Development of a mortality risk prediction score for patients with AML requiring critical care

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Abstract

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Background: Though patients with acute myeloid leukemia (AML) have high mortality after intensive care unit (ICU) admission, long-term survival is possible. There is no accepted model for predicting longer-term mortality after ICU admission. We examined the role of five AML and ICU related risk factors in mortality prediction in this population.

Methods: This was a retrospective cohort study of 238 patients with AML admitted to the ICU in a single academic medical system who survived at least 24 hours. The risk factors examined were AML composite model score (AML-CM) from the time of diagnosis, disease status at ICU admission, history of hematopoietic cell transplant (HCT), use of invasive mechanical ventilation (IMV) within 24 hours of ICU admission, and serum creatinine ≥2.0 mg/dl within 24 hours of ICU admission. The outcome was 90-day mortality after ICU admission. Risk factors were compared using sensitivity, specificity, and AUC, and added sequentially to a multivariable logistic regression model. Sequential multivariable models were compared using AUC. A mortality score was created from the regression model with the best balance of fit and simplicity by dividing the beta coefficients in the model by 0.25. The score was the sum of those coefficients. Cut-points for the score were examined using sensitivity and specificity.

Results: The final model used AML-CM, the presence of relapsed or resistant disease, HCT, and IMV within 24 hours of ICU admission to predict 90-day mortality. A term was included for interaction between relapsed/resistant disease and HCT. The AUC of the multivariable logistic regression model was 0.74 (95% CI 0.68-0.8). The AUC of the final mortality score was 0.74 (95% CI 0.68-0.8). The score ranged from 0 to 18. A cut-point of ≥4 had a sensitivity of 93% and a specificity of 30%; a cut-point of ≥10 had a sensitivity of 25% and a specificity of 94%.

Conclusions: This mortality score is the first that examines 90-day mortality from the time of ICU admission for patients with AML. While it shows some promise at distinguishing patients with exceptionally high or low mortality, in a number of patients the use of the score will lead to an erroneous assessment of prognosis.

Background:

Patients with acute myeloid leukemia (AML) who require intensive care unit (ICU) admission have very high hospital mortality, ranging from 41-75%[1-7]. Yet, some patients with AML have prolonged survival after ICU admission, with 1-year survival ranging from 25-41%[1,4,8]. With frequent intensive care unit (ICU) needs during treatment, AML represents an important context for assessing and improving care in the ICU[2,9-12]. Traditional ICU mortality prediction models are insufficient to predict survival beyond the acute care setting[13-15], although longer-term survival is arguably a more relevant end-point for patients and families than survival to ICU or hospital discharge. Improved counseling for those at high risk of 90-day mortality may diminish the use of life sustaining therapies that do not have appreciable longer-term survival benefit (for example, the use of invasive mechanical ventilation or hemodialysis in some cases), improve patient-goal oriented care, and reduce moral distress and burn-out in critical care providers[16-19]. We do not have a model acceptably accurate to predict 90-day mortality for AML patients admitted to the ICU.

The AML-CM is a novel tool that incorporates cytogenetic risk as described by ELN 2017 classification criteria[20], age, and presence of comorbidities including diabetes, coronary artery disease, congestive heart failure, valvular disease, arrhythmia, inflammatory bowel disease, cerebrovascular disease, psychiatric disease, liver test abnormalities, history of infection, rheumatologic disease, peptic ulcer disease, obesity, kidney dysfunction, thrombocytopenia, elevated lactate dehydrogenase, prior solid tumor, and lung function abnormalities into one score that predicts (to some extent) 8-week and 1-year mortality after AML diagnosis[21]. This tool was developed and validated in a large multicenter cohort of patients with AML published by Sorror et al. in 2017[21]. Whether the AML-CM can be combined with other ICU variables to improve prognostic assessment in an ICU population is unknown. The goal of this project is to

develop a mortality prediction tool that can be used at 24 hours of ICU admission to predict 90-day mortality.

Methods

Study population: A retrospective cohort of 238 adult patients treated for AML at the Seattle Cancer Care Alliance (SCCA) between 2008 and 2016, admitted to a University of Washington or Harborview Medical Center ICU at any point after induction, and who lived for at least 24 hours after admission.

Primary exposures: We collected the AML-CM score from the time of diagnosis, disease status at the time of ICU admission (dichotomized into those with relapsed or resistant disease vs. all other disease statuses), history of prior hematopoietic cell transplant (HCT) at the time of ICU admission, use of invasive mechanical ventilation within the first 24 hours (IMV) of ICU admission, and highest serum creatinine during the first 24 hours of ICU admission.

Outcome: Mortality at 90-days after ICU admission was the primary outcome.

Statistical Analyses: The AML-CM, disease status, prior receipt of HCT, use of invasive mechanical ventilation, and highest serum creatinine (as a binary variable of ≥2.0 mg/dl or not) were evaluated for inclusion in a multivariable logistic regression model. We first assessed univariate logistic regression, as well as the sensitivity, specificity, and AUC of each individual variable for predicting 90-day mortality. Multivariable models were fit sequentially by adding the covariates one-by-one to the model from highest sum of sensitivity + specificity to lowest, with AUC of the resulting model calculated at each step. An interaction term was included in these models for HCT and disease status a priori based on prior evidence suggesting worse

outcomes when relapse occurs after transplant[22,23]. The AUCs were used to select the multivariable model that balanced best fit with simplicity. We first simplified the final model by rounding the beta coefficients (log odds ratios) to the nearest integer weights, with the new score as the sum of all the integer weights[24]. We considered alternate weighting schemes by dividing the beta coefficients by 0.5 and in a subsequent score, by 0.25. These new weights were rounded to the nearest integer, and the sum of these weights formed the alternate scores. These models were compared using AUC, and again the model with the best balance of fit and simplicity was chosen. All possible cut-points for this score were evaluated. Cut-points were chosen for which either sensitivity or specificity were ≥90%.

Results:

During the study period there were 238 patients undergoing treatment for AML at the SCCA who had been admitted to a UW ICU at any point after treatment. The median age at time of ICU admission was 60 years (range 19-83), with 58% males and 79% whites. The median AML-CM score was 7 (interquartile range (IQR) 5-10). Patients were admitted to the ICU a median of 88 days after induction (IQR 20-260), and the median length of ICU stay was 3 days (IQR 2-6). The disease status at admission was categorized as: in remission (28%), newly diagnosed (40%), or relapsed or resistant (32%). Of our patients, 29% had previously undergone hematopoietic cell transplant.

Within 24 hours of admission, the mean worst creatinine was 1.4 mg/dl (standard deviation 1), and 17% had at least one serum creatinine ≥2.0 mg/dl within the first 24 hours. Invasive mechanical ventilation (IMV) was required by 22%. Mortality was 48% by 90 days after admission (Table 1). Figure 1 shows the Kaplan-Meier survival curve up to 1-year after ICU

admission. There was only one missing value noted: creatinine in 1 patient. In this case, the closest serum creatinine value was used, from the day after ICU admission.

Univariate logistic regression of the exposures of interest showed an association of each with 90-day mortality (Table 2). In order of highest to lowest sensitivity + specificity, we found: disease status at 1.23, AML-CM≥7 at 1.22, IMV at 1.16, transplant at 1.12, and creatinine≥2 at 1.09. These variables were added sequentially to create multivariable models to estimate 90-day mortality. The results of these analyses, including odds ratio and relative risks calculated for each factor, as well as AUC for each sequential model are shown in Table 3. The AUC improved from 0.68 (95% CI 0.62-0.75) in model 1 (disease status + AML-CM) to 0.74 (95% CI 0.68-0.8) in model 3, which included all variables except creatinine. Adding creatinine in model 4 minimally changed the AUC to 0.75 (0.69-0.81). Based on the minimal change in AUC between models 3 and 4, model 3 was chosen to proceed with creating a simplified model for risk prediction.

For the first mortality score, the beta coefficients for each variable in model 3 were rounded to the nearest integer to generate the weight for that variable; in this model each factor had a weight of 1, and the interaction term between transplant and relapsed/resistant disease was excluded. The sum of each of these weights became the score.

Mortality Score 1 = 1(AML-CM≥7) + 1*(IMV) + 1*(Transplant) + 1*(Relapsed/resistant disease)*

This score was assessed against 90-day mortality with logistic regression and yielded an AUC of 0.72 (95% CI 0.66-0.78).

A second mortality score was generated by dividing each beta coefficient in model 3 by 0.5, and then rounding each weight to the nearest integer. By this method, the disease status had a weight of 3, and all the other variables a weight of 2, and the interaction term between HCT and disease status had a weight of 1.

Mortality Score 2 = 2(AML-CM≥7) + 2*(IMV) + 2*(Transplant) + 3*(Relapsed/resistant disease) + 1*(Transplant*Relapsed/resistant disease)*

The AUC of this model was 0.73 (95% CI 0.67-0.79).

A third mortality score was generated by dividing each beta coefficient in model 3 by 0.25, and then rounding each weight to the nearest integer. Disease status was given a weight of 5, IMV and AML-CM≥7 were given a weight of 4, transplant was given a weight of 3, the interaction term between transplant and disease status had a weight of 2.

Mortality Score 3 = 4(AML-CM≥7) + 4*(IMV) + 3*(Transplant) + 5*(Relapsed/resistant disease) + 2*(Transplant*Relapsed/resistant disease)*

The AUC of this model was 0.74 (95% CI 0.68-0.8). Histograms of the distribution for each of these scores are given in Figure 2, and the receiver operating curves (ROC) are shown in Figure 3.

The third mortality score had the highest AUC and was selected for further evaluation. Kaplan-Meier curves were generated for each level of the score. (figure 4). A cut-point of ≥4 yielded a sensitivity of 93% and a specificity of 30%, whereas a cut-point of ≥10 yielded a sensitivity of 25% and a specificity of 94%. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of all the potential cut-points are listed in Table 4.

Discussion:

Using a retrospective cohort of patients with AML admitted to the ICU, we derived a mortality prediction score that uses four variables to predict 90-day mortality after ICU admission. 24% of patients had a score of less than 4, and in those patients only 7% died during the 90 days following ICU admission. In contrast, 15% of patients had a score of 10 or more, and they had a

90-day mortality risk of 80%. This score shows promise for use as an aid to counseling patients and families within 24 hours of admission to the ICU. While a high score may not be enough to preclude the use of any particular treatment in the ICU, a score above the cut-off of 10 should trigger an early conversation regarding goals of care with the patient and their family, including the consideration of limits to further escalation of care. Patients with relapsed disease after HCT constitute a unique group, in that these patients have a score of 10 prior to consideration of any ICU factors. Presence of those factors could generate a conversation about whether admission to an ICU lies within the patient's goals of care prior to ICU transfer, given the high mortality associated with ICU admission for these patients. Conversely, a low score could be used to allay patient and provider concerns about possible futility of care. For patients who fall between the two cut-points, the prognostic information can still be used to counsel patients and families early in the ICU stay.

This study has several strengths. One is the use of a large cohort of AML patients for model development. Our data were complete, and we had good follow-up to the study end-point. The variables used in this score are readily available to clinicians within 24 hours of admission without ordering additional tests, and the score may be calculated easily at the bedside.

Prior ICU mortality prediction scores examined for use in patients with AML have focused mostly on mixed populations with hematologic malignancy[8,25-27], or have focused on shorter-term outcomes, such as ICU or hospital mortality, rather than longer-term outcomes[5,15]. One study did look at a large group of patients with AML and examined a prediction score for 1-year mortality after ICU discharge, with the following predictors for 1-year mortality: relapsed or refractory disease, days in hospital prior to ICU admission, ICU length of stay in days, decreased 24-hour urine output after ICU admission, decreased Glasgow Coma Scale at ICU admission, and decreased hematocrit at ICU admission. The authors of this study also evaluated a score for in-ICU mortality prediction which had a high AUC (0.84)[5]. One limitation of

this score is that it relies on data obtained from an arterial blood gas evaluation, a measure which may not be routinely present for risk calculation in ICU patients at the time of admission[28,29].

The primary limitations of the present study are that 1) our cohort was recruited from just one academic institution, potentially limiting its applicability to patients treated at other institutions; and 2) this score has not yet been validated. The next step in our research plan is to validate this score using patients from two collaborating outside institutions, and to compare this score to commonly used ICU mortality prediction scores for general patient populations.

Table 1. Overview of variables of interest, including exposures and outcomes	
Demographic Variables	
Age, years (median, range)	60 (19-83)
Male sex (n,%)	137 (57.6)
White (n,%)	189 (79.4)
Variables from Diagnosis:	
AML-CM score (Median, IQR)	7 (5-10)
AML-CM score ≥7 (n,%)	127 (53.4)
Variables from ICU admission	
Days from induction to admission (median, IQR)	88 (20-260)
ICU Length of Stay, days (median, IQR)	3 (2-6)
Disease status (n,%)	
Remission	67 (28.2)
Newly diagnosed	95 (39.9)
Relapsed/Resistant	76 (31.9)
Prior transplant (n,%)	69 (29)
Variables from 24 hours after ICU admission	
Creatinine (mean, sd)	1.4 (1)
Creatinine ≥2.0 mg/dl (n,%)	41 (17.2)
Required invasive mechanical ventilation (n,%)	52 (21.8)
Outcome	
90-day Mortality (n,%)	113 (47.5)

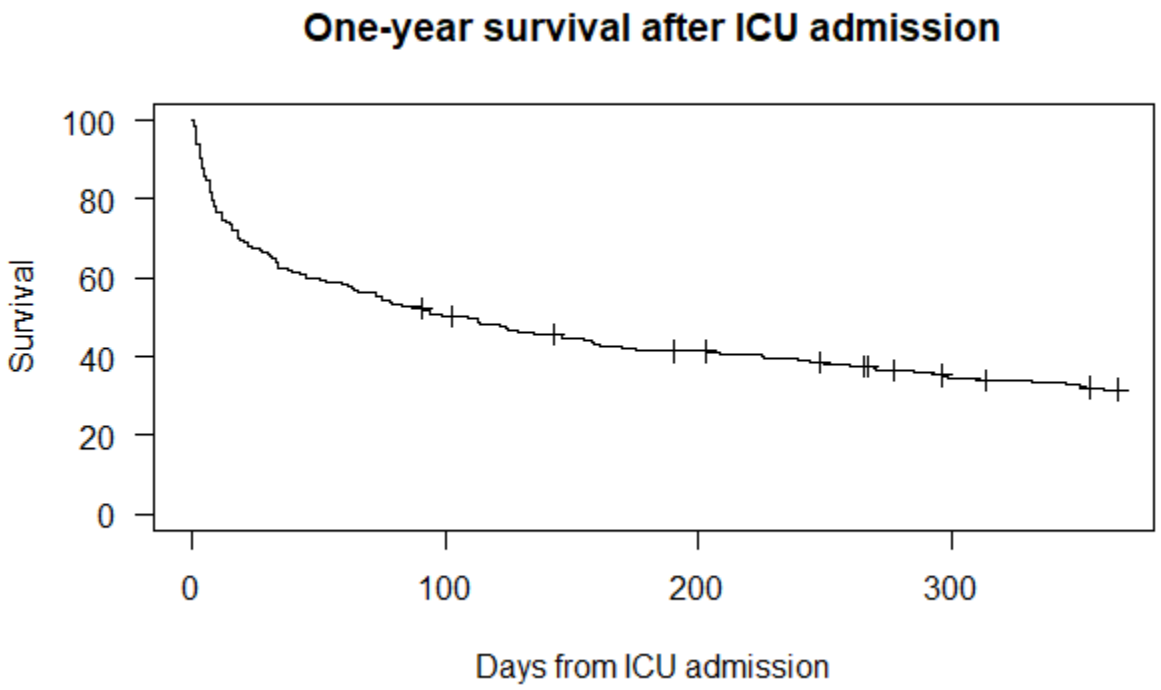

Figure 1: One-year survival after ICU admission

Table 2. Univariate analyses of exposure variables vs. 90-day mortality						
	OR (95% CI)	RR (95% CI)	P	Sensitivity	Specificity	AUC
AML-CM ≥7	2.4(1.43-4.07)	1.44(1.19-1.66)	0.001	0.65	0.57	0.61 (0.54-0.67)
Relapsed/ resistant disease	3.02(1.72-5.4)	1.54(1.28-1.75)	<0.001	0.44	0.79	0.62 (0.56-0.68)
Prior transplant	1.81(1.03-3.22)	1.31(1.02-1.57)	0.039	0.35	0.77	0.56 (0.5-0.62)
Creatinine ≥2.0 mg/dl	1.94(0.98-3.91)	1.34(0.99-1.64)	0.06	0.22	0.87	0.55 (0.5-0.6)
Invasive mechanical ventilation	2.56(1.36-4.94)	1.47(1.16-1.72)	0.004	0.3	0.86	0.58 (0.53-0.63)
* Reference groups for each analysis consisted of those without the characteristic; OR = Odds ratio; RR = Relative risk; 95% CI = 95% Confidence Interval; AUC = Area Under the receiver operating characteristic Curve						

Table 3. Progressive multivariable models with Beta, OR, and RR of each variable								
	Model 1				Model 2			
	Beta (95% CI)	OR (95% CI)	RR (95% CI)	P	Beta (95% CI)	OR (95% CI)	RR (95% CI)	P
AML-CM >=7	0.87(0.33-1.41)	2.38(1.39-4.11)	1.44(1.17-1.66)	0.002	0.91(0.36-1.48)	2.49(1.44-4.38)	1.46(1.19-1.68)	0.001
Relapsed/ Resistant (Rel/Res)	1.1(0.52-1.69)	3(1.69-5.42)	1.54(1.27-1.75)	<0.001	1.24(0.65-1.87)	3.47(1.91-6.46)	1.6(1.33-1.8)	<0.001
IMV	*NA*	*NA*	*NA*	*NA*	1.18(0.5-1.9)	3.26(1.65-6.65)	1.57(1.26-1.81)	0.001
Prior HCT	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
HCT*(Rel/Res)	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
Creatinine >=2	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
AUC	0.68(0.62-0.75)				0.72(0.66-0.78)			
*OR = Odds ratio; RR = Relative risk; 95% CI = 95% Confidence Interval; AUC = Area Under the receiver operating characteristic Curve								

Table 3 continued.								
	Model 3				Model 4			
	Beta (95% CI)	OR (95% CI)	RR (95% CI)	P	Beta (95% CI)	OR (95% CI)	RR (95% CI)	P
AML-CM >=7	1.07(0.5-1.67)	2.93(1.65-5.32)	1.53(1.26-1.74)	<0.001	1.05(0.48-1.65)	2.87(1.61-5.22)	1.52(1.25-1.74)	<0.001
Relapsed/ Resistant	1.17(0.47-1.89)	3.21(1.6-6.62)	1.57(1.24-1.8)	0.001	1.16(0.46-1.89)	3.19(1.58-6.59)	1.56(1.24-1.8)	0.001
IMV	1.12(0.43-1.85)	3.07(1.54-6.34)	1.55(1.22-1.79)	0.002	1.08(0.38-1.81)	2.93(1.46-6.09)	1.53(1.2-1.78)	0.003
Prior HCT	0.69(-0.04-1.43)	2(0.96-4.2)	1.36(0.98-1.67)	0.064	0.69(-0.04-1.43)	1.99(0.96-4.19)	1.35(0.98-1.67)	0.065
HCT*(Rel/Res)	0.39(-0.97-1.85)	1.48(0.38-6.38)	1.21(0.54-1.8)	0.58	0.39(-0.98-1.85)	1.48(0.38-6.37)	1.2(0.53-1.79)	0.587
Creatinine ≥2	*NA*	*NA*	*NA*	*NA*	0.35(-0.41-1.14)	1.42(0.66-3.11)	1.19(0.79-1.55)	0.368
AUC	0.74(0.68-0.8)				0.75(0.69-0.81)			
*OR = Odds ratio; RR = Relative risk; 95% CI = 95% Confidence Interval; AUC = Area Under the receiver operating characteristic Curve								

Figure 2: Histograms of points in each mortality score

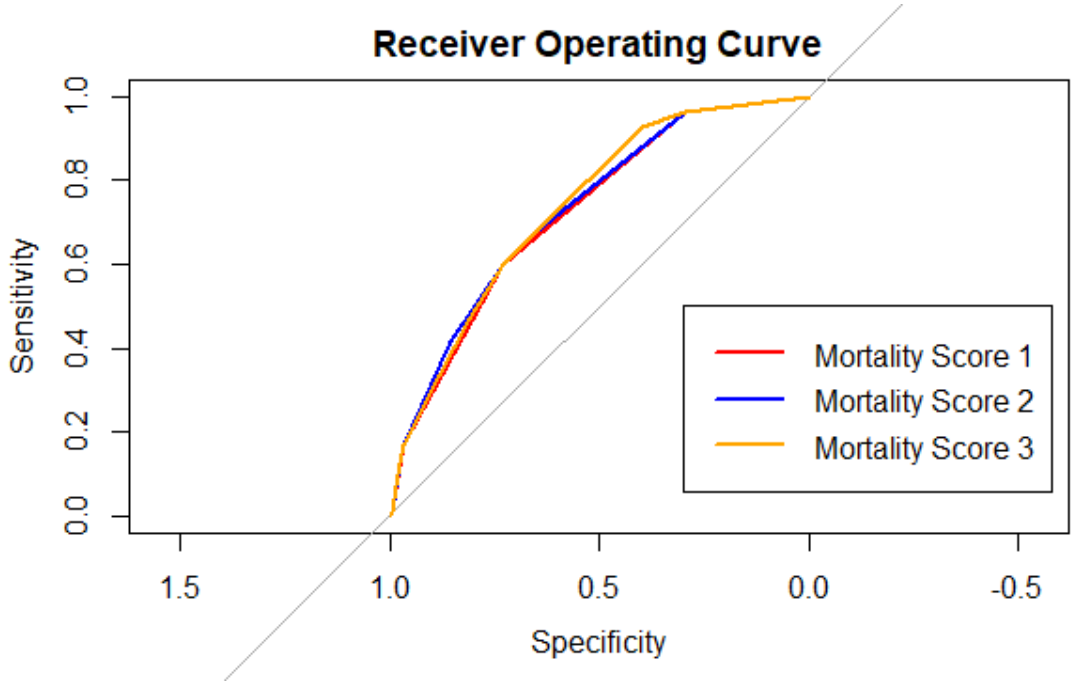

Figure 3 Receiver operating curve for mortality scores

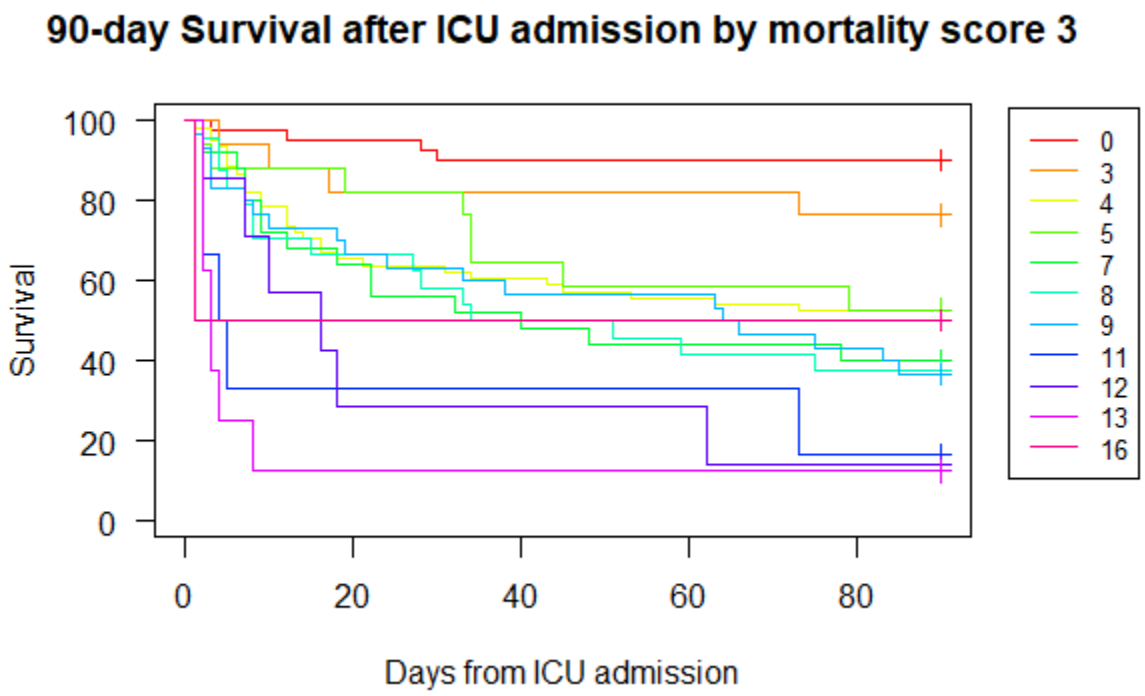

Figure 4: Survival by mortality score 3

Table 4. Cut-points for mortality score 3 with sensitivity, specificity, positive predictive value, and negative predictive value:

Cut-point	Scores below cut-point	Sensitivity	Specificity	PPV	NPV
3	41	0.96	0.3	0.55	0.9
4	58	0.93	0.4	0.58	0.86
5	119	0.67	0.66	0.64	0.69
7	136	0.6	0.73	0.67	0.67
8	161	0.47	0.81	0.69	0.63
9	173	0.42	0.86	0.72	0.62
10	203	0.25	0.94	0.8	0.58
11	215	0.17	0.97	0.83	0.56
13	221	0.12	0.98	0.82	0.55
14	229	0.06	0.98	0.78	0.54
18	236	0.01	0.99	0.5	0.53

* A positive score was one that fell at or above the cut-point indicated; PPV = Positive Predictive Value; NPV = Negative Predictive Value

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