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Development and internal validation of a metabolism-related model for predicting 30-day mortality in neonatal sepsis

Xiangwen Tu[1†], Junkun Chen[1†] and Wen Liu[2*]

Abstract

Objective Neonatal sepsis, a severe infectious disease associated with high mortality rates, is characterized by metabolic disturbances that play a crucial role in its progression. The aim of this study is to develop a metabolism-related model for assessing 30-day mortality in neonatal sepsis.

Methods The clinical data of neonatal sepsis at Ganzhou Women and Children's Health Care Hospital from January 2019 to December 2022 were retrospectively analyzed. Neonatal sepsis cases were divided into survival and non-survival groups. Multivariate logistic regression analysis was used to identify the independent risk factors for 30-day mortality. A nomogram model was developed based on these risk factors. Internal validation of the model was performed using 10-fold cross-validation. The predictive performance was evaluated through receiver operating characteristic (ROC) curves and calibration curve analyses. Decision curve analysis (DCA) was conducted to evaluate the clinical applicability of the developed model.

Results The study included a total of 156 cases of neonatal sepsis. Multivariate logistic regression analysis revealed that alanine(ALA), citrulline(CIT)), octadecanoylcarnitine(C18) and methionine(MET) were identified as independent risk factors for 30-day mortality of neonatal sepsis. The ROC curve showed an area under the curve of AUC = 0.866 (95% CI 0.796–0.936, $P < 0.05$). The calibration curve and DCA indicated excellent performance of the model.

Conclusion This study establishes a predictive model for neonatal sepsis-associated 30-day mortality, effectively capturing the perturbations in amino acid metabolism and fatty acid oxidation, thereby demonstrating robust predictive capabilities.

Keywords Amino acids, Acylcarnitines, Mortality, Neonatal sepsis, Prognosis

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Background

Sepsis is a leading cause of neonatal mortality, and its early diagnosis poses challenges due to the lack of specificity in clinical manifestations and variable laboratory indicators. Although blood culture serves as the gold standard for neonatal sepsis diagnosis, it is not suitable for early detection due to its long culture time and low positive predictive value. Many researchers have explored reliable biomarkers such as antithrombin III [1], cytokine profiles [2], serum resistin [3], and prognostic nutritional index [4] to assess prognosis. Nonetheless, these biomarkers demonstrate limitations in terms of sensitivity and specificity. Therefore, achieving early detection of neonatal sepsis remains an ongoing challenge.

Amino acid and fatty acid metabolism play a pivotal role in the development and progression of neonatal sepsis [5]. As essential nutrients with unique physiological, biochemical, and immunological functions, amino acids have significant implications for the prognosis of neonatal sepsis. Disorders in amino acid metabolism may have a direct impact on disease prognosis [6]. Acylcarnitine serves as an intermediate product of fatty acid β-oxidation, closely associated with mitochondrial function and energy metabolism. Mitochondrial dysfunction and abnormal energy metabolism are important features of neonatal sepsis [7]. The documented alterations in amino acid and fatty acid metabolism during sepsis provide valuable insights into disease pathogenesis. Several amino acids, such as citrulline, arginine [8], and homocysteine [9], have demonstrated alterations in sepsis. Additionally, two separate studies have shown that alanine and acetylcarnitine are associated with the prognosis of sepsis [10, 11]. Consequently, we monitored variations in amino acids and acylcarnitines in neonatal sepsis to identify reliable biomarkers for disease assessment and mortality prediction.

However, the prediction of mortality risk in neonatal sepsis is limited by the low sensitivity and specificity of a single biomarker. To effectively assess the likelihood of adverse outcomes, clinical models are incorporating multiple independent risk factors associated with disease progression. An increasing array of models is currently being developed to aid in assessing sepsis mortality [12–14]. Nevertheless, there is a lack of available models that utilize metabolic markers such as amino acids and acylcarnitines to predict 30-day mortality risk in neonates. Therefore, this study aims to develop a model that leverages multiple amino acids and acylcarnitines to estimate 30-day mortality in neonatal sepsis.

Method

Study population

Clinical data and laboratory indicators of neonatal sepsis patients admitted between January 2019 and December 2022 were collected. Admission information was obtained from the medical records. Patient information was complete and within 28 days of age. A total of 156 patients with neonatal sepsis were included in the study, (Fig. 1). The diagnosis of neonatal sepsis was based on the International Consensus on Pediatric Sepsis [15]. Neonatal sepsis was defined as the presence of clinical signs suggestive of sepsis together with one of the following criteria: positive blood culture or detection of pathogenic DNA in blood; two or more positive nonspecific blood tests (CRP, total white blood cell count, platelet count, immature neutrophil/total neutrophil ratio > 0.2); and cerebrospinal fluid examination for purulent meningitis changes or positive cerebrospinal fluid culture. The exclusion criteria encompassed cases with incomplete clinical data, including but not limited to birth weight, gestational age, laboratory test results, as well as those with other inherited metabolic diseases or organ dysfunction. The study protocol followed the principles set forth in the Declaration of Helsinki, and the study was approved by the Medical Ethics Committee of the Ganzhou Women and Children's Health Care Hospital(2023-007).

Data collection

The following clinical data of neonatal sepsis patients were obtained from the electronic medical records system: sex, age, gestational age, weight, Apgar scores at 5 min and 10 min, and blood culture. Within 24 h after admission, neonatal plantar blood drops were collected and spotted onto dry filter paper blood cards. Blood spots were punched and placed in the holes of microtitre plates using an automated punching machine (Panthera-Puncher™ 9). After nonderivative pretreatment, amino acids and acylcarnitines in the blood spots were detected via tandem mass spectrometry (Waters TQD). A NeoBase Nonderivatized MS/MS Kit manufactured by PerkinElmer was used as a reagent. The analytes included 11 amino acids and 10 acylcarnitines: the 11 amino acids were alanine (Ala), arginine (Arg), citrulline (Cit), glycine (Gly), leucine (Leu), methionine (Met), ornithine (Orn), phenylalanine (Phe), proline (Pro), tyrosine (Tyr), and valine (Val); the 10 acylcarnitines were free carnitine (C0), acetylcarnitine (C2), propionylcarnitine (C3), butyrylcarnitine (C4), isovalerylcarnitine (C5), hexanoylcarnitine (C6), octanoylcarnitine (C8), decanoylcarnitine (C10), tetradecanoylcarnitine (C14), and octadecanoylcarnitine (C18). The levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea nitrogen (UREA), creatinine (CREA), albumin (ALB) and other biochemical indicators were determined via an automated biochemical analyser (Roche Cobas8000).

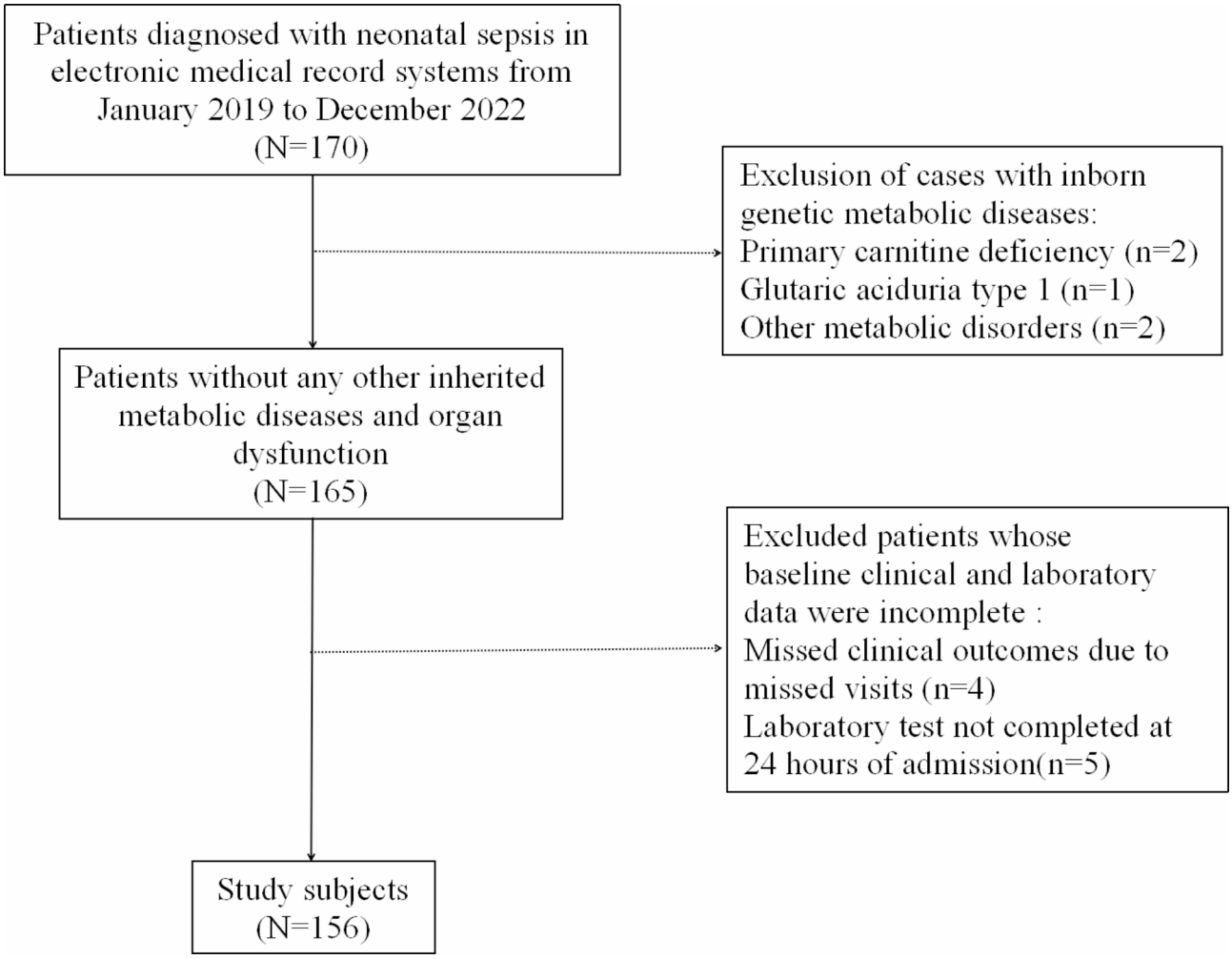

Fig. 1 The flowchart for selection procedure of neonatal sepsis

Statistical methods

Statistical analysis of the data was conducted using SPSS(Version 25; IBM, Armonk, NY, USA) software. The normality of the data was assessed via the Shapiro-Wilk test, normally distrbuted quantitative variables are expressed as the means ± standard deviations, and non-normal distrbuted quantitative variables are expressed as medians. Categorical variables are reported in numbers and percentages. Comparisons between the two groups were analysed using t-tests and Mann-Whitney U tests. Univariate and multivariate logistic regression were used to identify independent risk factors for 30-day mortality due to neonatal sepsis. The predictive accuracy of the model was evaluated using receiver operating characteristic (ROC) curves. Model calibration and DCA curves were generated via R software(version 4.4.0). 10-fold cross-validation was used to assess the model's performance. A p-value of less than 0.05 was considered indicative of a statistically significant difference.

Results

Clinical characteristics of the study population

At the time of enrolment, 156 patients with neonatal sepsis were evaluated. These patients fulfilled all the inclusion criteria. Among these patients, 131 patients were classified as surviving and 25 patients died after 30 days of follow-up, all of whom were did not surviving. The demographic and clinical characteristics of the patients are shown in Table 1. There was no difference in weight, gestational age and Apgar score between the two groups (all $p > 0.05$). Comparison of amino acid metabolic indices between the two groups revealed that ALA was greater in the nonsurvival group than in the survival group ($p < 0.05$), and ARG, CIT, GLY and MET were lower in the nonsurvival group than in the survival group (all $p < 0.05$); C4, C5 and C18 in the non-survival group were lower than those in the survival group (all $p < 0.05$); Comparing the liver and kidney function indices of the two groups, TBIL and ALT were greater in the nonsurvival group than in the survival group (all $p < 0.05$), and

Table 1 Characteristics of patients

Variables	Survivors ($n=131$)	Non-survivors ($n=25$)	*p*-value
Gender (male/female), n	90/41	14/11	0.217
Median age (range), day	3 (1, 27)	5 (1, 28)	0.407
Weight (g)	2700.00 (1920.00, 3350.00)	3100.00 (2700.00, 3400.00)	0.075
Gestational age at birth (weeks)	36.00 (32.00, 39.00)	38.00 (37.00, 39.00)	0.074
Apgar score (1 min)	9.00 (8.00, 10.00)	9.00 (8.00, 10.00)	0.947
Apgar score (5 min)	10.00 (9.00, 10.00)	10.00 (9.00, 10.00)	0.627
Respiratory distress syndrome, n(%)	34(25.95)	7 (28.00)	0.831
Hyperbilirubinemia, n(%)	31 (23.66)	6 (24.00)	0.971
Purulent meningitis, n(%)	41 (31.30)	6 (24.00)	0.466
Pneumonia, n(%)	49 (37.40)	10 (40.00)	0.806
Culture positive, n (%)	24(18.32)	6(24.00)	0.701
ALA(μmol/L)	201.67 (172.84, 239.88)	237.96 (205.94, 303.26)	0.006
ARG(μmol/L)	9.16 (4.77, 18.56)	5.64 (3.26, 8.76)	0.003
CIT(μmol/L)	12.46 ± 4.53	10.51 ± 3.59	0.044
GLY(μmol/L)	348.32 (288.76, 411.51)	279.45 (257.14, 356.53)	0.026
LEU(μmol/L)	162.29 (125.55, 199.34)	154.97 (143.90, 179.26)	0.714
MET(μmol/L)	23.26 (19.17, 30.61)	18.78 (17.67, 25.06)	0.049
ORN(μmol/L)	94.24 (70.60, 129.98)	88.79 (82.58, 123.47)	0.961
PHE(μmol/L)	56.05 (43.66, 69.88)	53.81 (42.29, 64.29)	0.300
PRO(μmol/L)	146.29 (119.34, 192.79)	136.28 (123.63, 174.15)	0.411
TYR(μmol/L)	70.37 (55.54, 95.75)	59.78 (49.69, 77.80)	0.104
VAL(μmol/L)	123.02 (95.44, 155.47)	125.14 (100.70, 142.96)	0.790
C0(μmol/L)	18.48 (14.36, 23.15)	18.14 (14.82, 23.95)	0.958
C2(μmol/L)	10.22 (6.18, 13.29)	9.73 (7.15, 12.76)	0.967
C3(μmol/L)	0.93 (0.61, 1.48)	0.82 (0.76, 1.03)	0.309
C4(μmol/L)	0.19 (0.14, 0.24)	0.16 (0.14, 0.19)	0.049
C5(μmol/L)	0.11 (0.08, 0.15)	0.07 (0.06, 0.10)	0.004
C6(μmol/L)	0.03 (0.02, 0.05)	0.03 (0.03, 0.05)	0.466
C8(μmol/L)	0.05 (0.04, 0.06)	0.04 (0.03, 0.06)	0.249
C10(μmol/L)	0.04 (0.03, 0.06)	0.05 (0.03, 0.06)	0.891
C14(μmol/L)	0.08 (0.06, 0.11)	0.08 (0.06, 0.11)	0.985
C18(μmol/L)	0.47 ± 0.22	0.38 ± 0.11	0.002
TBIL(μmol/L)	52.70 (37.40, 111.50)	87.80 (45.93, 170.53)	0.024
ALB(U/L)	31.82 ± 4.55	31.37 ± 3.81	0.648
ALT(U/L)	7.00 (4.00, 11.00)	10.00 (7.00, 17.75)	0.003
AST(U/L)	38.00 (23.00, 59.00)	43.00 (30.25, 65.75)	0.483
CHE(U/L)	4977.58 ± 1526.80	4276.50 ± 1223.61	0.044
UREA(mmol/L)	3.44 (2.80, 5.30)	3.60 (2.58, 5.80)	0.713
CREA(μmol/L)	53.00 (43.00, 66.00)	55.00 (37.50, 70.50)	0.750

ALA, alanine; ALB, albumin; ALT, alanine aminotransferase; ARG, arginine; AST, aspartate transaminase; CHE, cholinesterase; CIT, citrulline; CREA, creatinine; C0, carnitine; C2, acetylcarnitine; C3, propionylcarnitine; C4, butyrylcarnitine; C5, isovalerylcarnitine; C6, hexanoylcarnitine; C8, octanoylcarnitine; C10, decanoylcarnitine; C14, tetradecanoylcarnitine; C18, octadecanoylcarnitine; GLY, glycine; LEU, leucine; MET, methionine; ORN, ornithine; PHE, phenylalanine; PRO, proline; TBIL, total bilirubin; TYR, tyrosine; VAL, valine; UREA, urea

CHE was lower in the nonsurvival group than in the survival group ($p<0.05$).

Variables in the cohort

Variables with $p<0.1$ in Table 1 were selected and converted to categorical variables. Univariate analysis was first performed on selected variables with $p<0.1$, and the results indicated that the levels of ALA, ARG, CIT, GLY, MET, C5, C18, TBIL, ALT, and CHE were significantly associated with the differences observed between the two groups (all $p<0.05$), Table 2. The inclusion of the above variables in the multivariate logistic regression analysis revealed that high ALA and low levels of CIT, C18, and MET at admission were independently associated with increased 30-day mortality from neonatal sepsis(Table 2).

Establishment of a clinical prediction model with a nomogram

The variables ALA, CIT, MET and C18 were included in the final model after multivariate logistic regression

Table 2 Analysis of factors for mortality in neonatal sepsis

Variables	Univariate analysis			Multivariate analyses			
	OR	95%CI	*P*	β	OR	95%CI	*P*
Weight<2706.68 g	2.65	1.04–6.78	0.042				
Gestational age<35.69 weeks	4.86	1.58–14.95	0.006				
ALA>233.86μmol/L	4.35	1.77–10.70	0.001	2.46	11.74	3.05–45.12	< 0.001
ARG<6.35μmol/L	0.25	0.10–0.61	0.002				
CIT<10.36μmol/L	0.31	0.13–0.77	0.011	-1.76	0.17	0.05–0.59	0.005
GLY<285.06μmol/L	0.24	0.10–0.59	0.002				
MET<20.05μmol/L	0.26	0.11–0.64	0.003	-1.60	0.20	0.06–0.66	0.008
C4<0.18μmol/L	0.42	0.17–1.05	0.063				
C5<0.075μmol/L	0.23	0.10–0.57	0.001				
C18<0.52μmol/L	0.16	0.04–0.69	0.014	-2.59	0.08	0.01–0.41	0.003
TBIL>43.85μmol/L	3.08	1.09–8.71	0.034				
ALT>4.50U/L	6.22	1.40–27.57	0.016				
CHE<3602.50U/L	0.39	0.16–0.96	0.041				

ALA, alanine; ALT, alanine aminotransferase; ARG, arginine; CHE, cholinesterase; CIT, citrulline; C4, butyrylcarnitine; C5, isovalerylcarnitine; C18, octadecanoylcarnitine; GLY, glycine; MET, methionine; TBIL, total bilirubin

analysis. On the basis of the independent risk factors and their regression coefficients, multivariate regression equations were constructed for the prediction model. The prediction formula is as follows: LogitP = 2.46×ALA-1.76×CIT—1.60×MET—2.59×C18—8.21. On the basis of the logistic regression model, we constructed a nomogram to predict 30-day mortality of neonatal sepsis patients (Fig. 2A).

Performance of the clinical prediction model

The ROC curve was used to assess the predictive performance, as shown in Fig. 2B, and the AUC of this model was 0.866 (95% CI 0.796–0.936, $P < 0.05$). After cross-validation, the AUC was 0.832, Fig. 2B. This finding indicates that the current model is stable; The calibration curve of the clinical model was good, as shown in Fig. 2C. The Hosmer-Lemeshow test showed that $\chi^2 = 6.249$, $P = 0.715$, and the model had a large differential predictive value. In addition, decision curve analysis (DCA) shows that using the model to make decisions can lead to better results than alternative strategies or not using the model at all (Fig. 2D).

Clinical model statistics and independent markers

Other statistics for the clinical model and independent risk factor markers are shown in Table 3, and the ROC curves for the clinical model and independent risk factor markers are shown in Fig. 3. Clinical model has good predictive power.

Discussion

Neonatal sepsis is a systemic inflammatory response syndrome triggered by infection, and due to the immaturity of neonates' immune systems, sepsis progresses rapidly and carries a high mortality rate [16]. The excessive release of inflammatory mediators and stress hormones leads to hemodynamic disturbances and metabolic alterations in neonatal sepsis, ultimately resulting in multi-organ failure [17]. Monitoring changes in metabolites during the early stages of neonatal sepsis and identifying metabolic markers for early diagnosis will help clinicians to improve individual treatment strategies and clinical decision-making. In this study, we examined 11 amino acids and 10 acylcarnitine markers within 24 h of admission for neonatal sepsis patients, unveiling that elevated ALA levels along with decreased CIT, MET, and C18 levels independently contribute as risk factors for mortality in neonatal sepsis.

Alanine is a non-essential amino acid that undergoes hepatic metabolism in the human body [18]. A systematic review study shows that during neonatal sepsis, glucose metabolism is altered [19]. Alanine, as an important precursor for gluconeogenesis, plays a significant role in maintaining stable blood glucose levels in neonates [20]. Therefore, monitoring the level of alanine is crucial for the management of neonatal sepsis. Previous studies have identified elevated levels of ALA in cases of sepsis-related brain injury and acute kidney injury [10]. In the present study, higher concentrations of ALA were observed in the non-survival group compared to the survival group. This potentially indicates impaired liver function induced by sepsis and an associated nitrogen imbalance that impairs brain and kidney function [21, 22]. The multi-organ damage caused by elevated ALA may act as a substantial risk factor for neonatal sepsis mortality. Citrulline, a non-protein amino acid, plays important roles in cellular metabolism and organ function regulation [23]. It is mainly involved in the synthesis of urea, nitric oxide, and arginine. CIT has been shown to alleviate sepsis-induced immunosuppression by restoring T-cell function through increasing effective arginine levels [24]. Existing research has confirmed that during neonatal sepsis, there

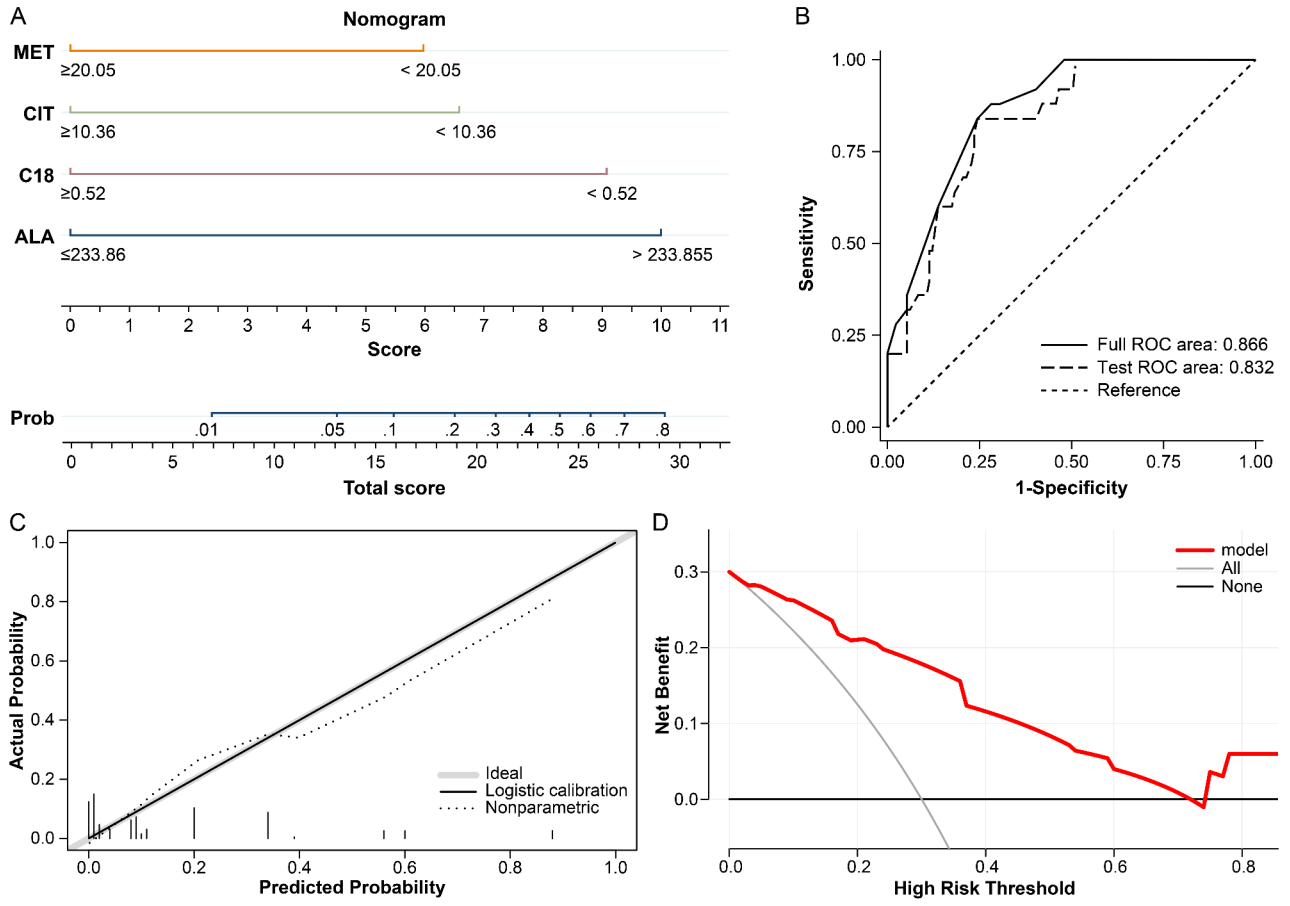

Fig. 2 Model Nomogram and Performance Assessment. (**A**) predictive nomogram for 30-day mortality in neonatal sepsis. ALA, alanine; CIT, citrulline; C18, octadecanoylcarnitine; MET, methionine; (**B**) ROC curve for the clinical model and 10-fold cross-validation; (**C**) Calibration curve of predictive model; (**D**) Decision curve analysis (DCA) of predictive model

Table 3 Diagnostic statistics for independent markers

Variables	AUC (95%CI)	Yuden	Sensitivity	Specificity	PPV	NPV	Cut off
ALA	0.675 (0.561–0.790)	0.35	0.71	0.64	0.91	0.30	233.86
C18	0.626 (0.521–0.731)	0.28	0.36	0.92	0.96	0.21	0.52
CIT	0.631 (0.511–0.751)	0.28	0.64	0.64	0.88	0.23	10.36
MET	0.626 (0.511–0.741)	0.32	0.60	0.72	0.90	0.29	20.05
Model	0.866 (0.796–0.936)	0.60	0.76	0.84	0.96	0.40	0.173

ALA, alanine; CIT, citrulline; C18, octadecanoylcarnitine; MET, methionine; NPV, negative predictive value; PPV, positive predictive value; Model: ALA + CIT + MET + C18

is an abnormality in glutamine metabolism [25]. Glutamine serves as a precursor for citrulline, suggesting that during neonatal sepsis, the synthesis of citrulline may be weakened. In the present study, CIT levels were found to be lower in the non-survival group compared to the survival group, which could be attributed to reduced plasma synthesis of citrulline and increased consumption during neonatal sepsis [26]. Whereas low levels of CIT weaken autoregulation, the present study identified reduced CIT as a risk factor for mortality in neonatal sepsis. Methionine, an amino acid containing sulfur, can be converted to glutathione and plays a role in reducing sepsis-induced oxidative stress [27]. Animal studies have shown an elevation in methionine transsulphurisation during sepsis in rats [28]. An investigation into metabolic biomarkers in neonatal sepsis uncovered a disruption in the neonatal glutathione metabolic pathway during the course of the condition [29]. Since methionine, as a sulfur-containing amino acid, can be transformed into glutathione, this research supports our perspective. The decreased levels of methionine observed in this study were identified as a risk factor for mortality. This may be due to inadequate basal nutritional vitamin B12 deficiency in neonatal sepsis and the subsequent increase in methionine transsulphurisation, resulting in elevated homocysteine levels

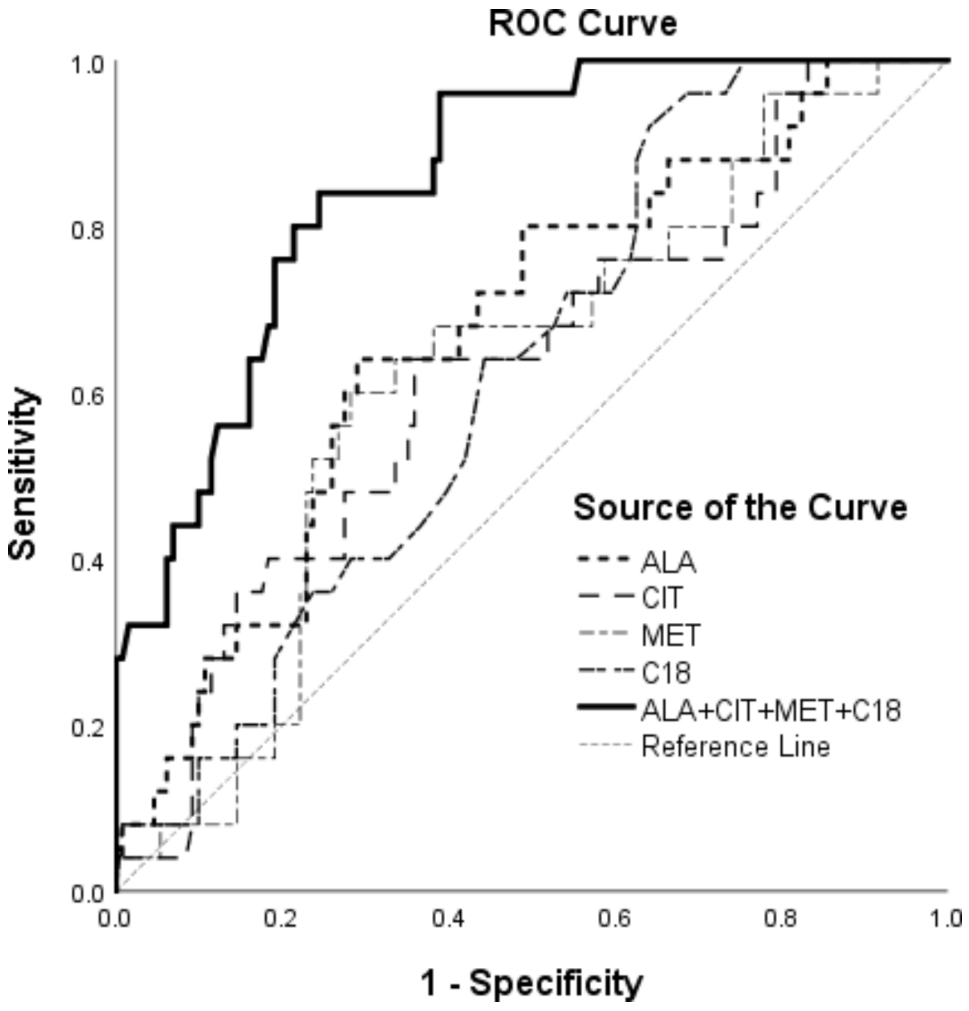

Fig. 3 Area under the curves (AUC) of factors for predicting mortality
ALA, alanine; CIT, citrulline; C18, octadecanoylcarnitine; MET, methionine; Clinical Model: ALA + CIT + MET + C18

[30]. Decreased methionine may function as a potential prognostic marker for neonatal sepsis.

Mitochondrial dysfunction is another prominent feature of sepsis [31]. A study revealed a significant reduction in biopsy ATP/ADP ratios in the skeletal muscle of patients with fatal sepsis [32]. Another study showed that higher plasma short- and medium-chain acylcarnitines levels are linked to sepsis prognosis, with acetylcarnitine significantly associated with 28-day mortality [11]. Significant changes in lipid metabolism have been reported in infants with sepsis [33]. Acylcarnitines play a crucial role as transporters in fatty acid β-oxidation, and their levels can serve as biomarkers to assess fatty acid oxidation status, reflecting early imbalance and mitochondrial stress [34]. In the present study, several acylcarnitines were found to be lower in the non-survival group compared to the survival group, specifically C4, C5, and C18 (all $p < 0.05$). Multivariate analysis revealed an independent association between mortality and C18, indicating a relative carnitine deficiency in neonatal sepsis among non-survivors. Our findings suggest that carnitine deficiency may serve as a predictor for impaired fatty acid oxidation and abnormal energy metabolism associated with multiorgan dysfunction in neonatal sepsis, thus identifying C18 as a risk factor for 30-day mortality.

In this study, a model incorporating multiple amino acid and acylcarnitine indicators was successfully developed to effectively assess 30-day mortality in neonatal sepsis. This comprehensive model provides an early reflection of the metabolic status associated with neonatal sepsis, demonstrating its significant predictive value. Previous research on metabolic alterations in sepsis aligns with the findings of this study; however, investigations into metabolic indicators specific to neonatal sepsis remain scarce. As a distinct demographic, neonates exhibit underdeveloped metabolic functions, necessitating further exploration into the variations of their metabolic markers. Existing studies have substantiated disruptions in energy metabolism associated with neonatal sepsis [35], enhancing our comprehension of

amino acid and acylcarnitine dynamics in this condition. In summary, our research provides valuable insights into the metabolism of amino acids and acylcarnitines in neonatal sepsis, enabling clinicians to monitor early changes in metabolic indicators. This, in turn, facilitates the development of personalized treatment strategies. For example, by optimizing nutritional support and adjusting antibiotic therapy based on dynamic metabolic profiling, clinicians can make more informed decisions tailored to the individual needs of neonates with sepsis.

The study, however, has certain limitations that should be acknowledged. For example, since it was conducted as a single-centre study with a limited sample size, there is a possibility of data bias. Henceforth, it is essential to validate these findings by using a larger patient cohort and multicentre data. Conversely, the analysis did not incorporate additional metabolic indicators due to insufficient available data. Future clinical work will focus on optimizing and validating the proposed model.

Conclusion

In the present study, a model incorporating multiple amino acids and acylcarnitines was developed to assess the prognosis of neonatal sepsis and predict 30-day mortality. This model can effectively capture alterations in amino acid and fatty acid metabolism during the early stages of neonatal sepsis, facilitating prompt assessment, personalized treatment, and informed clinical decision-making.

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Author contributions
J-K C and W L designed the study. All the authors contributed to the generation, collection, assembly, analysis and/or interpretation of data. X-W T wrote the manuscript, J-K C prepared Fig. 1 L prepared Figs. 2 and 3. All the authors revised the manuscript. All the authors have read manuscript and approved the final manuscript.

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Data availability
The datasets are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol followed the principles set forth in the Declaration of Helsinki, and the study was approved by the Medical Ethics Committee of the Ganzhou Women and Children's Health Care Hospital(2023-007), Jiangxi Province, China, and informed consent was waived by this ethics committee due to the retrospective design of the study. The ethics committee waived the need for individual informed consent because personally identifiable information was not used in this analysis.

Consent for publication
Not applicable.

Clinical trial
Not applicable.

Competing interests
The authors declare no competing interests.

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