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ORIGINAL RESEARCH INTENSIVE CARE

A tertiary care center-based study of a novel 'ICU Mortality and Prolonged Stay Risk Scoring System'

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ABSTRACT

Background & objective: Intensive care has been associated with high cost and resource-intensive medical care. Therefore, a risk prediction model is required to plan time allocation, human resources, and the required equipment. Various risk predictions for ICU mortality and 'Prolonged Length of Stay' (PLOS) scores are already available. Still, the established model, such as the APACHE IV score or SAPS II, sometimes became impractical since they required many laboratory parameters. A model based on co-morbidities and demographic factors may be more useful in limited resources setting. Hence, we developed a simple ICU mortality and PLOS risk prediction model based on co-morbidities and demographic data.

Methodology: This retrospective cohort study was performed to develop a risk scoring for mortality and PLOS, using data from Dr. Sardjito Hospital Yogyakarta database between January 01-December 31, 2019. Logistic regression and bootstrap methods were used to create a risk score for estimating the risk. The discrimination performance of the model was evaluated using the area under the curve (AUC) of the receiver operating characteristic (ROC). The Hosmer-Lemeshow test was employed to assess the model's calibration.

Results: A total of 415 patients were included in this study. The risk factors for mortality were perioperative support medication, kidney failure, neurologic disorder, respiratory failure, and intraoperative blood transfusion. The mortality score of 6 was associated with a 100% probability of mortality. Medical cases, GCS < 8, vasoactive/inotropic medication, sepsis, respiratory failure, and kidney failure were the risk factors for PLOS. PLOS score of 3 was associated with a 100% probability of PLOS. The discrimination for either mortality or PLOS was considered excellent with the AUC (± 95% CI) for mortality 0.896 (0.853-0.94), while for PLOS 0.878 (0.80-0.90). The calibration test found that both models had good calibration with P values of 0.53 and 0.55 for mortality and PLOS, respectively.

Conclusion: The 'Mortality and Prolonged Length of Stay Prediction Score' based on co-morbidities and demographic data upon admission to ICU had good accuracy and can be applied as a potential new scoring system in healthcare institutions.

Abbreviations: APACHE- Acute Physiologic Assessment and Chronic Health Evaluation; AUC; Area Under the Curve GCS- Glasgow Coma Scale; ICU- Intensive Care Unit; PLOS- 'Prolonged Length of Stay'; PRC- Packed Red Cells; SAPS- Simplified Acute Physiology Score

Keywords: Risk Scoring; Mortality; Prolonged Length of Stay; ICU

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1. INTRODUCTION

The Intensive Care Unit (ICU) is a high-cost and resource-intensive treatment unit. One of the efforts to improve ICU service quality is by designing a risk prediction system for mortality and prolonged length of stay (PLOS). The scoring system is needed for comparative audit and service evaluation, more focused planning, assistance for the decision-maker, allocation plans for time, human resources, and equipments in ICU.[1]

Several instruments have been adopted to predict the outcomes of ICU patients as well as their survival rates while in the hospital. The most commonly utilized risk scoring systems in clinical practice to measure the disease's fatality rate is mortality risk estimations based on acute physiology scores such as 'Simplified Acute Physiology Score' (SAPS) and 'Acute Physiology and Chronic Health Evaluation' (APACHE) score. Both techniques are based on a logistic regression test of physiology-specific signals collected within the first day after ICU admission.[2] In European and Asian countries, the APACHE and SAPS have been used to predict mortality and PLOS.[3,4] However, they require extensive laboratory and vital sign data. The performance of APACHE IV and SAPS II varied in predicting mortality, and only had moderate accuracy in predicting PLOS.[2,4,5]

A locally developed risk prediction system for ICU mortality and PLOS based on co-morbidity and demographic data may be more applicable. Therefore, we aomed to design a risk prediction system based on simple variables to predict ICU mortality and length of stay in our hospital.

2. METHODOLOGY

A single-center retrospective study was performed between January 1-December 31, 2019. Ethical clearance approval for the study was obtained from the Medical and Health Research Ethical Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada. The inclusion criteria were adult (≥18 y old) patients admitted to the ICU of Dr. Sardjito General Hospital. The exclusion criteria were: post-cardiac surgery, length of stay less than 24 hours, referred out of the hospital, and patients whose medical record data could not be collected during the sampling period. The dependent variable was mortality, defined as ICU mortality, and PLOS, defined as the length of ICU stay of more than seven days. The patients data collected included: demographic variables (age, gender, height, body mass index (BMI), comorbidity variables (cardiovascular disease, neurological disorder, heart failure, respiratory failure, kidney failure, sepsis, malignancy, Glasgow Coma Scale upon admission), history of readmission to ICU, and surgical variables (surgery urgency), treatments upon admission like packed red cell (PRC) transfusion and inotropic/vasopressor support, as well as mechanical ventilation were included.

The entire data set was used for model development since this strategy resulted in better predictive accuracy than data-splitting.[6] Candidate variables were selected based on literature, clinical experience, and hypotheses regarding their relationship to the outcomes.

Demographic data were presented as mean and standard deviation for numeric variables and as a percentage for nominal or categorical data. Bivariate analyses were performed using the Student's t-test for numeric data and the chi-square test for categorical/dichotomous data. Variables with $P < 0.25$ were candidates for the logistic regression test. Variables with $P < 0.05$ from univariable logistic regression were included in the multivariable analysis. Significant variables in the multivariate test and a constant formed a logistic regression equation formula. The bootstrapping method was employed for internal validation of the model. The risk score was developed based on the final logistic regression model using the method described by Sullivan et al.[7] The lowest beta coefficient was used as the base point. The score was obtained by dividing the beta coefficients of each significant variable by the lowest beta coefficients. The score was then summed up and yielded a score for assessing the likelihood of mortality and PLOS.

The discriminatory performance of the model was evaluated using receiver operating characteristics (ROC) curves. The area under the curve (AUC or C-statistic)

Table 1: Patients' Characteristics in relation to mortality

Variable		Total	Survived	Died	p
Gender	F	228 (54.94)	183 (59.80)	45 (41.28)	**0.027***
	M	187 (45.06)	123 (40.20)	64 (58.72)	
Age (year)		41.74 ± 15.69	39.11 ± 14.35	46.09 ± 16.65	**0.003***
Weight (kg)		60.42 ± 13.40	60.46 ± 13.19	60.38 ± 15.79	0.970
Height (cm)		160.91 ± 8.93	160.87 ± 8.01	159.12 ± 15.97	0.262
BMI (kg/m^2)		23.20 ± 4.57	23.27 ± 4.65	23.33 ± 4.62	**0.005***
Surgical case		275 (66.2)	237 (86.2)	38(13.8)	**< 0.001***
Emergency surgery		107 (25.8)	83 (77.5)	24(22.4)	**0.068***
PRC transfusion		216(52.5)	182 (84.3)	34(15.7)	**0.001***
Vasopressor support[a]		94 (22.7)	31 (33.0)	63 (67.0)	**< 0.001***
Sepsis		84 (20.3)	28 (33.3)	56 (66.7)	**< 0.001***
Coronary Heart Disease		69(16.7)	48 (74.2)	21(25.8)	**0.053***
Low GCS		81 (19.5)	34 (42.0)	47 (58.0)	**0.00***
Heart Failure		37(8.9)	23(62.2)	14(13.1)	**0.114***
Kidney Failure		73 (17.6)	37 (50.7)	36 (49.3)	**< 0.001***
Respiratory Failure		117 (28.3)	52 (44.4)	65(55.6)	**< 0.001***
Malignancy		95(22.9)	72 (87.7)	23(12.3)	0.790
Neurological disorder		184 (44.4)	122 (66.3)	62(33.7)	**0.041***
Diabetes Mellitus		41 (9.8)	23 (56.1)	18(43.9)	**0.008***
Mechanical ventilation		342 (82.4)	247 (72.2)	95(27.8)	**0.055***
Readmission		12 (2.9)	10 (83.3)	2(16.7)	0.74
Prolonged Length of Stay		175 (42.2)	66(38.2)	107(61.8)	< 0.001
Mortality rate		109 (26.3)			

Data presented as mean ± SD or n (%); P < 0.25, included in univariable logistic regression test*

BMI: Body Mass Index, GCS: Glasgow Coma Scale, PLOS: Prolonged Length of Stay

[a]: vasopressor = dobutamine, dopamine, epinephrine, norepinephrine, or vasopressin

compared the discrimination between the various models. Values ≥ 0.7 were considered acceptable, and values ≥ 0.8 were good. The calibration was evaluated with the Hosmer–Lemeshow test by allocating patients to the predicted probability outcome. P > 0.05 indicated adequate goodness of fit. Statistical analysis was performed using the IBM SPSS software package (version 27 SPSS Inc., Chicago, IL).

3. RESULTS

A total of 420 patients were admitted to the ICU of a tertiary hospital between 1st January 2019 through 31st December 2019. Five patients were excluded for being less than 18 y old. The subject's characteristics are presented in Table 1.

Of these 415 patients, 228 (54.9%) were women with a mean age of 41 ± 15 y. There were 109 deaths (26.3%), and PLOS was reported in 175 (41.7%) patients. Of 275 (66.2%) postsurgical cases, 25.8% were emergency surgery. A total of 342 patients (82.4%) received mechanical ventilation support during the ICU stay.

Table 1 presents the variables related to mortality and PLOS. Variables with P < 0.25, were emergency surgery, perioperative support medication, sepsis, cardiovascular disease, neurological disorder, heart failure, kidney failure, respiratory failure, perioperative transfusion, gender, age, and BMI.

Table 2, in the bivariate test, was included in logistic regression test. The logistic regression for mortality model is presented in Table 2. From the univariable logistic regression test and followed by the multivariable logistic regression test, we found that vasopressor/inotropic support, low GCS, respiratory failure, kidney failure, and intraoperative PRC transfusion therapy were identified as predictive factors for ICU mortality.

Table 2: Patients' Characteristics in relation to Prolonged Length of Stay (PLOS)

Variable		Total	No PLOS	PLOS	P-value
Gender	F	228 (54.94)	137(57.08)	91(52.0)	0.053
	M	187 (45.06)	103(42.92)	84(48.0)	
Age (y)		41.74 ± 15.69	39.29 ± 14.14	45.16 ± 17.08	**< 0.001***
Weight (Kg)		60.42 ± 13.40	60.76 ± 13.34	59.94 ± 13.49	0.539
Height (cm)		160.91 ± 8.93	160.88 ± 8.42	160.95 ± 9.61	0.935
BMI (Kg/m^2)		23.20 ± 4.57	23.38 ± 4.77	22.94 ± 4.27	0.326
Surgical case		274 (66.2)	204(74.5)	70(25.5)	**< 0.001***
Emergency surgery		102 (25.3)	61(58.1)	44(41.9)	**1.000**
PRC transfusion		216(52.0)	155(71.8)	61(28.2)	**< 0.001***
Vasopressor support [a]		94 (22.6)	14(14.9)	80(85.1)	**< 0.001***
Sepsis		84 (20.2)	8(9.5)	76(90.5)	**< 0.001***
Coronary Heart Disease		69(16.7)	35(50.7)	34(49.3)	0.258
Low GCS		81 (19.6)	23(28.4)	58(71.6)	**< 0.001***
Heart Failure		37(8.9)	14 (37.8)	23 (62.2)	**0.014***
Kidney Failure		73 (17.6)	26(35.6)	47(64.4)	**< 0.001***
Respiratory Failure		117 (28.3)	25(21.4)	92(78.6)	**< 0.001***
Malignancy		95(22.9)	62(65.3)	34(34.7)	**0.157***
Neurological disorder		184 (44.4)	95(51.6)	89(48.4)	**0.016**
Diabetes Mellitus		41 (9.9)	17(41.5)	24(58.5)	**0.029***
Mechanical ventilation		342 (82.6)	195(57.0)	147(43.0)	**0.294**
Readmission		12 (2.9)	9(75.0)	3(25.0)	0.235
PLOS		175 (41.7)			
Mortality rate		109 (26.0)	0	109(100)	< 0.001

Data presented as mean ± SD or n (%); P < 0.25, included in univariable logistic regression test*
BMI: Body Mass Index, GCS: Glasgow Coma Scale, PLOS: Prolonged Length of Stay
[a]: vasopressor = dobutamine, dopamine, epinephrine, norepinephrine, or vasopressin

The cut-off points show that a mortality score of 4 was associated with a mortality probability of 84%, while a score of 6 was associated with a mortality probability of 100%. A mortality score of -1 was associated with a 2.7% mortality probability, and each one-point increase corresponds to a 6.4%, 25%, 36%, 47.8%, 84%, 85.7%, and 100% mortality probability.

The mortality prediction model yielded an AUC of 0.896 (95% CI 0.853-0.940), indicating excellent discrimination performance, with an accuracy of 89.6%, as shown in Figure 1A. The Hosmer-Lemeshow test found that the mortality score had good calibration in predicting mortality, indicating no difference between predicted and actual mortality (P = 0.53).

For PLOS, multivariable logistic regression test found that medical case, GCS < 8, vasoactive/inotropic drugs, sepsis, respiratory failure, kidney failure were the predictors of PLOS in ICU; while transfusion was a protective factor of PLOS with OR < 1 (95% CI).

Based on significant variables from multivariable analysis, therefore mortality and PLOS prediction scores were made (Table 3 and 4).

A PLOS score of 3 was associated with 100% PLOS probability. PLOS score of -1 was associated with a 12.8% probability of PLOS, and each increase of one point correlated to 17.2%, 33.9%, 63.3%, and 100% probability of PLOS, respectively.

The PLOS score model also had an excellent discriminatory performance. PLOS score had an AUC of 0.878 (CI 95%; 0.800-0.900) (Figure 1B). Results from the Hosmer-Lemeshow test suggested that the PLOS score had good calibration (P = 0.50).

4. DISCUSSION

4.1. Mortality Prediction Model

Table 3: Logistic Regression Test and Risk Scoring of Mortality Risk in ICU

Variable	Univariable			Multivariable					Score
	P	OR	CI 95%	B	SE	P	OR	CI 95%	
Female Gender	**0.02***	**2.13**	1.13-4.01	0.62	0.32	0.35	1.49	0.64-3.45	
Age (year)	**0.003***	**1.03**	1.01-1.05	0.35	0.01	0.09	1.02	0.98-1.05	
BMI(Kg/cm^2)	0.93	1.00	0.94-1.07						
Medical case	**< 0.001***	**5.51**	3.45-8.80	0.56	0.513	0.275	1.75	0.64-4.79	
Surgical	**< 0.001***	**0.18**	0.11-0.29	1.70	0.24	< 0.000	0.182	0.11-0.29	
Emergency Surgery	0.05	0.41	0.17-1.00						
Vasopressor support[a]	**< 0.001***	**14.60**	7.20-29.29	**1.92**	**0.385**	**< 0.001+**	**10.17**	3.75-27.56	3
Sepsis	**< 0001***	**8.06**	3.99-16.30	0.532	0.420	0.12	2.36	0.80-6.94	
Coronary Heart Disease	**0.035***	**2.15**	1.06-4.38	-1.33	0.70	0.53	0.57	0.09-3.49	
GCS< 8	**0.018***	**2.13**	1.14-4.00	**1.60**	**0.41**	**0.002+**	**4.10**	1.66-10.12	1
Heart Failure	**0.003***	**3.47**	1.53-7.86	1.85	0.84	0.07	6.95	0.83-57.83	
Kidney Failure	**< 0.001***	**3.57**	1.76-7.23	**0.75**	**0.40**	**0.047+**	**2.81**	1.02-7.78	1
Respiratory Failure	**< 0.001***	**8.46**	4.38-16.52	**0.84**	**0.38**	**0.01+**	**3.10**	1.26-7.65	1
PRC Transfusion	**0.001***	**0.34**	0.17-0.65	**-0.88**	**0.39**	**0.03+**	**0.35**	0.13-0.91	-1

BMI: Body Mass Index; CI: confidence interval; GCS: Glasgow coma scale; OR: odds ratio; PRC: packed red cell,
[a]: vasopressor/inotropic = dobutamine, dopamine, epinephrine, norepinephrine, or vasopressin
**: P < 0.05, significant variables on univariable logistic regression test*
+: P < 0.05, significant variables on mulivariable logistic regression test

Predicting mortality in ICU patients is critical for assessing illness severity and the risk and benefit of potential treatments, interventions, and healthcare policies. Most ICU mortality prediction scores, such as the APACHE IV and the SAPS II, demonstrated good accuracy.[2,8] However, their complexity can be cumbersome in ICUs with limited resources in developing countries.

This study discovered that a mortality prediction score developed from the ICU database could perform accurately with excellent discrimination (AUC 0.896; 95% CI 0.853-0.940) and calibration performance.

Table 4: Logistic Regression Test Model and Risk Scoring of Prolonged Hospital Stay

Variable	Univariable				Multivariable						Score
	p	OR	95% CI		B	SE	p	OR	95%CI		
			Lower	Upper					Lower	Upper	
Age	< 0.001*	1.03	1.01	1.04	0.01	0.01	0.438	1.01	0.99	1.03	
Medical	< 0.001*	8.04	5.07	12.76	**1.12**	0.40	**0.005***	**2.82**	1.36	5.83	1
DM	0.023	2.132	1.108	4.102	-0.36	0.51	0.477	0.70	0.26	1.89	
GCS< 8	< 0.001*	4.36	2.59	7.34	**0.983**	**0.39**	**0.010***	**2.72**	1.26	5.82	1
Inotropic support	< 0.001*	13.89	7.50	25.73	**1.92**	**0.41**	**< 0.001***	**6.93**	3.12	15.40	2
Sepsis	< 0.001*	22.74	10.58	48.89	**2.01**	**0.50**	**< 0.001***	**7.15**	2.72	18.79	2
Respiratory Failure	< 0.001*	10.21	6.14	16.99	**0.91**	**0.35**	**0.008***	**2.53**	1.27	5.01	1
Kidney Failure	0.002*	3.09	1.83	5.23	**0.56**	**0.43**	**0.040***	**2.34**	1.04	5.28	1
PRC Transfusion	< 0.001*	0.30	0.21	0.45	**-0.96**	**0.33**	**< 0.001***	**0.25**	0.14	0.469	1

*CI: Confidence Interval, GCS: Glasgow Coma Scale, OR: odds ratio, PRC: packed red cell; *: P < 0.05 considered as significant*

Table 5: Mortality and PLOS Score

Mortality Score	
Predictors	**Scores**
Vasopressor/ inotropic support	3
GCS < 8	1
Respiratory Failure	1
Kidney failure	1
Transfusion of PRC	-1
PLOS Score	
Medical case	1
GCS < 8	1
Vasopressor/ inotropic support	2
Sepsis	2
Respiratory Failure	1
Kidney Failure	1
Transfusion of PRC	-1

Intraoperative vasopressor/inotrope use, low GCS, respiratory failure, kidney failure, and intraoperative red cell transfusion therapy were the independent variables. A cut-off point score of more than three is associated with a high mortality rate.

The variables in our mortality prediction score have also been identified as independent predictors of ICU mortality in other studies. Vasopressor/inotropic support has been associated with a high probability of ICU mortality.[9,10] Multiple organ dysfunction score (MODS), Sequential organ failure assessment (SOFA), and SAPS II scores also included low GCS, acute respiratory failure, and kidney failure.[11–13]

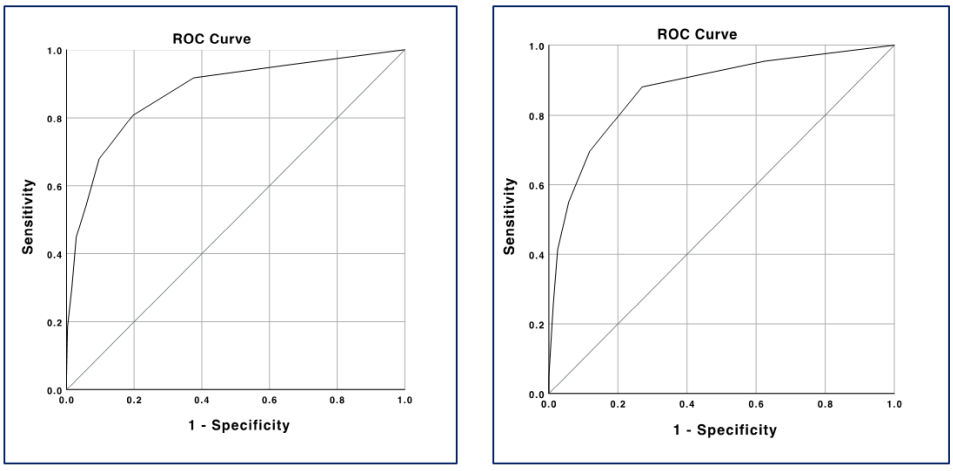

Figure 1: ROC of mortallity score (A) and PLOS (B). AUC of mortality score was 0.896 (95% CI 0.853–0.940) and for PLOS was 0.878 (95% CI 0.800-0.900)

Patients with norepinephrine ≥0.7 μg/kg/min had a relative risk of 9.353 and were independent predictors of ICU death.[14] Inotropic or vasopressor support has been associated with increased myocardial oxygen consumption, myocardial ischemia, and arrhythmias in critically ill patients.[15]

Vasopressors and inotropes treatment for critically ill patients has been associated with the potential risk of decreased renal and visceral blood flow. It is based on the rationale that noradrenaline increases MAP through vasoconstriction via α-adrenergic stimulation, and excessive vasoconstriction in regional vascular beds may decrease organ blood flow, especially in the kidney. However, the data is somewhat lacking, and the evidence may suggest otherwise. Restoring blood pressure with norepinephrine may even improve microvascular flow and tissue oxygenation in pathological vasodilation.[16]

In acute myocard infarct complicated by shock, inotropic agents preserve noninfarcted myocardial cells by improving their mitochondrial function. However, dopamine may increase the already high cytosolic Ca^{2+} in cardiac myocytes post-ischemia. This, in turn, activates proteolytic enzymes, proapoptotic signal cascades, mitochondrial damage, and cell necrosis. Therefore, clinicians should administer the lowest possible doses of inotropic and vasopressors that optimize vital tissue perfusion while preventing potential adverse events.[15]

Kidney failure has been associated with many complications. Erythropoietin, a hormone secreted mainly by the kidneys, stimulates red blood cell production. Kidney failure may result in reduced production and anemia. Chronic Kidney Disease (CKD) may also harm the cardiovascular system. Hypertension and fluid excess are two other factors that can aggravate heart function and lead to congestive heart failure. CKD is also linked to uremic syndrome, electrolyte disorders such as potassium retention, and metabolic acidosis, all of which can be fatal.[17,18]

Neurological disorders defined as impaired consciousness based on GCS were also identified as an independent mortality predictor. Nik et al.[19] found that low GCS was associated with a higher risk of mortality and the discrimination ability was comparable with APACHE II score.

Low GCS has been associated with the risk of aspiration pneumonia, which may lead to respiratory failure. Therefore, it is essential to identify low GCS to prevent the development of aspiration pneumonia.

Perioperative blood transfusion was identified as a protective variable against mortality in this study. Blood transfusion was reported to have an association with lower patient mortality in the ICU in a study of 4,470 critically ill patients. When compared to anemic patients who were not transfused, patients who received 1 to 3 blood units had an adjusted odds ratio (OR) of 0.61 (95% CI; 0.37-1.00, P = 0.026) and 0.49 (95% Cl; 0.23-1.03, P = 0.03).[20] PRC transfusion is commonly administered in critically ill patients to increase oxygen delivery and oxygenation, especially in shock patients. The use of transfusion is justified because an increase in hemoglobin improves blood oxygen transport capacity, allowing for more oxygen supply to oxygen-dependent tissues.[21]

4.2. PLOS Prediction Model

This study found a highly accurate PLOS prediction score. A cut-off score of > 2 was associated with a high probability of mortality (> 84%). The score had excellent discrimination performance and calibration. Intraoperative vasopressor/inotropic usage, low GCS, respiratory failure, kidney failure, and intraoperative PRC transfusion were identified as predictive mortality factors in ICU. The use of vasopressor/inotropic consistenly had high score in predicting both mortality and PLOS in our population.

Several studies found various predictors of ICU PLOS including age, comorbidity, prolonged mechanical ventilation, sepsis and laboratory finding. Renal failure, the use of vasopressor/inotropic, and mechanical ventilator are the most predictor found in previous studies.[22–25]

APACHE IV seems to have less accuracy to predict PLOS in ICU despite the good discrimination and calibration in predicting mortality in our population. The AUC for predicting PLOS is 0.68 (0.62–0.74) and p value =0.01 for Hosmer-Lemeshow test for calibration, which considered poor.[5]

Different study design, sample size, population characteristics, operational definitions, inclusion and exclusion criteria and different methods of modelling may affect the results. Some studies used different definitions for prolonged ICU length of stay varied, for instance 14 days in Tobi and Amadasun, 30 days in Cevic et al. For the current study, we defined ICU prolonged length of stay as >7 ICU days, similar used in a study by Bohmer et al.[25] Despite different characteristic of the population, methods, and operational definition of PLOS we found common variables predicting PLOS in ICU.

5. CONCLUSION

Perioperative vasoactive/inotropic agents support, neurological disorder, respiratory failure, kidney failure, and perioperative blood transfusion were predictors of ICU mortality. Meanwhile, medical cases, GCS <8, vasoactive/inotropic support, sepsis, respiratory failure, kidney failure, and transfusion were predictors of ICU PLOS. Both ICU mortality and PLOS score had excellent discrimination performance.

6. Data availability

Numerical data generated in the course of this study is available with the correspondence author.

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8. Conflicts of interest

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9. Authors' contribution

All authors contributed in the preparation of the study protocol, conduct of the study, literature search and manuscript preparation.

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