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ARTICLE

Development and Validation of a Prognostic Nomogram for Terminally Ill Cancer Patients

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Background Determining life expectancy in terminally ill cancer patients is a difficult task. We aimed to develop and validate a nomogram to predict the length of survival in patients with terminal disease.

Methods From February 1, 2003, to December 31, 2005, 406 consecutive terminally ill patients were entered into the study. We analyzed 38 features prognostic of life expectancy among terminally ill patients by multivariable Cox regression and identified the most accurate and parsimonious model by backward variable elimination according to the Akaike information criterion. Five clinical and laboratory variables were built into a nomogram to estimate the probability of patient survival at 15, 30, and 60 days. We validated and calibrated the nomogram with an external validation cohort of 474 patients who were treated from June 1, 2006, through December 31, 2007.

Results The median overall survival was 29.1 days for the training set and 18.3 days for the validation set. Eastern Cooperative Oncology Group performance status, lactate dehydrogenase levels, lymphocyte levels, albumin levels, and time from initial diagnosis to diagnosis of terminal disease were retained in the multivariable Cox proportional hazards model as independent prognostic factors of survival and formed the basis of the nomogram. The nomogram had high predictive performance, with a bootstrapped corrected concordance index of 0.70, and it showed good calibration. External independent validation revealed 68% predictive accuracy.

Conclusions We developed a highly accurate tool that uses basic clinical and analytical information to predict the probability of survival at 15, 30, and 60 days in terminally ill cancer patients. This tool can help physicians making decisions on clinical care at the end of life.

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Determining a prognosis in advanced cancer patients is a difficult task for all physicians. There are no defined criteria to determine survival time more accurately. This uncertainty can affect medical decisions regarding treatment and end-of-life care (1). A reliable prognostic tool would be useful for 1) planning diagnostic and therapeutic strategies in accordance with life expectancy while avoiding unnecessary toxicities and treatments, 2) providing adequate information to patients and their families so that they can organize their time, economic resources, and foremost, their feelings, 3) optimal utilization of social and medical benefits, 4) making decisions regarding patient care, and 5) identifying groups of patients with similar prognoses to carry out future investigations (2,3).

The estimation of survival based on physicians' clinical experience is usually inaccurate and optimistic. (3). A number of parameters with prognostic value have been identified: performance status, symptoms associated with the cancer anorexia–cachexia syndrome, dyspnea, delirium, and abnormalities on some laboratory parameters (eg, high white cell count, lymphopenia, hypoalbuminemia, and elevated lactate dehydrogenase or C-reactive protein) (4,5). Several scoring systems have been developed using clinical and laboratory data in conjunction with quality-of-life scales (3,6). Nevertheless, some of these scoring systems have methodological problems or have not yet been validated.

We have performed a prospective multicenter study to identify more relevant clinical and laboratory variables and to develop a nomogram that predicts survival at 15, 30, and 60 days in terminally ill cancer patients.

Patients and Methods

Study Sample

We evaluated 974 terminally ill cancer patients. Terminal disease was defined as 1) evidence of progressive malignancy, 2) an assessment that it is unrealistic to expect therapy to prolong life

CONTEXT AND CAVEATS

Prior knowledge

It is often very difficult for physicians to predict how long terminally ill cancer patients will survive. An accurate validated prognostic scoring system might be useful.

Study design

A nomogram to estimate the probability of patient survival at 15, 30, and 60 days was built based on data from 406 terminally ill patients. Five of 38 possible clinical and laboratory variables were selected as the most predictive of survival time. The model was validated and calibrated with data from an independent set of 474 patients.

Contribution

Eastern Cooperative Oncology Group performance status, lactate dehydrogenase and albumin levels, lymphocyte counts, and time from initial diagnosis to diagnosis of terminal disease (TTD) were the factors most predictive of survival time. The nomogram that used these factors was 70% accurate in predicting survival time for the first group of patients and was 68% accurate for the validation set of patients.

Implication

The nomogram may be useful in making clinical decisions about end-of-life care.

Limitations

The nomogram was designed and validated based on a typical patient sample from a limited region of Spain. One of the five predictive factors, TTD, is a subjective parameter. Furthermore, for approximately 30% of patients, the nomogram does not accurately predict survival time.

From the Editors

substantially, 3) lack or discontinuation of specific antitumor therapy, and 4) an expected survival time of less than 6 months. First, we evaluated 448 consecutive patients in three different oncology and palliative care units (Hospital Universitario La Paz, Hospital San Rafael, and Residencia los Nogales de Madrid) between February 1, 2003, and December 31, 2005. Nine patients did not provide consent, 22 were lost during follow-up, and 11 did not have recent laboratory data. Finally, 406 patients were included. The data obtained were analyzed to create the survival prognostic nomogram. We then evaluated 526 consecutively attended patients in eight other oncology and palliative care units (Equipo de Soporte y Atención Domiciliaria del area 5 de Madrid, Equipo de Cuidados Domiciliarios de la Asociación Española contra el Cáncer de Madrid, Residencia Virgen de la Luz de Madrid, Hospital Universitario de Getafe, Hospital Universitario Ramón y Cajal de Madrid, Hospital Universitario Príncipe de Asturias de Alcalá de Henares, Hospital de Alcorcón, and the Hospital Universitario La Paz de Madrid), between June 1, 2006, and December 31, 2007, to validate the prognostic scale. In this second group, 18 patients did not have laboratory data, six did not give their consent, and 28 were lost during follow-up. Finally 474 patients were recruited to validate the scale. Every patient gave written informed consent for a specific interview and data collection from the medical record. In case of serious cognitive impairment, the consent was obtained from their relatives. The study design was in accordance with local hospital ethics committee rules.

Collection of Data

A total of 38 clinical and laboratory variables for each cancer patient were obtained from the clinical record; a brief personal interview was also performed. The following clinical variables were tabulated as follows: age, sex, primary cancer site, number and location of metastases, time from initial diagnosis to diagnosis of terminal disease (TTD), and survival time. Symptoms noted included nausea, vomiting, insomnia, cognitive failure [evaluated by the Mini-Mental State Examination (7)], bleeding, anorexia, percent weight change in the last months ([current − previous weight/previous weight] × 100%), dyspnea, pain, asthenia, dysphagia, anxiety [evaluated by the Zung Scale (8)], depression [using the Montgomery–Asberg Scale (9)], number of symptoms, performance status [evaluated by the Eastern Cooperative Oncology Group (ECOG) Scale (10)], capacity to carry out activities [measured by Katz Activities of Daily Living (11)], and quality of life [using the Spitzer QoL-Index (12)]. A blood analysis was performed within 1 week from the interview to assess albumin, hemoglobin (Hb), lactate dehydrogenase (LDH), gamma glutamyl transferase (GGT), alkaline phosphatase (AP), neutrophils, lymphocytes, creatinine, cholesterol, corrected calcium, bilirubin, uric acid, sodium, and potassium were obtained within 1 week of the personal interview and studied. Blood samples were obtained only for clinical purposes. Patients without these data were not included.

Statistical Analysis

Descriptive statistics characterizing patient groups are provided. Differences between groups were evaluated with independent t tests for continuous variables and χ^2 tests for categorical variables. The primary outcome was overall survival, defined as the time between date of diagnosis of terminal disease and date of death. The Kaplan–Meier and log-rank methods were used to estimate overall survival and to compare the survival in both samples (training and validation sets). The proportional hazards assumption was verified by test of correlations with time and examination of residual plots. Multivariable Cox regression was used to estimate the prognostic factors and their weights, and Cox regression was also used for univariate analyses on continuous and categorical prognostic factors. We used the Akaike information criterion to develop different multivariable models by systematically removing predictors that were not statistically significant ($P > .05$) starting from a (full) model containing all common prognostic factors (including factors that were statistically nonsignificant in the univariate analysis). P values were calculated using two-sided log-rank tests. The proportional hazard assumption for each predictor was verified by log [−log (probability)] plot. All statistical tests were two-sided, and P values less than .05 were considered to be statistically significant.

We evaluated the predictive performance of models by considering measures of discrimination and calibration. We used the bootstrapping method (1000 repetitions) to obtain a relatively unbiased estimate of the models' performance. Discrimination refers to the models' ability to distinguish between high-risk and low-risk patients; it was quantified using the area under the

receiver operating characteristic curve (ROC) and the concordance index (c-index) (13). The c-index—a generalization of the area under the ROC curve—is a probability of concordance between predicted and observed survival, with $c = 0.5$ for random prediction and $c = 1$ for a perfectly discriminating model (14). Patients who were censored at the time of each analysis (15, 30, and 60 days) were excluded in the calculation of ROC curves. Calibration (or reliability) refers to whether the predicted probabilities agree with observed probabilities. We performed the calibration using graphic representations of the relationship between the observed outcome frequencies and the predicted probabilities (calibration curves).

All statistical analyses were carried out with SAS 9.1.3 (SAS Institute Inc, Cary, NC) and R version 2.9.1 (The R Foundation for Statistical Computing, Vanderbilt University, Nashville, TN) using the Hmisc and Design libraries (http://biostat.mc.vanderbilt.edu/wiki/Main/Hmisc, http://biostat.mc.vanderbilt.edu/s/Design, http://biostat.mc.vanderbilt.edu/rms).

Results

The general characteristics of the 880 patients whom we finally analyzed (406 from the training analysis and 474 from the validation

Table 1. Characteristics of patients in the training set and the validation sets*

Patient characteristic	Training set, No. (%)	Validation set, No. (%)	P†
No. of patients	406	474	
Median survival, d	29.1	18.3	.72
Sex			.83
Female	159 (39)	190 (40)	
Male	247 (61)	284 (60)	
Age, median (range), y	66.4 (18–95)	67.2 (17–96)	.61
Primary cancer sites			
Lung	102 (25)	128 (27)	
Colorectal	77 (19)	100 (21)	
Other gastrointestinal tumors	63 (16)	62 (13)	
Breast	21 (5)	33 (7)	
Head and neck	18 (4)	14 (3)	
Hematologic	12 (3)	9 (2)	
Urinary organs	22 (5)	33 (7)	
Female reproductive	11 (3)	19 (4)	
Others	80 (20)	76 (16)	
No. of metastatic sites			.02
0–1	179 (44)	171 (36)	
>1	227 (56)	303 (64)	
Number of symptoms, median (range)	9.3 (2–19)	9.9 (2–18)	.01
Time from diagnosis to terminal phase, median (range), mo	8.1 (0–129)	7.8 (0–112)	.29
ECOG performance status			.16
0–2	119 (29)	161 (34)	
3–4	286 (71)	313 (66)	
Weight change in the last month, %			.03
<5	242 (59)	246 (52)	
≥5	166 (41)	228 (48)	
Cognitive impairment (MMSE)			.37
>24	240 (59)	265 (56)	
≤24	166 (41)	209 (44)	
Daily living activity scale (Katz index)			.32
Light dependence (A–C)	146 (36)	156 (33)	
Moderate–serious dependence (D–E)	260 (64)	318 (67)	
Quality of life (Spitzer QoL-Index)			.39
Good (5–10)	106 (26)	137 (29)	
Bad (0–4)	300 (74)	337 (71)	
Baseline laboratory values, median (IQR range)			
Hemoglobin, g/dL	10.9 (9.2–12.7)	10.6 (9.1–12.6)	.68
Neutrophils, No. × 10^3/μL	6740 (4788–9835)	6954(4912–10161)	.09
Lymphocytes, No. × 10^3/μL	1200 (770–1710)	1000 (653–1652)	.34
Albumin, g/dL	3.2 (2.7–3.8)	2.9 (2.5–3.6)	.03
Lactate dehydrogenase, units/L	464 (301–750)	471 (321–761)	.38
Uric acid, mg/dL	5.3 (4–6.7)	5.4 (4.1–6.8)	.26
Cholesterol, mg/dL	176 (146–210)	171 (142–201)	.21
Creatinine, mg/dL	1 (0.5–1.2)	1 (0.7–1.2)	.76
Bilirubin, mg/dL	0.8 (0.5–1.2)	0.8 (0.4–1.2)	.58
Corrected calcium, mg/dL	8.3 (7.1–9.2)	8.1 (7.3–9.3)	.91

* ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; MMSE = Mini-Mental Examination; QoL-Index = quality of life index.

† *P* values were calculated using two-sided *t* tests for continuous variables and χ^2 test for categorical variables.

cohort) show that both groups were similar respect to all variables except number of metastatic sites, number of symptoms, and weight change in the last month (Table 1). A total of 388 (95.5%) of 406 patients in the training cohort and 462 (97.4%) of 474 patients in the validation cohort had died by the time of data analysis. Median survival in the two groups was 29.1 days (95% confidence interval [CI] = 25.2 to 33.7) and 18.3 days (95% CI = 15.1 to 21.4) (Figure 1). Only 20(4.9%) of 406 patients survived beyond 6 months in the training cohort and seven (1.4%) of 476 patients survived beyond 6 months in the validation cohort.

In the univariate survival analysis from the training cohort, we identified 22 factors that were associated with survival time (Table 2). In the Cox model, only five independent variables were directly associated with survival time: ECOG performance status, serum albumin levels, serum LDH levels, lymphocyte counts, and TTD (Table 3). All of the cancer diagnosis groups had similar distributions for these prognostic variables.

A nomogram for predicting the probability of survival at 15, 30, and 60 days was constructed with the five variables (Figure 2). The concordance index for the model was 0.70. Therefore, 70% of the time the nomogram correctly predicted the ordering of the outcome between two randomly selected patients. Remodeling the nomogram to include other variables did not improve its discriminatory capacity and led to unnecessary model complexity (data not shown: c-index ranging from 0.65 to 0.70). When we tried to simplify the model by including only the three most statistically significant variables (Table 3), that is, ECOG performance status, albumin, and LDH, predictive accuracy was reduced (c-index = 0.68). ROC curves with three and five variables performed similarly at 15 days (at 15 days, area under the curve [AUC] = 0.778 vs 0.770), but the ROC curves with three variables did not do as well as those with five variables at 30 and 60 days (at 30 days, AUC = 0.761 vs 0.781; at 60 days, AUC = 0.745 vs 0.776).

Cumulative survival could be grouped into quartiles according to the score generated by the nomogram (Figure 3). Four groups were obtained with the score quartiles of all patients. Median survival of patients of in quartile 1 was 83 days (95% CI = 64 to 102 days) vs in quartile 2, 33 days (95% CI = 22 to 44 days), in quartile 3, 24 days (95% CI = 20 to 28 days), and in quartile 4, 10 days (95% CI = 8 to 12 days). The nomogram-predicted survival was well calibrated with the Kaplan–Meier observed survival (Figure 4).

Two patients from the series were selected to provide an example on how the nomogram works (Supplementary Figure 1, available online). For the first patient, the chance of being alive at 15, 30, and 60 days was predicted at 50%, 25%, and 8%, respectively (Supplementary Figure 1, A, available online), whereas for the second patient, it was predicted at 82%, 65%, and 48%, respectively

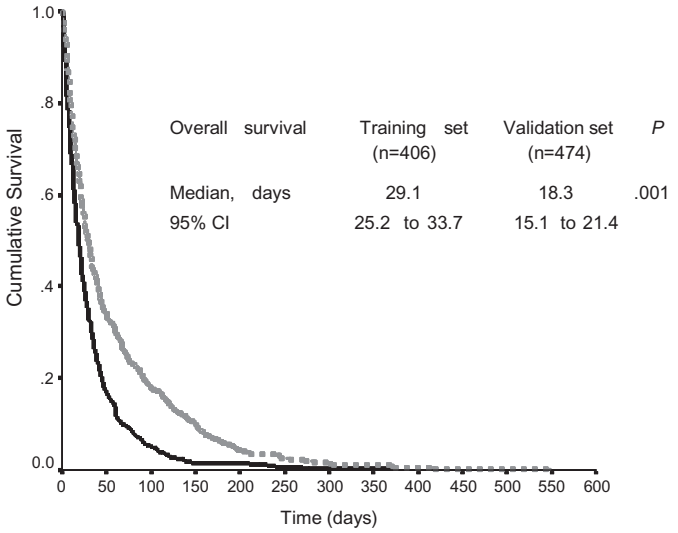

Figure 1. Cumulative survival curves of the two series of patients included in the study. The **lighter dotted line** represents the training set (**gray**), and the **solid dark line** represents the validation set (**black**). CI = confidence interval.

Table 2. Univariate Cox proportional hazards regression survival analysis*

Variable	*P*†	β (SE)
Statistically nonsignificant factors		
Sex	.72	0.028 (0.107)
Number of metastases	.21	0.124 (0.056)
Lung metastases	.14	−0.137 (0.108)
Liver metastases	.10	0.205 (0.109)
Bone metastases	.92	−0.001 (0.144)
Central nervous metastases	.051	0.287 (0.138)
Lung cancer	.69	0.046 (0.145)
Colorectal cancer	.70	−0.052 (0.134)
Other gastrointestinal tumors	.82	−0.032 (0.145)
Breast cancer	.70	−0.089 (0.231)
Dyspnea	.24	0.088 (0.041)
Dysphagia	.31	0.034 (0.046)
Pain	.87	0.039 (0.043)
Insomnia	.37	0.138 (0.048)
Bleeding	.25	0.082 (0.077)
Potassium, mEq/L	.13	−0.151 (0.088)
Sodium, mEq/L	.19	−0.028 (0.01)
GGT, U × 10^3/L	.14	0.384 (0.143)
Alkaline phosphatase, U × 10^3/L	.052	0.182 (0.057)
Neutrophils, No. × 10^9/L	.12	0.016 (0.007)
Uric Acid, mg/dL	.84	0.014 (0.022)
Statistically significant factors		
Age	.036	−0.01 (0.004)
Time from diagnosis	.020	−0.004 (0.003)
ECOG	.000	0.524 (0.068)
Katz Index	.000	−0.019 (0.003)
IQL Spitzer	.000	−0.227 (0.031)
No. of symptoms	.000	0.071 (0.015)
Weight loss >5%	.002	0.188 (0.04)
Asthenia	.000	0.236 (0.056)
Anorexia	.000	0.244 (0.049)
Cognitive impairment	.000	0.117 (0.05)
Nauseas	.001	0.166 (0.048)
Vomiting	.003	0.202 (0.065)
Depression	.020	0.014 (0.005)
Anxiety	.015	0.014 (0.005)
Creatinine, mg/dL	.039	0.074 (0.07)
Corrected calcium, mg/dL	.007	−0.022 (0.017)
Hemoglobin, g/dL	.006	0.065 (0.021)
Lymphocytes, No. × 10^9/L	.000	−0.124 (0.054)
Bilirubin, mg/dL	.001	0.042 (0.012)
LDH, U × 10^3/L	.000	0.147 (0.03)
Cholesterol, mg/dL	.009	−0.002 (0.001)
Albumin, g/dL	.000	−0.472 (0.075)

* ECOG = Eastern Cooperative Oncology Group; GGT = gamma glutamyl transferase; IQL = Spitzer Quality of Life (QoL) Index; LDH = lactate dehydrogenase; β = Cox regression coefficient.

† *P* values were calculated using two-sided log-rank test.

Table 3. Variables statistically significantly associated with survival in the Cox regression analysis*

Variable	β	SE	P†	HR (95% CI)
ECOG performance status	0.399	0.074	.000	1.490 (1.289 to 1.723)
TTD, mo	−0.006	0.003	.025	0.994 (0.988 to 0.999)
Albumin, g/dL	−0.316	0.082	.000	0.729 (0.621 to 0.856)
Lactate dehydrogenase, units × 10^3/L	0.119	0.032	.000	1.127 (1.058 to 1.200)
Lymphocytes, No. × 10^3/μL	−0.132	0.052	.011	0.876 (0.791 to 0.970)

* CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; TTD = time from initial diagnosis to diagnosis of terminal disease.

† *P* values were calculated using a two-sided Wald test for multivariable analyses.

(Supplementary Figure 1, B, available online). The actual survival for the first patient was 11 days. The second patient survived 76 days.

We validated the nomogram with an external dataset that included 474 patients from nine oncology and palliative care units from 2006 to 2007. Patients in the validation set had more metastases, more weight loss, and a higher overall symptom burden compared with patients in the training set (Table 1). Median survival was statistically significantly shorter from that of the validation set ($P < .001$) (Figure 1). The nomogram assigned a score to each patient in this validation cohort, and this score had a good correlation with survival (concordance index = 0.68, ie, 68% predictive accuracy). ROC analysis for the nomogram showed a good discrimination at 15, 30, and 60 days (AUC = 0.776, 0.778, and 0.774, respectively; see Supplementary Figure 2, available online). The nomogram prediction was calibrated at 15, 30, and 60 days by the training and validation sets (Figure 4). Nomogram predictions seemed to be well calibrated with actuarial survival in both cohorts.

The Palliative Prognostic Score (PaP) (6) was calculated for 459 patients from the validation series for whom clinical prediction of survival was available. We assessed the concordance between the actual survival and the estimated chance of survival using the PaP Score vs our nomogram (Figure 5). Our nomogram provided better AUC values (at 15 days, AUC = 0.682 [95% CI = 0.623 to 0.741] vs 0.775 [95% CI = 0.721 to 0.823]; at 30 days, AUC = 0.681 [95% CI = 0.628 to 0.735] vs 0.776 [95% CI = 0.729 to 0.821]; and at 60 days, AUC = 0.671 [95% CI = 0.613 to 0.729] vs 0.774 [95% CI = 0.725 to 0.828], respectively).

Discussion

In patients with advanced disease, predicting survival continues to be a major challenge for health-care providers. Although survival is not the goal of care for palliative medicine patients, many potentially unnecessary or futile interventions such as parenteral feeding or surgery could be avoided if a better survival tool was available. This kind of estimate is essential to better inform our patients and their relatives and also to optimize delivery of limited health resources.

We have developed an accurate tool that uses basic readily available clinical and analytical information to predict the probability of survival at 15, 30, and 60 days in terminally ill cancer patients. Independent prognostic factors included in the nomogram are ECOG performance status, LDH levels, lymphocyte

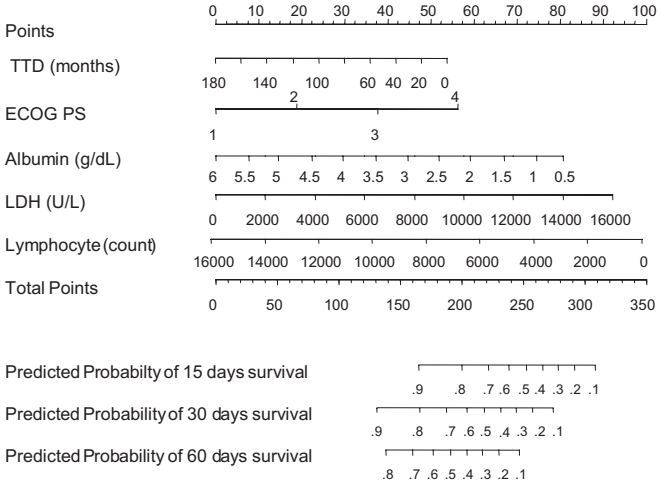

Figure 2. Nomogram for predicting the probability of 15-, 30-, and 60-day survival. Points are assigned for time from initial diagnosis to diagnosis of terminal disease (TTD), Eastern Cooperative Oncology Group performance status (ECOG PS), serum albumin levels, serum lactate dehydrogenase (LDH) levels, and lymphocyte count by drawing a line upward from the corresponding values to the Points line. The sum of these five points is plotted on the Total Points line. The Total Points line yields prediction of 15-, 30-, and 60-day survival by drawing a line downward.

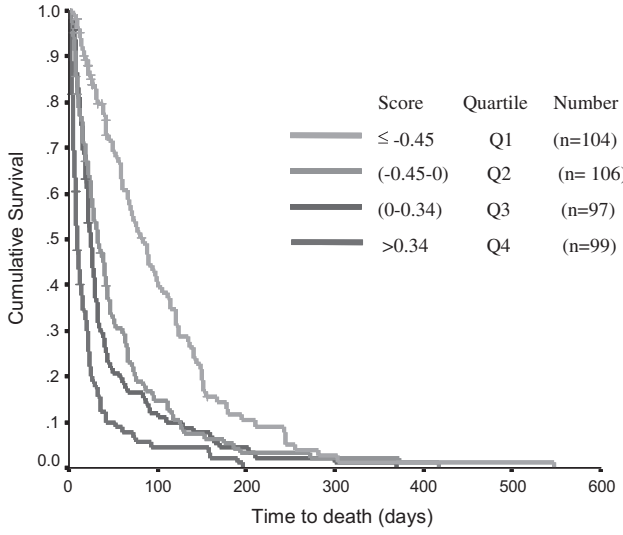

Figure 3. Cumulative survival curves of patients grouped into quartiles based on the score generated by the nomogram in training set. A score less than −0.45 is associated with a median overall survival (OS) of 83 days (95% confidence interval [CI] = 64 to 102 days); a score between −0.45 and 0, with a median OS of 33 days (95% CI = 22 to 44 days); a score between 0 and 0.34, with a median OS of 24 days (95% CI = 20 to 28 days); a score greater than 0.34, with a median OS of 10 days (95% CI = 8 to 12 days). Q = quartile; n = number of patients in every quartile.

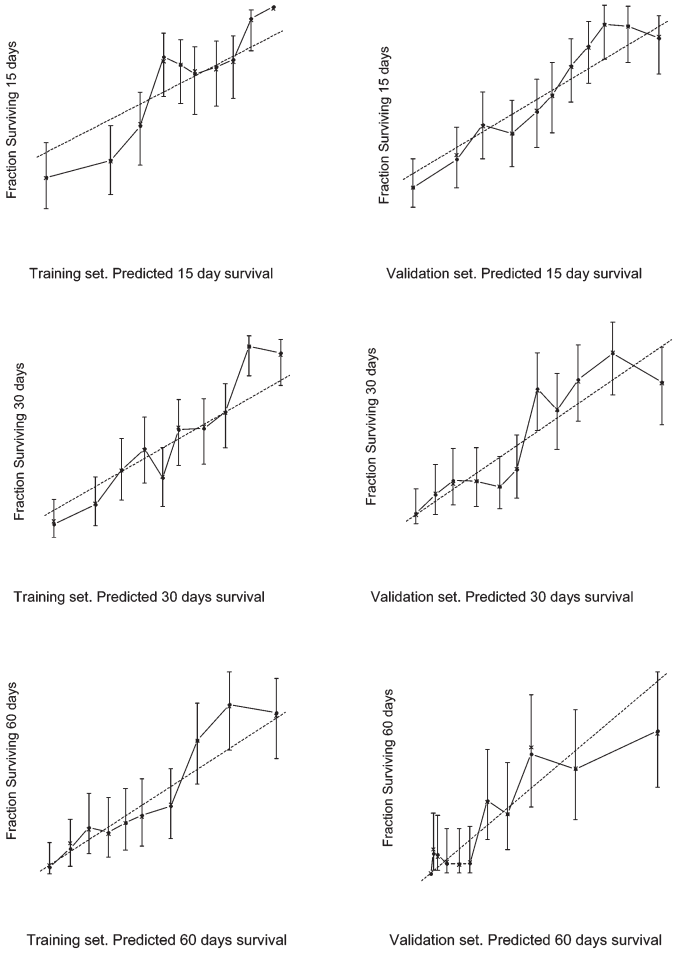

Figure 4. Calibration curves for the nomogram-predicted probability of 15-, 30-, and 60-day survival in the training and validation sets. **Curves** for a hypothetical ideal nomogram are represented by the **dashed lines** and those for the current nomogram are represented by **solid lines**. **Vertical bars** indicate 95% confidence intervals.

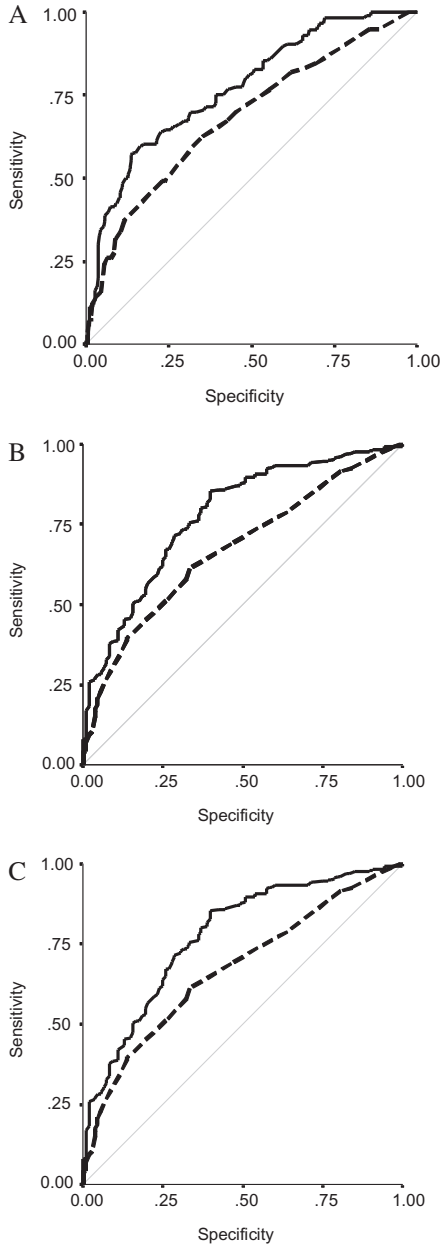

Figure 5. Receiver operating characteristic analyses to assess the abilities of the Palliative Prognostic score (PaP score) (6), and our nomogram to predict actual survival among the 459 patients in the validation set. **A**) 15 days, **B**) 30 days, and **C**) 60 days. Predictions by the PaP score are represented by the **black broken lines** and predictions by our nomogram are represented by the **black solid lines**.

levels, albumin levels, and TTD. The nomogram based on these variables predicted survival time well, with a bootstrapped corrected concordance index of 0.70, a good calibration, and a concordance index of 0.68 with an external independent validation patient cohort.

The Steering Committee of the European Association for Palliative Care established that to be "relevant" in this area, a study should fulfill at least five of seven quality criteria: a prospective design, well-defined cohort of patients, fewer than 20% of patients lost to follow-up, a ratio of 10:1 or greater between the number of events vs the number of predictors, fully defined prognostic variables and available data for a high proportion of patients, reliable measurement of outcome, and random patient selection. Our study fulfills all of them, and the clinical and biological characteristics associated with survival are similar to those previously reported (15). The association between performance status and survival has been frequently reported (16). Poor performance status and rapid deterioration have been associated with short survival, but good performance status is not necessarily related with long survival (17). This parameter, however, is evaluated with a subjective scale (ECOG) that can be substantially affected by other acute occurrences such as infections or pathological fractures (18).

This nomogram includes several other criteria for prediction of survival. Serum LDH is a nonspecific tumor marker that can reveal not only the presence of a tumor mass but also its potential aggressiveness (19). LDH has been investigated extensively as a prognostic factor of survival in different tumors (20,21), as well as an indicator of expected survival in patients with advanced cancer (22) and in terminally ill patients (18,23). The serum albumin level was used to evaluate protein reserves. This parameter also has been related to survival time in advanced cancer patients (20,22) and to hospital mortality in cancer (18) and noncancer patients (24). The

etiology of lymphopenia in terminally ill cancer patients is not clear, but it may arise from anorexia–cachexia syndrome (25) and it has also been mentioned in previous studies (18,26,27) as a possible negative prognostic factor in these patients. To our knowledge, this is the first study in which TTD was found to predict survival in terminally ill patients. This parameter may be related to disease aggressiveness, similar to relapse-free survival in tumors such as breast or kidney cancer (28,29). The type of primary tumor and the location of metastases did not have prognostic value in our series. There is general agreement that these parameters have a limited prognostic value in the final stages of life (3,15).

Survival scores for terminally ill cancer patients have previously been reported (6,23,30–33). The one that is most commonly used is the PaP, which is based on Karnofsky performance status, clinical prediction of survival, anorexia, dyspnea, leukocyte count, and percentage of lymphocytes. The PaP model also studied clinical and laboratory parameters in a large patient sample and classified the advanced cancer patients into three different prognostic groups with median survival times of 64, 32, and 11 days, and probabilities of survival at 30 days of greater than 70%, 30%–70%, and less than 30% (6). Nevertheless, at least 50% of the total PaP score is determined by the clinical prediction of survival, which is a subjective factor with wide variation between different observers (16). The authors themselves acknowledged that clinical predictions by a physician with a lack of experience in oncology and palliative care could reduce the score's predictive power (6). This score has been validated (34). The Palliative Prognostic Index developed by Morita includes performance status, oral intake, edema, dyspnea, and delirium (30). It has proven useful for determining which patients will survive after 6 weeks, but all of these variables are subjective. Furthermore, clinicians have to determine whether the delirium is a result of the medication and whether it is potentially reversible. This can be a problem, especially in very weak patients and those on multiple medications (5). Chuang et al. (31) proposed a model in which five out of eight variables were subjective; this model could only distinguish between patients with expected survival times of over 2 weeks and less than 2 weeks, severely limiting its clinical utility. The other prognostic models reported (32,33) were developed in small samples of patients and have not been validated in an independent cohort.

We sought to evaluate prognostic variables using a robust statistical approach. To our knowledge, the present nomogram is the first that has been developed specifically to predict the outcome for terminally ill cancer patient. Overall, prognostic nomograms give better prediction of the likelihood of events for individual patients than do staging systems that stratify patients into a few broad groups. Nomograms are based on statistical models that use a combination of prognostic variables to determine the likelihood of a certain event (35). The present nomogram can assign numeric predictions for the chances of survival at 15, 30, and 60 days. Although our c-index was good, some variation remains unexplained. The discrimination achieved here could be improved with the incorporation of additional variables. Some relevant survival parameters such as clinical prediction of survival, C-reactive protein, and comorbid conditions were not assessed in our study but might give additional prognostic information.

Our study also has some limitations. We included inpatients and outpatients from different cancer centers so that our findings could be generalized. Validation was performed in an external series with different clinical features and survival as compared with those of the training set. However, the validation cohort came from the same geographical area; so the validity of nomogram should be explored in other regions or, even better, in other countries. Second, we did not evaluate the influence of the clinical prediction of survival as a prognostic factor. Although this parameter has been suggested to be useful (15) and has been included in several prognostic survival scales (6), various studies have shown that these predictions only are correct for 20%–40% of patients, and 50%–83% of them are overly optimistic (4,18,36). The correlation between the clinical prediction of survival time and actual survival time does not surpass 0.51 (37). Additionally, this measure is considered to be too subjective and can vary among professionals (37,38). We chose to use parameters that were objective and easily measurable to make the elaboration of an accurate prognosis by clinicians as simple and reproducible as possible. Third, a blood sample needs to be obtained to make a prognosis. Although obtaining blood samples is a routine procedure with advanced cancer patients, it can sometimes be considered too invasive. This can be compensated by the relevance of the information obtained (23). Fourth, TTD is a subjective parameter, unlike the date of cancer diagnosis. There is no universal consensus on the definition of terminal disease, so its diagnosis depends on each physician's evaluation. However, this factor had a low weight in the prognostic nomogram, so even moderate variations had less influence on the final score.

Although our nomogram can help in making clinical decisions, we should keep in mind that predictions may be inaccurate in up to 32% of patients (c-index = 0.68). However, the nomogram provides an advantage over decisions based on clinical experience.

In conclusion, we have developed a validated nomogram for predicting the probability of survival at 15, 30, and 60 days in advanced cancer patients. This nomogram can aid in elaborating the survival prognosis and in making decisions to improve the care of our patients.

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