Multicenter Outcome Study of Cancer Patients Admitted to the Intensive Care Unit: A Probability of Mortality Model

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Purpose: **To develop prospectively and validate a model for probability of hospital survival at admission to the intensive care unit (ICU) of patients with malignancy.**

Patients and Methods: **This was an inception cohort study in the setting of four ICUs of academic medical centers in the United States. Defined continuous and categorical variables were collected on consecutive patients with cancer admitted to the ICU. A preliminary model was developed from 1,483 patients and then validated on an additional 230 patients. Multiple logistic regression modeling was used to develop the models and subsequently evaluated by goodness-of-fit and receiver operating characteristic (ROC) analysis. The main outcome measure was hospital survival after ICU admission.**

Results: **The observed hospital mortality rate was 42%. Continuous variables used in the ICU admission model are PaO_2/FiO_2 ratio, platelet count, respiratory rate, systolic blood pressure, and days of hospitalization pre-ICU. Categorical entries include presence of intracranial mass effect, allogeneic bone marrow transplantation, recurrent or progressive cancer, albumin less than 2.5 g/dL, bilirubin ≥2 mg/dL, Glasgow Coma Score less than 6, prothrombin time greater than 15 seconds, blood urea nitrogen (BUN) greater than 50 mg/dL, intubation, performance status before hospitalization, and cardiopulmonary resuscitation (CPR). The *P* values for the fit of the preliminary and validation models are .939 and .314, respectively, and the areas under the ROC curves are .812 and .802.**

Conclusion: **We report a disease-specific multivariable logistic regression model to estimate the probability of hospital mortality in a cohort of critically ill cancer patients admitted to the ICU. The model consists of 16 unambiguous and readily available variables. This model should move the discussion regarding appropriate use of ICU resources forward. Additional validation in a community hospital setting is warranted.**

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MANY PATIENTS WITH SOLID TUMORS and hematologic malignancies can now be cured of their underlying disease. However, when these patients become critically ill and require admission to the intensive care unit (ICU), their prognosis for short- and long-term survival is poor.[1-12] Specific variables to predict survival of critically ill cancer patients who require intensive care are not available, while data on the duration or quality of life after hospital discharge are limited.[1,8,9,12,13] In general hospitals, cancer patients are considered to have a particularly poor prognosis and frequently are not admitted to the ICU.[14] Clinical experience, as well as the medical literature, suggests that those patients with hematologic malignancies who require mechanical ventilation fare significantly worse than patients who do not require mechanical ventilation.[3-10,12,15-19]

Decisions to admit cancer patients to the ICU are exceptionally complex, as the chances of potentially curative cancer therapy or long-term palliation must be weighed against the associated risk of catastrophic morbidity or mortality. Disagreement may exist between those who initiate cancer treatment and those who render care of the complications. To some health care providers and patients, lack of desire to pursue all means of support may seem obstructionist, while to other health care providers or a different patient, such care may seem like an unwise consumption of medical and emotional resources.

There are few reliable predictors of ICU mortality for the general adult medical population[20-22] and none have been validated for patients with malignancy. We present the results of a multicenter study to develop an admission severity of illness model for cancer patients admitted to the ICU.

PATIENTS AND METHODS

Data were prospectively collected in four academic tertiary care hospitals beginning July 1, 1994 to develop and validate a multivariable logistic regression model to estimate the probability of hospital mortality among cancer patients admitted to the ICU. Participating units were the Medical/Surgical ICU of Memorial Sloan-Kettering Cancer Center (MSKCC), New York, NY, and of City of Hope National

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Medical Center, Duarte, CA, and the Medical ICU of The University of Texas M.D. Anderson Cancer Center, Houston, TX, and of Mount Sinai Medical Center, New York, NY. The study was approved by the institutional review board of all participating sites.

All cancer patients admitted to the ICU were included, with the exception of patients less than 18 years old, burn patients, and coronary patients, who were defined by a primary diagnosis of myocardial infarction (MI) or "rule out" MI (ROMI) with no secondary diagnosis. The outcome of interest was vital status at hospital discharge. Patients discharged to another hospital for an increased level of care were not included in the analysis. For patients with multiple admissions to the ICU during the study period, only the most recent admission was used in the analysis.

Demographic, clinical, laboratory, and physiologic variables were obtained on consecutive cancer patients at ICU admission, as well as their vital status at ICU and hospital discharge. Only laboratory results available to the clinician within 1 hour of ICU admission were used, provided they had been drawn within the prior 24 hours. When multiple determinations were available, the most recent result was used. The performance status of patients was determined for the week before hospitalization using the Zubrod performance scale.[23] Data elements in the Mortality Probability Model II (MPM II)[20] were also collected to evaluate the applicability of this admission tool in cancer patients. No specific clinical interventions or diagnostic tests were performed on any patient for the purpose of developing the outcome model. All categorical variables were defined before patient accrual and were available to each data collector.

Variables were recorded in duplicate on standardized study forms and then entered into a computerized data base available at each study center. A copy of the data form, as well as the computer data, were submitted to MSKCC for determination of quality and completeness of data entry. Validity checks for entry variables were incorporated within the study software. All computer entries were validated at MSKCC against the original paper copies. After 5 months of data collection, interrater reliability was evaluated on the variables from a random sample of 10% of the patients. Patient medical records were reviewed and data reentered by a single nonbiased data collector sent to the study center. Kappa statistics were used to examine interrater reliability. Results of these studies were discussed among all study coordinators and data collectors after analysis. After data were checked for validity and accuracy, we proceeded with model development. As MPM II had not been validated in our study population, individual scores were calculated from admission data at the model development site, not at individual clinical centers.

Patients were classified as being in one of three tumor groups: solid tumor, leukemia or bone marrow transplant, or lymphoma or myeloma. Patients with leukemia, bone marrow transplant, lymphoma, or myeloma were classified as having nonmetastatic disease. Patients were classified as either medical or surgical, with surgical patients being those who had a surgical procedure before ICU admission. Patients with leukemia, bone marrow transplant, lymphoma, or myeloma who had an open-lung biopsy for diagnosis of etiology of respiratory insufficiency were classified as medical patients.

Univariate analyses were conducted to examine the distribution of each variable. For variables for which no specific data were recorded for a patient, a response of no or never or normal was imputed if the variable was categorically scaled, and a value within normal limits was imputed if the variable was continuously scaled. Bivariate analyses were performed to test the significance of each variable in relation to vital status at hospital discharge, using χ^2 tests for categorical variables and t tests for continuous variables.

To determine the appropriate form for each continuous variable, an analysis using fractional polynomials[24] was performed to assess whether the variable was linear in relation to outcome, or whether the linear term required a transformation to reflect adequately its relationship with outcome. The test of the significance of the transformed variable was based on the gain achieved by the transformation, with gain being defined as the difference in the deviances of models, comparing several transformations to each other and to the linear model. If there was evidence that a variable was nonlinear, the appropriate transformation was applied.

To identify possible cutpoints to categorize nonlinear continuous variables, the continuous independent variables were plotted against the dependent variable, vital status at hospital discharge, using the locally weighted robust scatterplot smoothing function with locally weighted least squares.[25] The plots suggested cutpoints for categorizing the variable at a value or values associated with a change in the nature of the relationship between the independent and the dependent variable.

For categorical variables with multiple levels, a dummy variable for each level was created. Each dummy variable took on the value of 1 for patients in the category being defined and took on the value of 0 for patients not in the category. The referent group, against whom each level of the variable was compared, consisted of patients in none of the specified categories. The referent group for a variable was generally defined as those patients either not currently displaying a condition or having never displayed the condition.

To develop the initial logistic regression model, all of the variables that were significant in the bivariate analysis at a level of .10 were eligible for inclusion in the model. Using the appropriate dummy coding or transformations determined for each variable, all variables were entered into a logistic regression model. The significance of each variable in the multivariable context was assessed, and variables were then deleted, one at a time, until all variables in the model were significant, with statistical significance defined as $P \leq .05$.

The calibration and discrimination of models was assessed. The Hosmer-Lemeshow[26] goodness-of-fit test was used to evaluate model calibration. This tested the ability of the probabilities based on the model to generate expected numbers of patients who did or did not survive to hospital discharge that closely reflected the observed numbers of such patients across several strata of probabilities. For the Hosmer-Lemeshow test, a 20-cell table was formed by 10 deciles of probability and two categories of outcome. In each of the 10 strata, the expected frequency of patients who died was calculated by summing the probabilities for patients in each stratum, and the expected frequency of patients who lived was calculated as the difference between the total number of patients in the stratum and the expected number of patients who died. The χ^2 value was calculated in the usual manner, using the observed and expected frequencies in each cell. A low value of the statistic, and a corresponding high P value, indicated that there was good agreement between the observed and expected number of patients across all of the probability levels. For the test of the fit of the model in the data set in which the model was developed, the df was 8. When testing the fit of the model in the independent validation data set, the $df = 10$.

The area under the receiver operating characteristic (ROC) curve[27] was calculated to evaluate discrimination. Traditionally, ROC curve analysis is used to evaluate the performance of different diagnostic tests. The curve is constructed by varying the cutpoint of values of an observed variable considered to be abnormal, and then plotting resulting sensitivities against corresponding false-positive rates (1 - specificity). This tested the ability of the model to discriminate between patients who lived and patients who died by determining the percent of time that

the probability of mortality was higher for patients who died than for patients who lived, among all possible pairings of such patients. An area under the ROC curve greater than 70% is generally considered to be evidence of good model discrimination.

Diagnostic techniques were used to determine whether any patients, by virtue of their particular covariate patterns, were having a significant impact on the size of the model coefficients. Patients with a shared covariate pattern have exactly the same values for the set of model variables, and Pregibon's delta beta[26] was calculated as an indicator of the magnitude of the difference in the coefficients with and without the inclusion of data for patients sharing the same covariate pattern. If patients who had a particular covariate pattern were found to be exerting a significant impact on the coefficients, those data would be eliminated from the sample and the model would be refit. The goodness-of-fit of the resulting model would be tested to determine whether the model performed better without the data for the eliminated patient. The goal of this procedure was to generate a set of model coefficients that was free from the effect of overly influential covariate patterns. When the final model was developed, it was validated on an independent sample of cancer patients using tests of calibration and discrimination as described.

RESULTS

Our analysis was based on 1,483 cancer patients who met all of the inclusion criteria. Data were obtained on 1,653 patients, of which 37 had multiple ICU admissions. After keeping only the last hospitalization, we eliminated 16 patients under 18 years of age, 77 patients with unknown outcome or discharge to facilities for increased level of care, five patients missing malignancy information, 91 MI/ROMI, three patients with diagnosis of cancer after admission, and two patients in the initial modeling for whom critical data were missing. There was some overlap in the cases to be deleted by the several criteria, so that the model was based on 1,483 patients. The numbers of patients from each site were as follows: MSKCC, 541; M.D. Anderson, 505; City of Hope, 235; and Mount Sinai, 202.

There was generally good agreement demonstrated in the assessment of interrater reliability. Both the kappa statistics and the correlation coefficients performed on a random sample of 52 of the first 500 entries are presented (Table 1).

In the first 805 patients, admission MPM II values were calculated to determine the model's applicability in cancer patients. Table 2 lists the observed and predicted hospital mortality using MPM II for the cohort at large, as well as by particular types of tumors. MPM II significantly underpredicted mortality, with poor discrimination and calibration for all patients. The *P* values for the Hosmer-Lemeshow goodness-of-fit for all models were less than .001 and the largest area under ROC curve was .656 for the solid tumor group.

Model development commenced when MPM II was shown not to produce reliable estimates of hospital outcome. To assess the strength of the association of each continuous variable with the outcome, *t* tests were performed. Table 3 lists the mean ± SD for each variable among patients who died in the hospital and patients who survived to hospital discharge, along with the level of significance associated with the *t* test of the difference in the means of the two groups.

To assess the strength of the association of each categorical variable with hospital mortality, χ^2-tests were performed. The results are listed in Table 4, which presents the number and percent of patients who lived and patients who died for the patients with the variable of interest and patients without the variable, along with the level of significance of the associated test.

The next step of the analysis was to determine the

Table 1. Kappa and Correlation—Variables in Cancer Admission Model

Variable	Agreement (%)	Expected Agreement	Kappa	Z	*Pr* > Z
Kappa results for categorical variables					
Variable in model as collected					
CPR before ICU	98.04	90.66	0.7901	5.77	.0000
Intracranial mass	98.04	90.66	0.7901	5.77	.0000
Recoded categorical variables					
Intubation code	98.08	61.54	0.9500	6.86	.0000
BMT code	100	96.23	1.0000	7.21	.0000
Disease progression	96.15	50.07	0.9230	6.66	.0000
Performance status					
Zubrod 2-3	88.46	71.08	0.6010	4.50	.0000
Zubrod 4	96.15	85.72	0.7306	5.47	.0000
Continuous variables recorded to categorical					
GCS	96.15	85.72	0.7306	5.47	.0000
PT	100	96.13	1.0000	7.21	.0000
Albumin	92.31	50.22	1.0000	7.21	.0000
Bilirubin	96.15	79.59	0.8116	5.85	.0000
BUN	100	68.93	1.0000	7.21	.0000
Outcome	100	42.17	1.0000	9.65	.0000
Correlation results of continuous variables					
Variable	Correlation				
Respiratory rate	0.9702				
Systolic BP	0.9613				
PaO_2	0.7050				
FiO_2	0.9100				
Platelet count	0.9733				
Days before ICU	1.0000				

Abbreviations: CPR, cardiopulmonary recuscitation; BMT, bone marrow transplant; GCS, Glasgow Coma Score; PT, prothrombin time; BP, blood pressure.

Table 2. Applicability of MPM II for Cancer Patients

	All Patients	Solid Tumor	Leukemia	Lymphoma Myeloma	BMT
No. of patients	805	443	221	141	119
Observed mortality (%)	41	32	61	42	56
MPM predicted mortality (%±SD)	22 ± 21	25 ± 22	18 ± 19	17 ± 18	16 ± 17
ROC	.625	.656	.635	.626	.583

NOTE. The fit of MPM II in cancer patients was poor as evaluated by the Hosmer-Lemeshow goodness-of-fit test. $P < .001$ for all groups.

Table 3. Mean ± SD of Continuous Variables for Patients Who Lived and Patients Who Died

Variable	Died		Lived		P
	Mean	SD	Mean	SD	
Age	54.6	16.2	56.4	15.7	.030
Hospital days before ICU	11.3	17.1	5.8	11.3	<.001
Months since cancer diagnosis	31.1	56.9	31.2	53.2	.973
GCS	13	4	14	2	<.001
Body temperature (°C)	37.1	1.4	37.2	1.2	.410
Heart rate (beats/min)	115	25	109	24	<.001
Respiratory rate (breaths/min)	25	10	22	9	<.001
Systolic blood pressure (mm Hg)	116	28	123	27	<.001
PaO_2/FiO_2 ratio	205	134	268	138	<.001
pH	7.37	0.14	7.41	0.11	<.001
PCO_2 (mm Hg)	38	14	38	13	.681
Hematocrit (%)	29	7	31	7	<.001
WBC count (×1,000)	15.7	35.7	13.1	22.3	.129
Platelets (×1,000)	113	137	186	177	<.001
ANC (×1,000)	8.3	11.7	7.9	7.8	.530
PT (sec)	15.1	3.8	13.8	3.0	<.001
INR	1.6	0.8	1.4	0.6	<.001
PTT (sec)	34.4	13.8	31.0	11.2	<.001
Bilirubin (mg/dL)	2.8	4.2	1.4	2.2	<.001
LDH (IU)	1,508	3,406	870	1,458	.001
Albumin (g/dL)	2.8	0.7	3.2	0.6	<.001
Calcium (mg/dL)	8.2	1.2	8.4	1.1	<.001
Creatinine (mg/dL)	1.6	0.9	1.5	0.6	.521
BUN (mg/dL)	32	24	24	24	<.001
Glucose (mg/dL)	167	79	160	102	.217
Sodium (mEq/L)	136	6	136	5	.094
Potassium (mEq/L)	4.1	0.9	4.1	0.8	.886
HCO_3 (mEq/L)	23	7	24	5	<.001

Abbreviations: ANC, absolute neutrophil count; PTT, partial thromboplastin time; LDH, lactate dehydrogenase.

appropriate transformation or categorization of the continuous variables using fractional polynomials and the LOWESS smoothing procedure. Using all of the variables as transformed or categorized, all of the variables that were significant in the bivariate analyses were included in the generation of an initial logistic regression model. Once all of the variables were in the model, they were deleted stepwise, one at a time, based on the level of significance, until only the subset of significant variables was retained. Variables that had been eliminated early were then allowed to enter the model, one at a time, to determine if their level of significance increased given the subset of initially significant variables. Similarly, variables that had not been significantly associated with vital status in the analysis using the individual independent variables were allowed to enter so that their significance in the multivariable model could be evaluated.

The resulting model contained 21 variables, of which nine

Table 4. Number and Percent of Patients Who Lived and Patients Who Died by Level of the Categorical Variable

Variable	Died		Lived		P
	No.	%	No.	%	
Metastatic disease					
Yes	164	38.1	267	61.9	.055
No	456	43.5	593	56.5	
Tumor group					
Leukemia/BMT	244	57.1	183	42.9	<.001
Lymphoma/myeloma	107	43.5	139	56.5	
Solid	270	33.2	542	66.8	
Disease status					
Recurrent or progression	325	45.8	384	54.2	<.001
First treatment or newly diagnosed	255	40.6	373	59.4	
No evidence of disease	39	27.9	101	72.1	
Time since last chemotherapy					
Within 2 weeks	228	44.9	280	55.1	<.001
2-4 weeks	63	45.3	76	54.7	
>4 weeks	184	47.8	201	52.2	
Never	142	32.0	301	68.0	
Type of radiation therapy					
Total-body irradiation	102	60.7	66	39.3	<.001
Isolated port	168	40.0	252	60.0	
None	349	39.3	540	60.7	
Surgery status					
This admission	84	29.5	201	70.5	<.001
Prior admission	154	35.5	280	64.5	
Never	383	50.0	383	50.0	
Type of BMT					
Allogeneic	115	68.9	52	31.1	<.001
Autologous	26	30.2	60	69.8	
None	479	39.0	748	61.0	
Performance status					
Bedridden (Zubrod 4)	32	71.1	13	28.9	<.001
Assistance (Zubrod 2 or 3)	168	47.1	189	52.9	
Good (Zubrod 0 or 1)	420	38.8	661	61.2	
Source of admission					
Hospital floor	474	50.1	472	49.9	<.001
Emergency room	82	29.7	194	70.3	
OR or RR	43	28.3	109	71.7	
Other	22	20.0	88	80.0	
CPR before admission					
Yes	50	80.6	12	19.4	<.001
No	571	40.1	852	59.9	
Chronic renal failure					
Yes	22	39.3	34	60.7	.689
No	599	42.0	828	58.0	
Coronary artery disease					
Yes	60	37.5	100	62.5	.241
No	561	42.3	764	57.7	
Diabetes					
Yes	17	27.9	44	72.1	.024
No	604	42.4	820	57.6	
COPD					
Yes	99	43.2	130	56.8	.637
No	522	41.6	734	58.4	
Acute renal failure					
Yes	86	61.4	54	38.6	<.001
No	535	39.8	810	60.2	

Table 4. Number and Percent of Patients Who Lived and Patients Who Died by Level of the Categorical Variable (Cont'd)

Variable	Died		Lived		P
	No.	%	No.	%	
GI bleed					
Yes	66	43.7	85	56.3	.619
No	555	41.6	779	58.4	
DIC					
Yes	57	76.0	18	24.0	<.001
No	564	40.1	844	59.9	
Hepatic failure					
Yes	54	67.5	26	32.5	<.001
No	567	40.4	838	59.6	
Intracranial mass effect					
Yes	28	65.1	15	34.9	.002
No	593	41.1	849	58.9	
GCS ≤ 5					
Yes	62	87.3	9	12.7	<.001
No	559	39.5	855	60.5	
Probable infection					
Yes	508	50.9	490	49.1	<.001
No	113	23.2	374	76.8	
Ventilated, except post-op					
Yes	260	69.0	117	31.0	<.001
No	361	32.6	747	67.4	
DNR					
Yes	34	59.6	23	40.4	.005
No	587	41.1	841	58.9	
Limits on care					
Yes	39	60.9	25	39.1	.002
No	582	41.0	839	59.0	
Living will					
Yes	99	49.5	101	50.5	.008
No	402	39.4	618	60.6	
Vasopressors					
Yes	172	58.5	122	41.5	<.001
No	449	37.7	742	62.3	
Antibiotics					
Yes	542	47.5	598	52.5	<.001
No	79	22.9	266	77.1	

Abbreviations: OR, operating room; RR, recovery room; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; DIC, disseminated intravascular coagulation; DNR, do not recuscitate.

were continuously scaled and 12 were categorical. Except for respiratory rate, which was determined to be linearly associated with outcome by the fractional polynomial analysis, the other eight continuous variables had been entered into the model using the transformations suggested by the fractional polynomial results. Since those transformations were based on the bivariate association of each independent variable with outcome, the fractional polynomial procedure was repeated to determine whether the form of the variables was correct in the multivariable model. Three variables for which transformations had been suggested in the bivariate fractional polynomial analysis were found to have a linear association with outcome in the fractional polynomial analysis using the multivariable model as the base model (PaO_2/FiO_2, platelets, and systolic blood pressure). The diagnostic procedures were then conducted to evaluate whether one or more covariate patterns were having an undue impact on the size of the coefficients for each variable and whether the model performance was improved without the inclusion of the data for such covariate patterns. No patients were eliminated as a result of this analysis.

The initial modeling effort resulted in a model that was statistically sound, fit the data well, and demonstrated good discrimination. The model was then reviewed by project clinicians, who suggested changes in the form of some variables or the substitution of alternate variables for others. The number of days in the hospital before ICU admission was substituted for the source of admission, since it was a more clearly definable variable. Blood urea nitrogen (BUN) was used as a specific marker of acute renal failure, rather than the more general diagnostic term.

Variables for which complex transformations had been suggested by the fractional polynomials analysis were categorized so that the resulting coefficients and odds ratios were more easily interpreted. Cutpoints were used to categorize albumin (<2.5 g/dL), bilirubin (≥2 mg/dL), BUN (>50 mg/dL), and prothrombin time (>15 seconds) into bivariate variables. The final coding for all variables appears in the Appendix. Note that for the number of days in the hospital before ICU admission, a transformation was required so that the natural log of the actual number of days plus 0.5 was used to develop the model. Variables that took on the value of yes or no were coded as 1 or 0, respectively. Note also that there were three categories of the performance status variable. Patients were coded either as having a good performance status (Zubrod 0 or 1), assistance required (Zubrod 2 or 3), or bedridden (Zubrod 4).

The final model, based on the variables coded as described in the Appendix, is presented in Table 5. The coefficient for each variable and its associated standard error, as well as the corresponding odds ratio and 95% confidence interval for the odds ratio, are listed. For respiratory rate, systolic blood pressure, and PaO_2/FiO_2 ratio, the odds ratio represents the increased risk for a 10-U difference in the measure (eg, 10 breaths/min for respiratory rate). For platelets, the odds ratio represents the increased risk for a 10,000-U difference in platelet count.

The evaluation of the goodness-of-fit of the model in the developmental sample is listed in Table 6, which shows the correspondence between observed and expected mortality based on the model probabilities. The fit of the model was excellent, with a Hosmer-Lemeshow statistic of 2.93 and *P* value of .939. The area under the ROC curve was 0.812.

The calibration and discrimination of the model in a

Table 5. Coefficients, Standard Errors of the Coefficients, Odds Ratios, and 95% Confidence Intervals for the Odds Ratios for Model Variables

Variable	Coefficient	SE	Odds Ratio	95% Confidence Interval
CPR before admission	.83718	.41197	2.31	1.03-5.18
Intubated at admission	1.17430	.16015	3.24	2.36-4.43
Intracranial mass effect	.94427	.39642	2.57	1.18-5.59
Allogeneic BMT	.59239	.22309	1.81	1.17-2.80
Evidence of disease progression	.34794	.12823	1.42	1.10-1.82
Performance status				
Assistance required (Zubrod 2 or 3)	.43009	.14636	1.54	1.15-2.05
Bedridden (Zubrod 4)	.82296	.39509	2.28	1.05-4.94
Respiratory rate (breaths/min) (Odds ratio 10-U change in respiratory rate)	.03033	.00728	1.35	1.17-1.56
Systolic BP (mm Hg) (Odds ratio 10-U change in BP)	−.00688	.00245	.93	.89-.99
GCS ≤ 5	1.29508	.42872	3.65	1.58-8.46
PaO_2/FiO_2 ratio (Odds ratio 10-U change in PaO_2/FiO_2 ratio)	−.00275	.00050	.97	.96-.98
Platelets (×1,000) (Odds ratio 10,000-U change in platelet count)	−.00236	.00048	.98	.97-.99
Prothrombin time > 15 (seconds)	.58686	.19072	1.80	1.24-2.61
Albumin < 2.5 (g/dL)	.63454	.20559	1.89	1.26-2.82
Bilirubin ≥ 2 (mg/dL)	.61836	.20223	1.86	1.25-2.76
BUN > 50 (mg/dL)	.70206	.21790	2.02	1.32-3.09
Hospital days before ICU	.21935	.04666	1.25	1.14-1.36
Constant	−.43417	.40651		

validation sample of 230 patients is listed in Table 7. The fit was very good in the validation sample, with a Hosmer-Lemeshow statistic of 9.39 and P value of .310. The area under the ROC curve was 0.806 in the validation sample.

Also of interest in assessing the performance of the model was testing the fit of the model and its discrimination power by type of tumor and by medical/surgical status. The results of this analysis are listed in Table 8, which shows the number of patients, the value of the Hosmer-Lemeshow statistic, and the corresponding P value for each tumor group

Table 6. Goodness-of-Fit Table for the Model in the Developmental Sample

Group	P	Died		Lived		Total
		Observed	Expected	Observed	Expected	
1	.1119	12	12.4	137	136.6	149
2	.1591	19	20.3	129	127.7	148
3	.2108	24	27.4	124	120.6	148
4	.2759	40	36.2	109	112.8	149
5	.3582	51	47.1	97	100.9	148
6	.4500	59	59.6	89	88.4	148
7	.5665	75	75.4	74	73.6	149
8	.6904	87	92.4	61	55.6	148
9	.8363	117	113.5	31	34.5	148
10	.9981	136	135.7	12	12.3	148

Table 7. Goodness-of-Fit Table for the Model in the Validation Sample

Group	P	Died		Lived		Total
		Observed	Expected	Observed	Expected	
1	.1228	2	2.2	21	20.8	23
2	.1657	2	3.4	21	19.6	23
3	.2141	7	4.4	16	18.6	23
4	.2845	9	5.6	14	17.4	23
5	.3785	8	7.7	15	15.3	23
6	.4676	12	9.6	11	13.4	23
7	.5983	12	12.3	11	10.7	23
8	.6889	14	14.6	9	8.4	23
9	.8346	21	17.6	2	5.4	23
10	.9774	21	20.6	2	2.4	23

and for medical and surgical patients. It can be seen that the model fit in each tumor group and for medical patients and surgical patients.

Using the model coefficients from Table 5, the data for a cancer patient newly admitted to the ICU can be used to calculate the logit as follows: $g(x) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k$, where β_0 is the constant and $\beta_i x_i$ is the estimated coefficient for the ith variable times the value of the ith variable, with i taking on values from 1 to k, and k being the number of terms in the model.

Once the logit has been obtained by multiplying each appropriately coded variable value by its corresponding coefficient and summing, a simple calculation using the logit produces the probability of hospital mortality for the patient as follows: $[e^{g(x)}]/[1 + e^{g(x)}]$.

To illustrate, the information listed in Table 9 is provided to demonstrate how to calculate the probability of hospital mortality for a hypothetical cancer patient at the time of admission to the ICU. In this example, the patient is admitted to the ICU with evidence of disease progression and having required some assistance for daily functioning. The patient did not require cardiopulmonary resuscitation (CPR) before to admission, was not intubated, had no evidence of an intracranial mass effect, and had never had an allogeneic bone marrow transplant. The respiratory rate is 16 breaths/min, systolic blood pressure is 90 mm Hg, Glasgow Coma Score is 15, PaO_2/FiO_2 ratio is 78 mm Hg, platelet count is 85,000, prothrombin time is 18.1, albumin is 2.2 g/dL, bilirubin is 9.7 mg/dL, BUN is 19 mg/dL, and the

Table 8. Goodness-of-Fit of the Cancer Mortality Model by Tumor Group and by Medical/Surgical Status

Group	No.	H-L Statistic	P	ROC Area
Solid tumor	811	11.26	.1876	.79
Leukemia/BMT	426	6.28	.6163	.79
Lymphoma/myeloma	246	11.13	.1944	.83
Medical	1200	3.96	.8605	.82
Surgical	283	8.59	.3780	.76

Abbreviation: H-L, Hosmer-Lemeshow.

Table 9. Calculations for Each Variable Used to Generate the Probability of Hospital Mortality for a Hypothetical Cancer Patient at ICU Admission

Variable	$\hat{\beta}$	X	x	$\hat{\beta}x$
CPR before admission	.83718	No	0	.00000
Intubated at admission	1.17430	No	0	.00000
Intracranial mass effect	.94427	No	0	.00000
Allogeneic BMT	.59239	No	0	.00000
Evidence of disease progression	.34794	Yes	1	.34794
Performance status				
Assistance required (Zubrod 2 or 3)	.43009	Yes	1	.43009
or				
Bedridden (Zubrod 4)	.82296	No	0	.00000
Respiratory rate (breaths/min)	.03033	16	16	.48528
Systoic BP (mm Hg)	−.00688	90	90	−.61920
GCS ≤5	1.29508	15	0	.00000
PaO_2/FiO_2 ratio	−.00275	78	78	−.21450
Platelets (×1,000)	−.00236	85	85	−.20060
PT >15 (seconds)	.58686	18.1	1	.58686
Albumin <2.5 (g/dL)	.63454	2.2	1	.63454
Bilirubin ≥2 (mg/dL)	.61836	9.7	1	.61836
BUN >50 (mg/dL)	.70206	19	0	.00000
Hospital days before ICU [ln (no. of days + .5)]	.21935	3	1.25	.27479
Constant	−.43417. . .			−.43417*
Logit: $g(x) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k$				1.9094

*The value of the constant is applied to all patients in calculating the logit.

patient was in the hospital for 3 days before coming to the ICU.

For each variable in the model, the coefficient is shown under the column in Table 9 labeled β, and the observed value for the hypothetical patient is entered in the table under the column labeled X. The code or value to be used in the calculations is shown under the column labeled x, and the result of multiplying the code or value by the coefficient is shown under the column labeled βx. The values of are summed to obtain the logit, so that $g(x) = 1.9094$. The patient's probability of hospital mortality is then calculated as follows:

$$\frac{e^{g(x)}}{1 + e^{g(x)}} = \frac{e^{1.9094}}{1 + e^{1.9094}} = 0.8709.$$

Of 100 patients having this profile, 87 would be expected by the model to die before hospital discharge, and 13 would be expected to be discharged from the hospital alive.

DISCUSSION

We present the first model that can estimate the probability of hospital mortality in cancer patients at the time of admission to the ICU. This well-calibrated, prospectively validated model is independent of the admitting diagnosis and incorporates 16 readily obtainable clinical variables.

The prognosis for cancer patients who develop critical illness and are admitted to an ICU is grim, with hospital mortality rates reported as 50% to 80% depending on the cohort of patients studied.[1-12,15-19] In our study, the overall hospital mortality rate was 42%. Table 4 lists the differences in tumor groups with mortality rates of 33% in patients with solid tumors and 57% in those with hematologic malignancies. In one study, approximately 75% of hospital survivors lived less than 3 months after discharge and the cost per year of life gained was considerable ($82,843 for solid tumor patients and $189,339 for hematologic malignancy patients in unadjusted 1991 dollars).[12]

There is general agreement that patients who will not benefit from ICU care, either because they are too well or too sick, should not be offered ICU admission. The difficulty arises in identifying which patients will benefit from ICU care. It is imperative that critically ill patients who might benefit from ICU care receive it.[28] A prognostic scoring system that can accurately estimate a cancer patients chance of hospital survival when admitted to an ICU would help physicians identify which groups or types of patients would potentially benefit from ICU care.

General ICU prognostic scoring systems like the Acute Physiology and Chronic Health Evaluation (APACHE),[22] Simplified Acute Physiology Score II (SAPS II),[21] and MPM II[20] provide accurate and equivalent estimates of the probability of hospital mortality for consecutive patients admitted to a general medical or surgical ICU.[29,30] Physicians and general ICU prognostic scoring systems are roughly equivalent in their ability to predict which patients will die,[31,32] but prognostic scoring systems are better calibrated over the entire range of predictions and provide a reproducible method for describing and categorizing individual patients.[22,33,34] We report, as have others, that general ICU prognostic scoring systems consistently underestimate the chance of hospital mortality for cancer patients admitted to an ICU[35-38] and none of the general ICU prognostic scoring systems have been validated in cancer patients. Disease-specific mortality prediction models, which consist of a few core universally important variables supplemented by a small number of disease-specific variables, are the most accurate predictor of hospital mortality for a specific disease group.[34,39] This method was used to developed a model to predict 28-day mortality for patients with the sepsis syndrome.[40]

The derivation of our outcome model for cancer patients admitted to an ICU is based on the statistical approach used to develop MPM II.[20] Our cancer outcome model and MPM II share some common variables (CPR, mechanical ventilation, intracranial mass effect, and systolic blood pressure). The model for cancer patients contains three cancer-specific

variables (allogeneic bone marrow transplantation, disease progression, and performance status), six laboratory values (PaO_2/FiO_2, platelet count, prothrombin time, albumin, total bilirubin, and BUN), and three additional variables (respiratory rate, Glasgow Coma Score, and days of hospitalization before ICU admission). This cancer model deals with lead time and selection biases due to treatment before ICU admission by including the number of days the cancer patient was hospitalized before ICU admission. This model uses a limited number of clinical variables derived from the usual care of patients, which makes duplication of data collection methods easy. It also avoids the error and/or confusion associated with having to identify the single reason for ICU admission. The model variables are reflective of the development of multiorgan system failure and are well supported in the literature. Mechanical ventilation, respiratory rate, blood pressure, Glasgow Coma Score, intracranial mass effect, CPR, indices of oxygenation, albumin, BUN, bilirubin, and platelet count are each a component of either the MPM II, SAPS II, APACHE III, or Multiple Organ Dysfunction Score.[20-22,41] Additionally, many of these variables have been evaluated as singularly good predictors of hospital mortality.[42-47] While these models incorporate the presence of some malignancy diagnoses, our model is well calibrated and discriminates survivors and nonsurvivors for any cancer patient admitted to an ICU. No mortality distinction is found between individual malignancy groups, except for worse prognosis in patients having undergone allogeneic bone marrow transplantation, with relapsed or recurrent cancer and poor performance status as a marker for the clinical burden of the cancer or effects of cancer treatment.

Our severity model for cancer patients, like general ICU scoring systems, cannot be used to predict the outcome of any single patient as the ability to prognosticate on an individual patient with 100% specificity is unrealistic. Further, while this model can estimate the probability of death for a critically ill cancer patient upon ICU admission, it should not be used to deny admission to any single patient. Physicians need to be able to provide accurate and meaningful estimates of survival to cancer patients and their families before ICU admission. Physicians must realize that all prognostic scoring systems are limited and individual factors not included in the model may influence any single patient's prognosis. Analogy could be drawn to describing to a patient the benefits seen in adjuvant chemotherapy of breast or colorectal cancer. Some patients may benefit, but it is not possible to predict who will benefit or how much the benefit will be for an individual. Our scoring system, rather than replacing clinical decision-making, can aid physician decision-making by reducing uncertainty surrounding a patient's prognosis and improving the reproducibility of physicians mortality predictions.[22] In the Study to Understand Prognoses and Preferences for Outcomes and Risk of Treatments (SUPPORT) prognostic model, the most accurate predictions of patient survival at 180 days for seriously ill hospitalized patients were achieved by combining the physician predictions with the SUPPORT model.[48] Further, the prognostic model for cancer patients admitted to an ICU can be used to document comparable severity of illness for therapeutic trials, and as a performance improvement tool to compare actual and predicted patient outcomes between individual ICUs or with hospitals that do not deliver intensive care in aggregated ICUs.

The containment of medical costs will force physicians, insurers, and the government to scrutinize the costs and benefits of ICU care for cancer patients. Medical professionals should take the lead in determining guidelines for allocation of critical care resources. Failure to lead will result in insurers and/or the government imposing a rigid uncaring system that focuses on cost containment at the expense of providing quality medical care. Physicians should incorporate the general results of objective ICU prognostic scoring systems into clinical decision-making and the results of outcomes research should be used to discuss an ICU patients chances of meaningful survival. This discussion for cancer patients should occur before evaluation for ICU admission.

In conclusion, we have developed a disease specific multivariable logistic regression model to estimate the probability of hospital mortality in critically ill cancer patients who are admitted to an ICU. The model consists of 16 unambiguous and readily available variables, can be used at the time of ICU admission, and provides an accurate estimation of a cancer patient's probability of hospital mortality when admitted to an ICU. This model can aid physician's clinical decision-making and should move the discussion regarding appropriate use of ICU resources forward.

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APPENDIX

Variable Coding for ICU Cancer Mortality Model

Variable		Value or Coding	
CPR before admission		1 if CPR within 24 hours before admission 0 otherwise	
Intubated at admission		0 if not intubated or immediately postoperative 1 otherwise	
Intracranial mass effect		1 if intracranial mass effect present on computed tomographic scan 0 if intracranial mass effect absent	
Bone marrow transplant		1 if allogenic bone marrow transplant 0 otherwise	
Evidence of disease progression		1 if progression or recurrance of cancer 0 otherwise	
		Assistance	Bedridden
Performance status	Normal/Symptomatic	0	0
	Assistance/Nursing care	1	0
	Bedridden/Hospitalized	0	1
Respiratory rate (beats/min)		{Continuous variable; 16 substituted for missing	
Systolic blood pressure (mm Hg)		{Continuous variable; 120 substituted for missing	
Glasgow Coma Score		1 if ≤5 0 otherwise	
PaO_2/FiO_2 ratio		{Continuous variable; 380 substituted for missing	
Platelets (×1,000)		{Continuous variable; 250 substituted for missing	
Prothrombin time (seconds)		1 if >15 0 otherwise	
Albumin (g/dL)		1 if <2.5 0 otherwise	
Bilirubin (mg/dL)		1 if ≥2 0 otherwise	
BUN (mg/dL)		1 if >50 0 otherwise	
Hospital days prior to ICU		{ln (no. of days + 0.5)	

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