A nomogram to predict in-hospital mortality of neonates admitted to the intensive care unit

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Background: To explore the influencing factors for in-hospital mortality in the neonatal intensive care unit (NICU) and to establish a predictive nomogram.

Methods: Neonatal data were extracted from the Medical Information Mart for Intensive Care III (MIMIC-III) database. Both univariate and multivariate logit binomial general linear models were used to analyse the factors influencing neonatal death. The area under the receiver operating characteristics (ROC) curve was used to assess the predictive model, which was visualized by a nomogram.

Results: A total of 1258 neonates from the NICU in the MIMIC-III database were eligible for the study, including 1194 surviving patients and 64 deaths. Multivariate analysis showed that red cell distribution width (RDW) (odds ratio [OR] 0.813, p=0.003) and total bilirubin (TBIL; OR 0.644, p<0.001) had protective effects on neonatal in-hospital death, while lymphocytes (OR 1.205, p=0.025), arterial partial pressure of carbon dioxide ($PaCO_2$; OR 1.294, p=0.016) and sequential organ failure assessment (SOFA) score (OR 1.483, p<0.001) were its independent risk factors. Based on this, the area under the curve of this predictive model was up to 0.865 (95% confidence interval 0.813 to 0.917), which was also confirmed by a nomogram.

Conclusions: The nomogram constructed suggests that RDW, TBIL, lymphocytes, $PaCO_2$ and SOFA score are all significant predictors for in-hospital mortality in the NICU.

Keywords: in-hospital mortality, MIMIC database, neonates, nomogram.

Introduction

Despite a significant decrease in global childhood mortality, neonatal mortality remains relatively high, accounting for approximately 40% of all childhood mortality.[1,2] Each year 2.6 million neonates die globally, with 75% of neonatal deaths occurring in the first week of life and 99% die in low- and middle-income countries (LMICs).[1,3] Due to the lack of a surveillance system in developing countries, neonatal sepsis in LMICs is likely underreported, indicating the proportion of neonatal mortality may be even higher.[4] Neonatal mortality is becoming a prominent component of the overall mortality of children <5 y of age.[5] Prematurity, intrapartum-related complications like birth asphyxia and neonatal sepsis are thought to be the three leading causes of neonatal mortality.[6]

Currently neonatal deaths can be decreased via extra care for preterm newborns, provision of feeding support, improvement of resuscitation skills and infection prevention.[7] Recent global estimates indicate that increasing the coverage of existing interventions can prevent about 75% of newborn deaths.[8,9] Although these solutions are achievable, neonatal mortality is still a big challenge for LMICs, especially in southern Asia and sub-Saharan Africa.[10] Identifying the risk factors is beneficial to predict the mortality of neonates, especially where intervention is feasible with modest resources.[11,12] Houweling et al.[12] found that preterm birth, multiple births and poor condition at 5 min post-partum were associated with a significantly increased risk of neonatal mortality and thus they established prediction models for neonatal death. However, these prediction models are appropriate for assessing neonatal mortality in the general population of South Asia. The current study explores the influencing factors for neonatal mortality in the neonate intensive care unit (NICU) using the Medical Information Mart for Intensive Care III (MIMIC-III) database and to construct a nomogram for predicting neonatal mortality, aimed at providing more evidence for the prevention and treatment of neonatal mortality in the NICU.

Table 1. Comparison of the baseline characteristics of neonates with different outcomes

Variables	Survival group (n=1194)	Death group (n=64)	Total (N=1258)	Statistic	p-Value
Gestational age (weeks)	27.89±1.95	27.78±1.70	27.89±1.94	t=0.44	0.660
Gender, n (%)				χ^2=0.03	0.854
Male	695 (58.21)	38 (59.38)	733 (58.27)		
Female	499 (41.79)	26 (40.62)	525 (41.73)		
Birthweight (kg)	1.60 (1.13–2.40)	0.92 (0.68–1.50)	1.58 (1.11–2.36)	Z=−6.061	<0.001
Heart rate (bpm)	156 (144–166)	154 (144–165)	156 (144–166)	Z=0.783	0.434
Laboratory parameters					
Bicarbonate (mmol/L)	21.00 (19.00–23.00)	20.70 (19.00–22.00)	21.00 (19.0–23.00)	Z=−1.943	0.052
Haematocrit (%)	46.60 (41.70–50.90)	43.22 (40.05–47.05)	46.25 (41.60–50.80)	Z=−3.201	0.001
Haemoglobin (g/dl)	15.50 (13.90–17.00)	14.66 (13.50–15.60)	15.50 (13.80–17.00)	Z=−3.096	0.002
WBC count ($\times10^9$/L)	10.20 (6.90–14.50)	8.80 (5.00–11.55)	10.20 (6.90–14.50)	Z=−2.171	0.030
RBC count ($\times10^6/\mu$l)	4.16 (3.74–4.61)	3.83 (3.47–4.22)	4.14 (3.73–4.59)	Z=−4.319	<0.001
PLT count ($\times10^9$/L)	251.00 (198.00–311.75)	214.50 (174.00–240.75)	248.00 (197.00–309.00)	Z=−3.705	<0.001
RDW (%)	17.00 (16.30–17.80)	16.80 (15.75–17.26)	17.00 (16.30–17.70)	Z=2.892	0.004
Neutrophils (%)	29.00 (18.00–44.00)	23.50 (17.75–35.00)	29.00 (18.00–44.00)	Z=2.178	0.029
Lymphocytes (%)	57.00 (40.00–70.00)	62.00 (49.75–72.50)	57.00 (41.00–70.00)	Z=−2.220	0.026
Sodium (mEq/L)	139.00 (136.00–141.00)	139.68 (138.00–144.50)	139.00 (136.00–141.00)	Z=2.649	0.008
TBIL (mg/dL)	5.10 (4.00–6.20)	2.60 (2.25–3.10)	5.10 (3.90–6.20)	Z=−7.782	<0.001
FiO$_2$	30.00 (23.25–50.00)	40.00 (30.00–70.00)	30.00 (24.00–50.00)	Z=3.805	<0.001
PaCO$_2$ (mmHg)	47.00 (40.00–54.00)	47.00 (39.00–60.75)	47.00 (40.00–54.00)	Z=1.309	0.191
PaO$_2$ (mmHg)	50.00 (41.00–71.00)	58.00 (44.75–73.50)	50.00 (41.00–71.00)	Z=1.816	0.069
Scoring systems					
SOFA score	6.00 (4.00–7.00)	8.00 (6.00–9.00)	6.00 (4.00–7.00)	Z=5.593	<0.001
SAPS II	34 (30–39)	37 (33–41)	34 (30–39)	Z=2.376	0.018

Values are presented as median (IQR; quartile 1–quartile 3) unless stated otherwise.

Methods

Patients

The MIMIC-III database was used to extract data. The MIMIC-III is a large, free database that contains de-identified health data for >40 000 ICU patients from the Beth Israel Deaconess Medical Center (Boston, MA, USA) between 2001 and 2012.[13] It not only contains demographics, vital signs, medications and laboratory tests, but also includes observations and notes charted by care providers, procedures and diagnostic codes, fluid balance, imaging reports, length of stay and survival data. According to the MIMIC-III, 7874 neonates were admitted to the NICU.[14] Neonates with a gestational age of 23–31 weeks were included in our study, while those with missing data, including birthweight, vital signs and laboratory measurements, were excluded.

Since the data used in this study were accessed from MIMIC-III, an openly available dataset, the study did not get approval from the Institutional Review Board of Guangdong Second Provincial General Hospital.

Data collection

Data from the MIMIC-III used for analysis in this study included gender, birthweight, heart rate, laboratory parameters (bicarbonate, haematocrit, haemoglobin, white blood cell [WBC] count, red blood cell [RBC] count, platelet [PLT] count, red cell distribution width [RDW], neutrophils, lymphocytes, sodium, total bilirubin [TBIL], fraction of inspired oxygen [FiO$_2$], arterial partial pressure of carbon dioxide [PaCO$_2$], arterial partial pressure of oxygen [PaO$_2$]), sequential organ failure assessment (SOFA) score and the Simplified Acute Physiology Score II (SAPS II). These data could be downloaded from several sources, including archives from critical care information systems, hospital electronic health record databases and Social Security Administration Death Master File.[14]

Neonatal deaths in this study were defined as death occurring within 30 d following admission to the NICU. The SOFA score was developed to assess the acute morbidity of critical illness at the patient level based on six criteria—cardiovascular, respiratory, nervous, hepatic, renal and haematological systems—each scored on a scale of 0–4. The higher the SOFA score, the worse the organ dysfunction.[15] The SAPS II provides an estimate of the risk of death without specifying a primary diagnosis. It contains 17 variables: age, type of admission, 12 physiology variables and 3 underlying disease variables.[16] PaO$_2$ and FiO$_2$ are commonly used for diagnosis of lung injury and TBIL reflects liver metabolism.[17,18]

Statistical analysis

Categorical data were presented as number and percentage, while the χ^2 test or Fisher's exact test was used for compar-

Table 2. Factors associated with in-hospital death among neonates

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Gestational age (weeks)	0.971 (0.853 to 1.104)	0.649	0.968 (0.888 to 1.056)	0.464
Gender (female)	1.049 (0.629 to 1.751)	0.854		
Birthweight (kg)	0.335 (0.216 to 0.518)	<0.001		
Heart rate (bpm)	0.986 (0.972 to 1.001)	0.059		
Laboratory parameters				
WBC count ($\times 10^9$/L)	0.957 (0.914 to 1.001)	0.057		
RBC count ($\times 10^6/\mu$L)	0.495 (0.352 to 0.696)	<0.001		
PLT count ($\times 10^9$/L)	0.995 (0.993 to 0.998)	0.001		
Haematocrit (%)	0.957 (0.928 to 0.987)	0.006		
Haemoglobin (g/dL)	0.880 (0.801 to 0.966)	0.007		
RDW (%)	0.845 (0.723 to 0.990)	0.037	0.813 (0.710 to 0.932)	0.003
Neutrophils (%)	0.982 (0.967 to 0.998)	0.023		
Lymphocytes (%)	1.180 (1.022 to 1.361)	0.024	1.205 (1.024 to 1.417)	0.025
TBIL (mg/dL)	0.524 (0.439 to 0.624)	<0.001	0.644 (0.529 to 0.785)	<0.001
FiO$_2$	1.011 (1.004 to 1.020)	0.004		
PaCO$_2$ (mmHg)	1.262 (1.012 to 1.574)	0.039	1.294 (1.049 to 1.596)	0.016
PaO$_2$ (mmHg)	1.000 (0.994 to 1.006)	0.907		
Sodium (mEq/L)	1.089 (1.035 to 1.145)	<0.001		
Bicarbonate (mEq/L)	0.892 (0.827 to 0.963)	0.003		
SOFA score	1.533 (1.400 to 1.678)	<0.001	1.483 (1.334 to 1.649)	<0.001

ison. Continuous variables were expressed as medians and interquartile ranges (IQRs). Differences in baseline information of included neonates and clinical characteristics, as well as laboratory parameters between groups, were compared according to in-hospital survival outcomes for neonates in the NICU. With neonatal in-hospital death or survival as the dependent variable and demographic characteristics and laboratory indicators as independent variables, a univariate logit binomial general linear model (GLM) was performed. Independent variables with significant difference in the univariate analysis were included in a multivariate logit binomial GLM. In view of the multicollinearity among independent variables, a stepwise regression analysis was conducted to identify the risk factors and establish a predictive model. The receiver operating characteristics (ROC) curve and the area under the curve (AUC) were used to assess the predictive model, which was visualized by a nomogram. The nomogram is one method used to visualize the predictive model with graphic scoring.[19] All statistical tests were two-sided and p-values ≤0.05 were considered to be statistically significant. All statistical analyses were carried out using R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics of included neonates

Of 7874 neonates admitted to the NICU, there were 7800 with a gestational age of 23–31 weeks. After excluding 6542 patients with missing data (birthweight 621 patients, survival outcomes

1345 patients, laboratory parameters 3992 patients and scoring systems 584 patients), 1258 neonates (733 males [58.27%] and 525 females [41.73%]) were eligible for the study. In-hospital death occurred in 64 patients. All included subjects were included in the death group (n=64) and 1194 were included in the survival group. The baseline characteristics of the two groups are compared in Table 1. It can be observed that except for gender, heart rate, PaCO$_2$, PaO$_2$ and bicarbonate, the differences were all pronounced between the death group and the survival group regarding other variables, including birthweight (p<0.001), WBC count (p=0.030), RBC count (p<0.001), PLT count (p<0.001), haematocrit (p=0.001), haemoglobin (p=0.002), RDW (p=0.004), neutrophils (p=0.029), lymphocytes (p=0.026), TBIL (p<0.001), FiO$_2$ (p<0.001), sodium (p=0.008), SOFA score (p<0.001) and SAPS II (p<0.018).

Univariate and multivariate analysis of in-hospital death in neonates

Univariate and multivariate analysis of in-hospital death in neonates is presented in Table 2. As it shows, birthweight (odds ratio [OR] 0.335, p<0.001), RBC count (OR 0.459, p<0.001), PLT count (OR 0.995, p=0.001), haematocrit (OR 0.957, p=0.006), haemoglobin (OR 0.880, p=0.007), RDW (OR 0.845, p=0.037), neutrophils (OR 0.982, p=0.023), TBIL (OR 0.524, p<0.001) and bicarbonate (OR 0.892, p=0.003) were all associated with a reduced risk of in-hospital death in neonates, whereas lymphocytes (OR 1.180, p=0.024), FiO$_2$ (OR 1.011, p=0.004), PaCO$_2$ (OR 1.262,
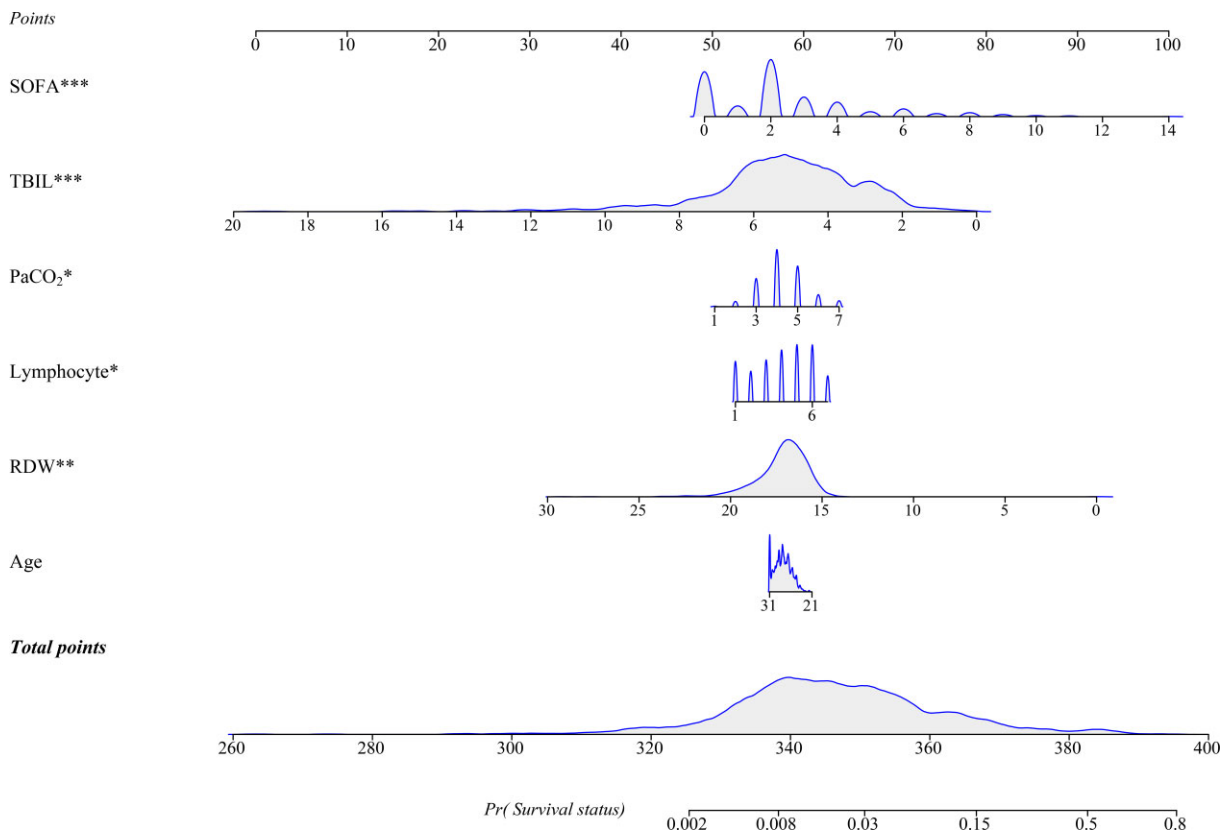
Figure 1. The nomogram for predicting 30-d in-hospital mortality in the NICU.

p=0.039), sodium (OR 1.089, p<0.001) and SOFA score (OR 1.533, p<0.001) related to an increased risk.

Through multivariate analysis, RDW (OR 0.813, p=0.003) and TBIL (OR 0.644, p<0.001) were found to have protective effects on neonatal in-hospital death, while the risk of in-hospital mortality was increased 1.205-fold and 1.294-fold for each increase in lymphocytes (OR 1.205, p=0.025) and $PaCO_2$ (OR 1.294, p=0.016), respectively. In addition, the SOFA score (OR 1.483, p<0.001) was also identified as an independent risk factor for neonatal in-hospital mortality.

Nomogram for predicting in-hospital mortality in the NICU

A nomogram was constructed using the determinants identified in multivariate analysis of in-hospital mortality (Figure 1). The score for each parameter was obtained through upward projection of each variable to the value of the small ruler (points). Adding the points assigned to the corresponding factors determined the total points. The higher the total score, the higher the risk of mortality. For each patient, the risk of in-hospital mortality could be individually predicted by the nomogram. The predictive accuracy of this model was then assessed and the AUC of the nomogram was 0.865 (95% CI 0.813 to 0.917) (Figure 2). The data from one patient in the training set were randomly extracted for validation. If the gesta-
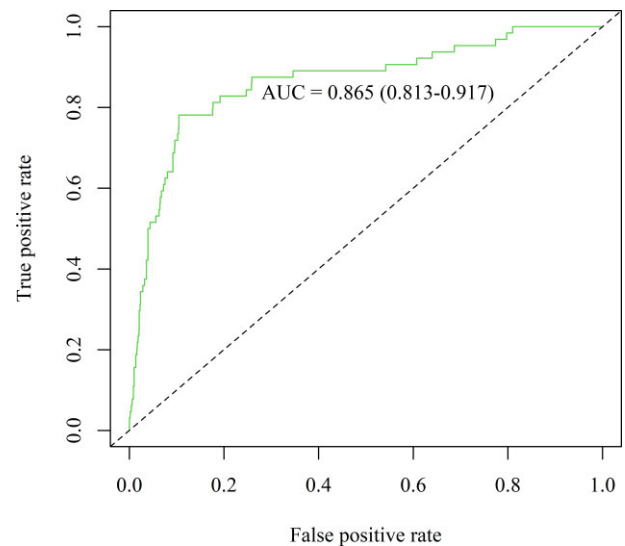

Figure 2. The ROC curve for the predictive model.

tional age of the baby was 28 weeks, the total score would be 383 by adding the variables ($PaCO_2$ 7 mmHg, RDW 17.19%, lymphocytes 47%, SOFA score 9, TBIL 3.1 mg/dL), with a risk of death of 0.517. This case was alive, highlighting the predictive accuracy (Figure 3).
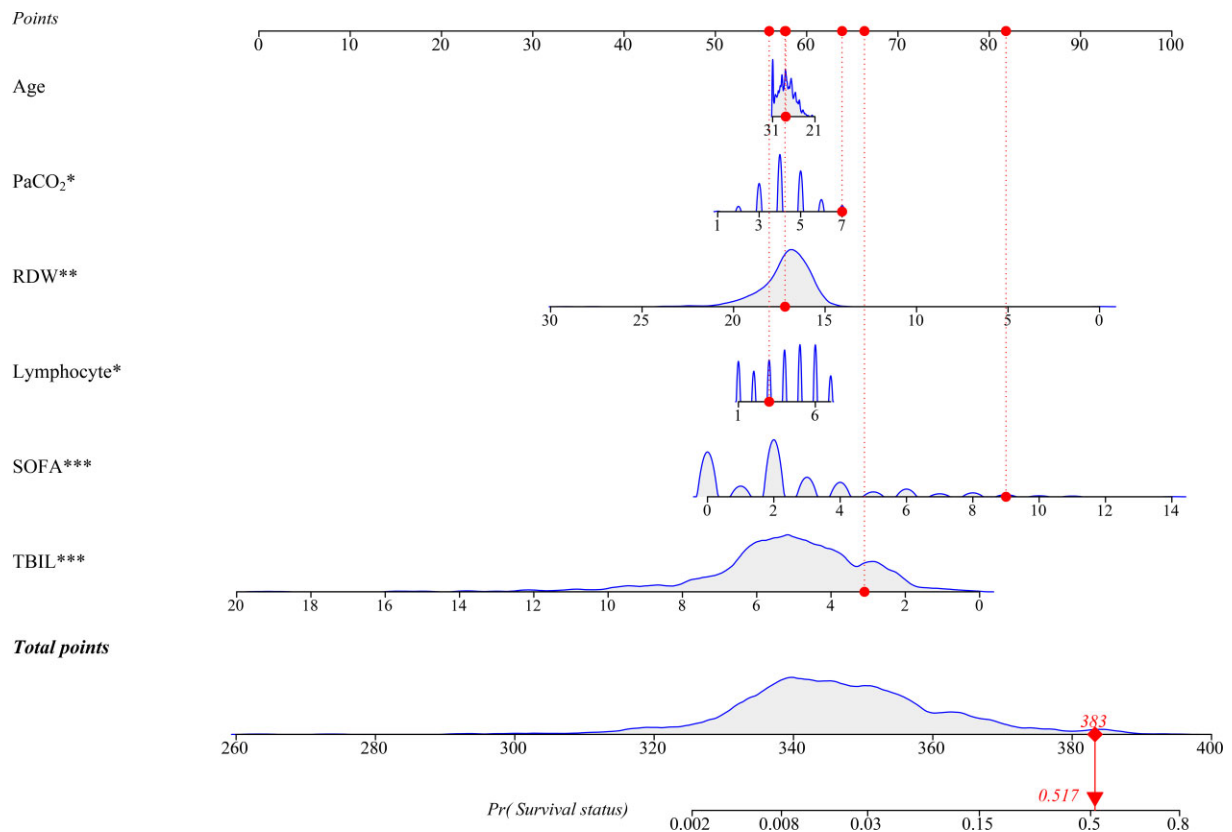
Figure 3. The validation for the predictive model.

Discussion

Considering the high neonatal mortality rates, neonatal health is still a matter of great concern around the world. In this study, we used data from 1258 NICU neonates in the MIMIC-III database, including 1194 surviving patients and 64 deaths. Our results indicated that RDW and TBIL had protective effects on neonatal in-hospital death, while lymphocytes, $PaCO_2$ and SOFA score were independent risk factors for neonatal in-hospital mortality. Using our findings, we constructed a nomogram that was easy to use in the prediction of in-hospital mortality in the NICU. The model, with its high accuracy, is helpful for the optimization of clinical management.

RDW, a standard parameter of the complete blood count, represents variability in RBC size. Its increase reflects greater variability in RBC size, usually suggesting dysfunctional erythropoiesis, premature release of reticulocytes or shortened RBC lifespan. RDW can not only help diagnose iron deficiency anaemia, but can also predict outcomes of various comorbidities in children and adults. Studies on the association of RDW with neonatal sepsis have shown that RDW is an independent outcome predictor for mortality related to neonatal sepsis, highlighting the prognostic value of RDW in neonatal sepsis, the third leading cause of neonatal deaths.[20–22] In our study, RDW was also identified as a significant protective factor for in-hospital mortality in the NICU, which was supported by the study of Said et al.[23] This finding

increased awareness of the association between RDW and the risk of neonatal mortality.

TBIL is a crucial diagnostic marker.[24] Our results showed the protective role of TBIL in NICU neonates, as the risk of death in neonates increase 0.644-fold at each 1 mg/dL addition. A study presented by Dani et al.[25] found a lower TBIL level in infants with moderate to severe hypoxic–ischaemic encephalopathy (HIE) than in those without HIE. They speculated that the increased TBIL was not a neuroprotective mechanism in infants with HIE. The correlation between TBIL levels and oxidative stress among newborns has been investigated and it was found that low physiologic TBIL levels are relevant to antioxidant effects, whereas high pathologic TBIL levels are correlated with prooxidant effects.[26] In contrast, Song et al.[27] showed that low TBIL levels appear to reduce resistance to oxidative stress and contribute to the disruption of lipid metabolism in neonates with nephrotic syndrome. However, the effect of TBIL on the prognosis of infants cannot be judged from data in the literature.

The SOFA score is a well-known scoring system in the ICU setting. It was designed for severity assessments of clinical status and the response examination to a given treatment.[28] Our study shows that the SOFA score was a significant risk factor for in-hospital mortality in the NICU, with 1.483-fold risk of mortality for each 1 point addition. This was in line with the findings of Ha et al.[29] that the sequential assessment of SOFA score within a few days following NICU admission was a good prognostic

predictor in oncology children mechanically ventilated >3 d, and it was strongly associated with mortality.

As a prognostic device, the nomogram has been extensively used in oncology and medicine to predict the probability of clinical events. It can help clinicians make quick and sound decisions due to the characteristics of better accuracy, straightforward digital interfaces and readily comprehensible prognosis.[30,31] To the best of our knowledge, this is the first study to construct a nomogram for predicting the risk of in-hospital mortality in the NICU, which simply and easily depicted the associations of each predictor with in-hospital mortality risk. Moreover, the AUC of the present nomogram in predicting neonatal in-hospital mortality was 0.865, showing good predictive accuracy. However, there are still some limitations that needed to be addressed. First, although the sample size retrieved from MIMIC-III database was large enough, the number of neonates in the death group was small, which may affect the statistical power of the current study. Second, MIMIC-III data were from a single medical centre. Additionally, some information, such as maternal height, maternal age, BMI, preterm birth, intrapartum-related complications, education and wealth, was missing in the MIMIC-III database, which may affect the applicability of our predictive model. In the future, more large-scale, multicentre studies on neonatal mortality should be conducted to further verify our results.

Conclusions

Increased RDW and TBIL were associated with a reduced risk of neonatal in-hospital death, while higher lymphocytes, $PaCO_2$ and SOFA score were related to an increased risk of neonatal in-hospital mortality. The constructed nomogram shows a high accuracy of prediction for in-hospital mortality in the NICU.

Competing interests: All the authors declare that they have no competing interests.

Ethical approval: Not required.

Data availability: The data that support the findings of this study are available from the first author and corresponding author upon reasonable request.

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