Sum of the longest diameter of target lesions, cm	1.03 (1.02–1.04)	<0.001	1.02 (1.01–1.03)	0.003
Prior Whipple procedure	0.63 (0.48–0.86)	0.001	0.79 (0.59–1.05)	0.107
Analgesic use	1.13 (0.98–1.31)	0.087	—	—
CA 19-9 level‡	1.00 (1.00–1.00)	0.001	—	—
No. metastatic sites	1.11 (1.03–1.20)	0.008	—	—
Location of pancreatic tumor				
Body	Reference	0.114	—	—
Head	1.06 (0.90–1.26)			
Tail	1.29 (1.07–1.56)			
Presence of biliary stent	0.98 (0.81–1.18)	0.825	—	—
Presence of peritoneum metastases	1.33 (1.04–1.71)	0.018	—	—
Prior chemotherapy	0.55 (0.37–0.81)	<0.001	—	—
Prior radiation therapy	0.64 (0.43–0.95)	0.017	—	—
Patient factors				
Age	1.01 (1.00–1.01)	0.053	—	—
Body mass index	1.00 (0.98–1.01)	0.804	—	—
Race/ethnicity				
Asian	Reference	0.212	—	—
Black	1.53 (0.79–2.96)			
Hispanic	1.78 (0.96–3.30)			
White	1.69 (0.98–2.93)			
Other	2.54 (1.05–6.11)			
Sex				
Female	Reference	0.050	—	—
Male	1.15 (1.00–1.33)			
Weight	1.00 (1.00–1.01)	0.526	—	—

*The 12 demographic and clinical factors analyzed in univariable analyses but not identified as multivariable prognostic factor candidates included body surface area, height, and presence of metastases in the axilla, bone, breast, groin, lung/thoracic, other, pelvis, peritoneal carcinomatosis, skin/soft tissue, and supraclavicular. Two factors (treatment assignment to *nab*-paclitaxel plus gemcitabine or gemcitabine alone) were excluded to allow the nomogram to be more generalizable.

†Only the factors that were significantly associated at the $P < 0.1$ level after backward selection remained in the multivariable model.

‡The large range of unique values demonstrated by CA 19-9 (0–252,181) results in an HR and 95% CI that are centered on 1.

CI indicates confidence interval; HR, hazard ratio.

gemcitabine alone as first-line treatment. Multivariable analyses have been conducted to determine which factors were independently predictive of survival in the study; however, these analyses did not allow for individualized patient prediction.[3,14,15]

The objectives of this analysis were to develop a nomogram to predict OS and to explore the relative importance of each factor in determining survival using data from a large, international, randomized phase 3 clinical trial.

MATERIALS AND METHODS

Analyses were based on MPACT survival data as of May 9, 2013.[15] No patients were excluded from the analysis because of missing data.

Prognostic Variables

A total of 34 factors were chosen to be included in the univariable analyses. These factors were considered either because prior prognostic studies had identified them to be significant or because they were considered to be of clinical interest by the study investigators. Treatment assignment (*nab*-paclitaxel plus gemcitabine or gemcitabine alone) was excluded as a factor of interest to allow the nomogram to be more generalizable. Two factors (metastases of the brain and of the extremities) were excluded because the values were the same for all patients, which resulted in 32 patient and clinical factors tested in the univariable analysis (Table 1).

For the sum of longest tumor diameters, ≤10 target lesions (maximum of 5 per organ) were selected; generally, the largest, most reliably measured, and most representative of the patient's sites of disease were chosen. For continuous variables, missing

data were replaced with the mean from the nonmissing data. For the continuous variable CA 19-9, the upper outliers (>75th percentile + 1.5 × interquartile range) were assigned the 95th percentile value. For discrete variables, missing data were assigned the new category level of "Missing." For CA 19-9, separate analyses were carried out for patients who did or did not have baseline CA 19-9 values; patients without CA 19-9 values were either CA 19-9 nonsecretors or were missing baseline values. Carbohydrate antigen 19-9 was not retained in the multivariable analysis after backward selection; therefore, the final Cox proportional hazards model included all patients, regardless of whether they expressed CA 19-9.

Nomogram Development and Validation

Univariable Cox proportional hazards model analyses were used to assess each of the 32 factors' association with OS. Overall survival in the MPACT trial was defined as the time from the date of randomization to the date of death from any cause. Factors that were associated with OS at $P < 0.1$ or that were of known clinical importance were carried forward to a Cox multivariable proportional hazards model. To remain in the multivariable model, factors had to remain significantly associated at the $P < 0.1$ level after backward selection. Factors identified in the multivariable model were used to develop a nomogram that assigned points equal to the weighted sum of the relative significance of each factor. The factor that was the most predictive was assigned a maximum point value of 100, and other factors' points were determined based on comparison with this most influential factor. Each factor was assigned points by drawing a line upward from the observed value to the Points line (Fig. 1). The sum of points for the 7 factors was then used to calculate the total points value. A line drawn down from the total points line to the lines for 6-, 9-, and 12-month survival probabilities provided the respective survival rates. A larger number of total points on the nomogram corresponds to a lower 6-, 9-, and 12-month survival probability.

The 3 nomogram-estimated risk groups were created using a risk-stratification method in which the nomogram scores from all patients were split into 4 quartiles; the first quartile constituted the low-risk group; the middle 2 quartiles, the intermediate-risk group; and the fourth quartile, the high-risk group. The resampling model calibration used bootstrapping to obtain bias-corrected estimates of predicted versus observed values based on categorizing predictions into 5 intervals. A single summary value was reported by taking the mean of the 5 interval values.

All nomograms were internally validated using bootstrapping (with 1000 iterations), a concordance index (C-index) to test the ability of the nomogram to distinguish

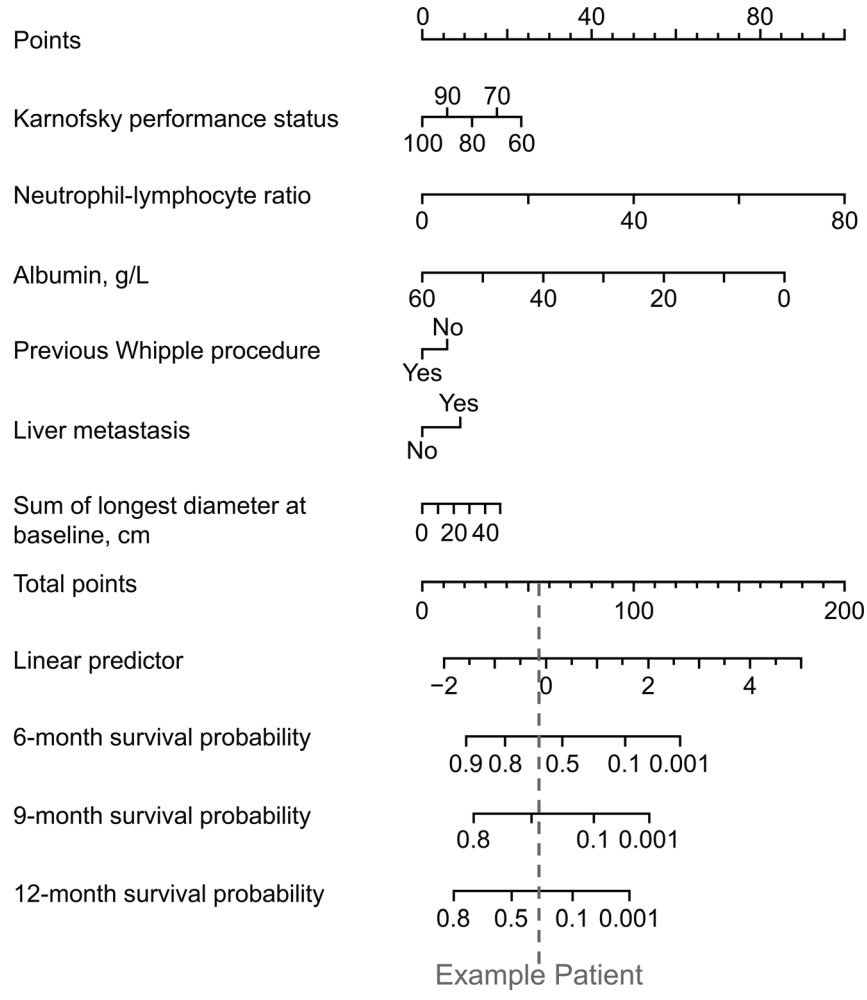

FIGURE 1. Nomogram to predict the OS of chemotherapy-naive patients with MPC.

between high- versus low-risk patients, and calibration plots to determine how accurately the nomogram-estimated risk corresponded to the actual observed risk.

After creating the primary nomogram, the effect of individually adding 5 factors that were not statistically predictive but were believed to be clinically important (CA 19-9, age, number of metastatic sites, number of lesions, and presence of lung metastasis) was examined to determine how much these factors would contribute to the predictive ability of the nomogram if forced into the model. For the analysis of CA 19-9, patients with missing values and nonsecretors were excluded.

Patient Population

Patients with metastatic adenocarcinoma of the pancreas, Karnofsky performance status of ≥70, and bilirubin level of less than or equal to the upper limit of normal (along with other eligibility criteria) enrolled in the MPACT study were included in the analyses.

MPACT Study Design

The design and patient characteristics of the phase 3, open-label, randomized MPACT study have been described previously.[14] In brief, patients with MPC undergoing first-line therapy for their disease were randomly assigned to receive either *nab*-paclitaxel plus gemcitabine or gemcitabine alone until disease progression by Response Evaluation Criteria in Solid Tumors or unacceptable toxicity. All independent ethics committees at each participating institution approved the trial, which was conducted in accordance with the International Conference on Harmonization E6 requirements for Good Clinical Practice.

RESULTS

Patients

Data from 861 patients enrolled in the MPACT study were included in this analysis.

Univariable and Multivariable Models

Fourteen of a total of 32 factors examined in univariable analyses of OS were determined to be statistically significantly associated with survival (Table 1). These factors plus 4 others (body mass index, presence of biliary stent, race/ethnicity, and body weight) with known clinical relevance or proximity to the prespecified α-level ($P < 0.1$) were entered into a multivariable model. Of the 18 factors entered into the multivariable model, 6 factors remained after backward selection and were identified as being significantly associated with OS (Table 1).

Primary Nomogram With Internal Validation

A nomogram was generated using the 6 factors identified by multivariable analysis (Fig. 1) and was shown to predict the survival probabilities at 6, 9, and 12 months. For example, a patient with a Karnofsky performance status of 100 (0 points), a neutrophil-lymphocyte ratio of 20 (25 points), a baseline albumin level of 50 g/L (14 points), a previous Whipple procedure (0 points), presence of liver metastasis (9 points), and a sum of longest diameter of tumors of 20 cm (7 points) has a total of 55 points (Table 2), which corresponds to 6-, 9-, and 12-month predicted survival probabilities of 63%, 44%, and 30%, respectively (Fig. 1; example patient). In this example, the sum of the longest diameter of tumors could theoretically involve 10 liver metastases, with the maximum number of 5 tumors summed to 16 cm and the primary lesion being 4 cm for a total of 20 cm.

TABLE 2. Scoring System for the Primary Nomogram to Predict OS

Factor	Points*
Neutrophil-lymphocyte ratio	
80	100
60	75
40	50
20	25
0	0
Albumin level, g/L	
0	86
10	72
20	57
30	43
40	29
50	14
60	0
Karnofsky performance status	
60	23
70	18
80	12
90	6
100	0
Sum of the longest diameter of target lesions, cm	
0	0
10	4
20	7
30	11
40	15
50	18
Presence of liver metastases	
Yes	9
No	0
Previous Whipple procedure	
Yes	0
No	6

*Higher score indicates higher risk.

Calibration plot comparisons used to evaluate the predictive ability of the nomogram demonstrated that the mean absolute errors between the observed and predicted probabilities for 6-, 9-, and 12-month survival were 0.07, 0.03, and 0.02, respectively (Fig. 2). The nomogram was able to discriminate between low-risk (n = 216), intermediate-risk (n = 430), and high-risk (n = 215) groups (C-index, 0.67; 95% confidence interval, 0.65–0.69) that had median OS values of 11.7, 8.0, and 3.3 months, respectively (Fig. 3).

Relative Contribution of Clinically Important Factors Added Individually to Primary Nomogram

In addition to the relative contribution of each factor shown in Table 2, analyses were carried out to evaluate the potential contribution of 6 clinically important factors if forced individually to the primary nomogram. Age would have contributed 8 points, and number of lesions at baseline would have contributed 6 points. Presence of lung metastases, thrombosis, CA 19-9 level, and

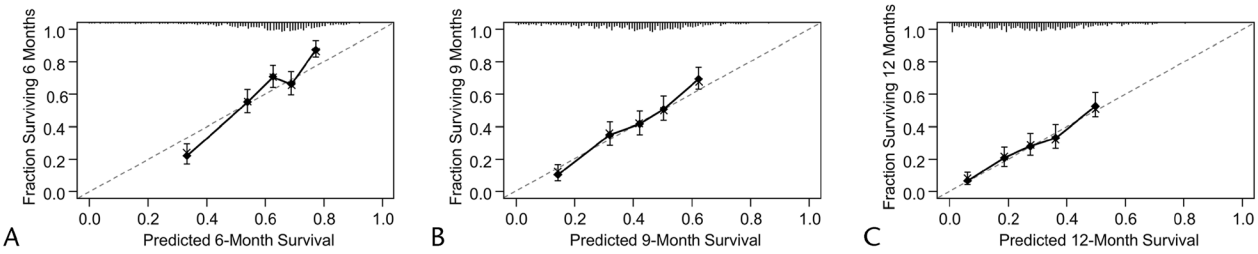

FIGURE 2. Calibration plots for (A) 6-month, (B) 9-month, and (C) 12-month survival adjusted by bootstrapping.

number of metastatic sites would have each contributed ≤2 points (Table 3).

DISCUSSION

Applying a nomogram to a specific patient may provide information that, along with other established prognostic parameters, may contribute to individualized decisions about systemic treatment and management of patients with cancer. The prognostic nomogram developed herein estimated survival using baseline factors, including neutrophil-lymphocyte ratio, albumin level, Karnofsky performance status, sum of the longest diameter of target lesions, presence of liver metastases, and previous Whipple procedure.

The set of factors identified in this analysis was largely consistent with previous analyses of survival using data from the MPACT study and in other trials.[3,14,15] For example, presence of liver metastases, baseline Karnofsky performance status, and neutrophil-lymphocyte ratio have all been demonstrated to be significantly associated with survival outcomes in prior publications in advanced pancreatic cancer.[15–17] Further supporting the findings of this analysis, a separate nomogram that included data from multiple sources, including the gemcitabine arm of the MPACT trial, retained similar factors: performance status, presence of liver metastasis, CA 19-9 level, absolute neutrophil count (a component of neutrophil-lymphocyte ratio), and albumin level.[18]

The current analysis identified CA 19-9 level as a potential predictive factor at the univariable level; however, the factor did not ultimately remain significant in the final multivariable model. When CA 19-9 was forced into the primary nomogram, it provided only a minimal additional contribution. This finding differs from those of a literature review that reported an association between CA 19-9 levels and response to chemotherapy in MPC.[19] Furthermore, decrease in CA 19-9 levels, which was not investigated in this analysis of baseline factors, remains a predictive biomarker of chemotherapy efficacy.[20,21] It is possible that in the current analysis CA 19-9 may have cosegregated with other factors, which would explain the lack of additional information contributed by this variable.

The final set of variables included in the nomogram reflected the impact of disease biology and progression. Both neutrophil-lymphocyte ratio and serum albumin levels are considered to be markers of inflammation,[22,23] which is thought to promote tumor progression and metastasis.[24] The sum of the longest diameters of tumor lesions likely reflects the extent of the disease, and the presence of liver metastasis, which is relatively common in patients with pancreatic cancer, has been associated with poorer clinical outcomes.[25]

Current prognostic markers of disease are generally qualitative, with little ability to account for the impact of a given factor in context of the overall patient profile.[3,15,26–28] This study's findings indicated that certain factors may be more influential in estimating a patient's prognosis and this nomogram may allow more accurate and individualized risk prediction by differentially weighting the factors within. The analysis of relative contribution for each factor indicated that the largest contributors to survival

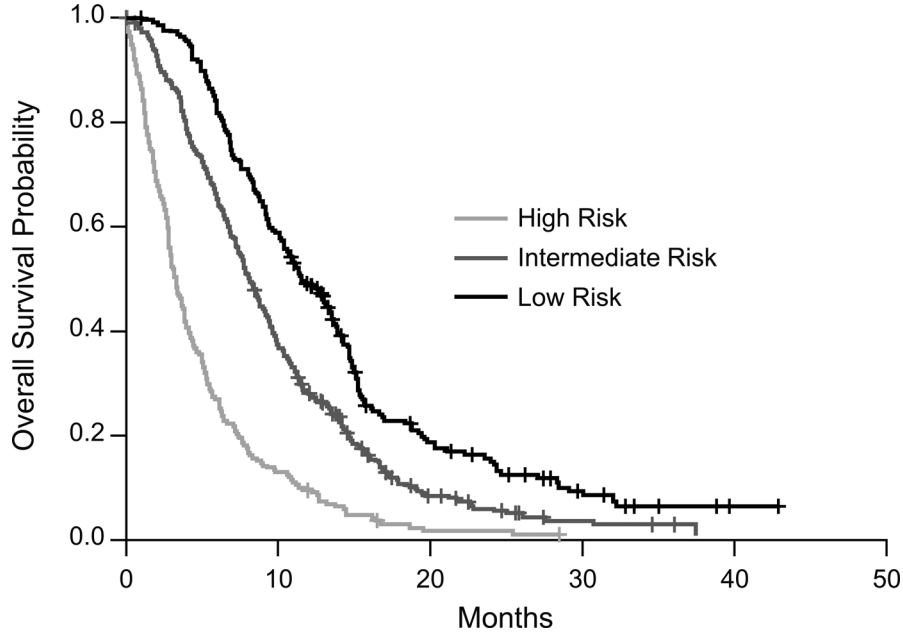

FIGURE 3. Kaplan-Meier survival curves according to nomogram-predicted survival probabilities of low-, intermediate-, and high-risk patients.

TABLE 3. Relative Contribution of Factors in a Nomogram for Prediction of OS in Patients With MPC

	Range per Factor		Nomograms, Points Contributed per Factor*						
				Primary Plus Each of the Below Factors Individually					
Factor	Value Worth Most Points (Worse Prognosis)	Value Worth Fewest Points (Better Prognosis)	Primary	CA 19-9†	Age	No. Metastatic Sites	No. Lesions	Lung Metastasis	Thrombosis
NLR	80	0	**100**	100	100	100	100	100	100
Albumin, g/L	0	60	**86**	87	85	85	86	86	86
KPS	60	100	**23**	23	24	23	23	23	23
SLD, cm	50	0	**18**	18	20	19	16	18	18
Presence of liver metastasis	Yes	No	**9**	9	9	9	9	9	9
Previous Whipple procedure	No	Yes	**6**	6	5	6	6	6	6
CA 19-9 level, U/mL	≥400,000	≤100,000	—	2	—	—	—	—	—
Age, y	90	20	—	—	8	—	—	—	—
No. metastatic sites	≤2	≥5	—	—	—	2	—	—	—
No. lesions	30	0	—	—	—	—	6	—	—
Lung metastasis	Yes	No	—	—	—	—	—	1	—
Thrombosis	Yes	No	—	—	—	—	—	—	1

*Points contributed to the nomogram as a measure of the relative importance of each factor; the greater the number, the greater the factor's contribution to the model.

†The CA 19-9 nomogram was created using data from a smaller subset of patients (n = 634) because nonsecretors (nonexpressors) were excluded.

KPS indicates Karnofsky performance status; NLR, neutrophil-lymphocyte ratio; SLD, sum of longest tumor diameters.

prognosis were neutrophil-lymphocyte ratio and albumin level. Other clinical factors that were forced into the nomogram contributed relatively little, with the possible exception of age and number of lesions. Indeed, the risk of forcing factors into the nomogram is evident in the potentially counterintuitive finding that having ≥5 metastatic sites would be associated with an incrementally longer OS prediction than having ≤2 sites. These results illustrate the problem with forcing nonsignificant individual factors from the univariable analysis into the nomogram.

A limitation of the present study was that the internal validation method used bootstrapping, which is a useful resampling method for reducing the propensity of a model to overfit to a specific data set but cannot ensure that the model will be applicable to an external cohort. External validation would be helpful to confirm that the nomogram based on the MPACT trial of patients treated with *nab*-paclitaxel plus gemcitabine or gemcitabine alone would apply to a more general patient population. Treatment arm was excluded from the current nomogram. Including treatment as a factor showed an interaction effect; however, considering that this was a multivariable analysis and that all variables outside of treatment were significant, this should not affect the generalizability of the nomogram. Nevertheless, because survival was clearly associated with treatment in the MPACT study, it is possible that the survival of patients receiving other treatments may be influenced by other sets of factors. The size and breadth of the MPACT data set partially address this lack of an external validation cohort and support the use of the current nomogram as a platform against which to compare new prognostic factors. Furthermore, internal validation of the nomogram demonstrated that it was reliable for the prediction of survival in low-, intermediate-, and high-risk groups, as indicated by the C-index score of 0.67. This indicates that it should be possible to establish risk categorization in MPC that might be applied to future trial stratification.

The factors presented in this nomogram are simple to evaluate from routinely collected information at baseline. Although the sum of longest diameter of target lesions and neutrophil-lymphocyte ratio may be less familiar to some physicians, both should be readily obtainable at little additional cost using existing patient measurements. Neutrophil and lymphocyte counts are routinely measured before treatment, and physicians can use a simple algorithm to calculate neutrophil-lymphocyte ratio. The sum of longest diameters of target lesions could also be obtained from radiographic scans. The remaining 4 factors (albumin level, Karnofsky performance status, presence of liver metastasis, and whether a patient has undergone a previous Whipple procedure) are all routinely collected in clinical practice.

In conclusion, data from a large, international, randomized phase 3 trial were used to develop a nomogram for patients with newly diagnosed MPC. Statistical analysis of 32 independent factors found that baseline neutrophil-lymphocyte ratio, albumin level, Karnofsky performance status, sum of the longest diameter of target lesions, presence of liver metastases, and previous Whipple procedure were associated with survival outcomes in patients with MPC (for online access, visit https://apps.pharmerit.com/mpc-nomogram). The information provided by this nomogram may be a guide to explore the range of OS outcomes and contribute to patient stratification in future prospective trials in MPC; however, external validation will be required to improve the reliability of the estimates and their applicability to a more general patient population. Caution should be exercised when interpreting these results for treatment decisions because patient-specific

characteristics could differ from those included in the nomogram. Although the nomogram cannot directly guide treatment decisions, it may help understand prognosis in pancreatic cancer.

Ethics Approval and Consent to Participate

The study was conducted according to the Good Clinical Practice guidelines and the Declaration of Helsinki. Ethical approval was obtained from the independent ethics committees at each participating institution for the MPACT trial. A listing of the independent ethics committees is available in Supplemental Table 1 in the Supplemental Digital Content (http://links.lww.com/MPA/A789). All patients provided written informed consent before initiating the trial.

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