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The predictive value of CysC combined with NGAL in critical newborns with acute kidney injury

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Abstract: To investigate the predictive value of cystatin C (CysC) combined with neutrophil gelatinase-associated lipocalin (NGAL) in critically ill newborns with acute kidney injury (AKI).The data of 143 critically ill newborns admitted to the NICU from October 2022 to October 2024 were retrospectively analyzed. They were divided into non-AKI group (114 cases) and AKI group (29 cases) based on whether they had AKI. The clinical data of the two groups were compared. CysC and NGAL were detected at admission to the NICU and 24 hours after admission to the NICU. The levels of CysC and NGAL were compared between the non-AKI group and the AKI group, and an ROC curve was drawn to evaluate the predictive value of CysC and NGAL on AKI in critical newborns.The levels of CysC and NGAL in the AKI group were measured upon admission to the NICU and 24 hours post-admission. Both markers were significantly higher compared to the non-AKI group ($P < 0.05$). The ROC curve showed that CysC and NGAL have predictive value for identifying critically ill neonates in the NICU. Specifically, the AUC values for predicting AKI in infants were 0.895 for CysC and 0.835 for NGAL, with a combined prediction AUC of 0.948. Furthermore, when measured 24 hours after NICU admission, the AUC values for predicting critical neonatal AKI were 0.798 for CysC and 0.806 for NGAL, with a combined forecast AUC of 0.847.CysC and NGAL have the value of predicting AKI in critically ill newborns. Compared with testing after admission to the NICU, the combined testing of CysC and NGAL when first admitted to the NICU has a better predictive effect on AKI.

Keywords: Cystatin C; Neutrophil Gelatinase-Associated Lipocalin; Acute Kidney Injury; Newborn; Predictive Value

Neonatal multiple organ dysfunction syndrome is an important cause of neonatal death. It is closely related to risk factors such as perinatal hypoxia, asphyxia, hyperbilirubinemia, premature delivery, very low birth weight and repeated invasive infections. Among various clinical neonatal multiple organ dysfunction disorders, acute kidney injury (AKI) is more common [1].Previous studies have shown that AKI can not only directly increase the probability of death in critically ill children, but also increase the long-term risk of chronic kidney disease. Therefore, it needs clinical attention. Early AKI assessment has become a key link to ensure the life and health of critically ill newborns[2]. However, it is worth noting that traditional renal function indicators such as blood creatinine change late during the occurrence of AKI, so they are not sensitive to early diagnosis of AKI, which restricts the timeliness of clinical intervention and reminds exploration of stability, reliability and clinical operability. New biomarkers have become a key research direction to improve the prognosis of neonatal AKI. In recent years, urinary neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C (CysC) have been supported by evidence-based medicine as potential biological indicators for early diagnosis of AKI [3-4].However, there are few reports on the effect of combined testing of NGAL and CysC on improving the diagnostic efficiency of AKI in newborns. Based on this, this study explored the predictive value of CysC combined with NGAL on AKI in critically ill newborns and provided evidence-based basis for optimizing early diagnosis strategies for AKI.

1. Data and methods

1.1 Clinical data

The data of 143 critically ill newborns admitted to the NICU from October 2022 to October 2024 were retrospectively analyzed. Inclusion criteria: ① Admission to NICU for more than 24 hours; ② Mother's renal function is normal; ③ Data are complete.Exclusion criteria: ① AKI before admission to NICU. They were divided into non-AKI group (114 cases) and AKI group (29 cases) according to whether they were complicated with AKI. The criteria for AKI [5]: blood creatinine increase>26.5μmol/L or>50% higher than the baseline value within 48

hours, with or without urine volume <0.5 ml (kg·h), for>6 hours. Referring to the Acute Kidney Injury Network Standards, the AKI group included 12 cases in stage I, 15 cases in stage II, and 4 cases in stage III.

1.2 Research methods

Collect data on critically ill newborns, including: ① General information: gestational age, gender, birth weight, Apgar score at 1 minute and 5 minutes after birth, of which Apgar score is 0 - 10, and normal newborns should score more than 7 points [6]; ② Biochemical indicators: CysC and NGAL levels at admission to the NICU and 24 hours after admission to the NICU; ③ Prognosis: total length of stay and death.

1.3 Detection methods

When critically ill newborns were admitted to the NICU and after admission, 2ml of blood were collected using an EDTA anticoagulant tube, and serum and plasma were separated by centrifugation at 3000rpm for 10 minutes. Plasma samples were taken for testing CysC and NGAL. Latex-enhanced immunoturbidimetry was used for CysC detection, and enzyme-linked immunosorbent assay was used for NGAL. The testing was carried out strictly in accordance with the kit instructions.

1.4 Statistical analysis

Quantitative data were tested for normal distribution using the K-S method, compliance indicators were expressed as ($\bar{x}$ ±s), t test was used to compare, non-compliance indicators were expressed as [M (Q1,Q3)], rank-sum test was used to compare, qualitative data were expressed as (%), and x2 test was used to compare. Prediction power was analyzed by drawing ROC curves. Data processing was all carried out in SPSS22.0, and the test level was all set to 0.05.

2. Results

2.1 Comparison of general data of critically ill newborns between non-AKI group and AKI group

There were no significant differences in gender and Apgar score at 5min after birth between the two groups (P>0.05); the gestational age and birth weight in the AKI group were lower than those in the non-AKI group, and the Apgar score at 1min after birth was lower than that in the non-AKI group (P<0.05). As shown in Table 1.

Table1 Comparison of general data of critically ill newborns in non-AKI group and AKI group [M (Q1,Q3), %]

Group	Number	Gender (case)		Geothermal age (case)		Birth weight (case)		Apgar score 1 minute after birth (points)	Apgar score at 5min after birth (points)
		Male	Female	<34 weeks	≥34 weeks	<2500g	≥2500g		
Non-AKI group	114	68(59.65)	46(40.35)	23(20.18)	91(79.82)	50(43.86)	64(56.14)	8(7,9)	9(8,10)
AKI group	29	19(65.52)	10(34.48)	11(37.93)	18(62.07)	19(65.52)	10(34.48)	7(6,9)	7(7,9)
χ2/Z		0.334		4.022		4.343		2.313	0.858
P		0.563		0.045		0.037			
				0.021		0.391			

2.2 Comparison of CysC and NGAL levels in critically ill newborns between non-AKI group and AKI group

The levels of Cys C and NGAL in the AKI group were higher than those in the non-AKI group at the time of check-in and 24h after check-in in the NICU (P < 0.05). As shown in Table 2.

Table2 Comparison of CysC and NGAL levels in critically ill newborns between non-AKI group and AKI group ($\bar{x} \pm s$)

Group	Number	Cys C(mg/L)		NGAL(μg/L)	
		At Admission to NICU	24h after Admission to NICU	At Admission to NICU	24h afte Admission to NICU
Non-AKI group	114	1.43±0.43	1.62±0.48	67.11±13.84	70.86±15.36
AKI group	29	2.17±0.46	2.15±0.52	87.25±17.16	89.75±15.34
t		8.158	5.220	6.651	5.915
P		<0.001	<0.001	<0.001	<0.001

2.3 Effectiveness of CysC and NGAL levels in predicting AKI in critically ill newborns

The ROC curve showed that: when admitted to NICU, the AUC of Cys C and NGAL in predicting AKI in critically - ill neonates was 0.895 and 0.835 respectively, and the combined prediction AUC was 0.948; 24h after admission to NICU, the AUC of Cys C and NGAL in predicting AKI in critically - ill neonates was 0.798 and 0.806 respectively, and the combined prediction AUC was 0.847. As shown in Table 3.

Table3 Effectiveness of CysC and NGAL levels in predicting AKI in critically ill newborns

Index	AUC	Specificity	Sensitivity	Cut-off value	95%CI	Standard error
At Admission to NICU						
Cys C	0.895	84.21	79.31	> 1.7mg/L	0.833~0.940	0.031
NGAL	0.835	74.56	79.31	> 73.1μg/L	0.764~0.892	0.040
United	0.948	92.11	82.76	-	0.898~0.978	0.019
24h afte Admission to NICU						
CysC	0.798	77.19	72.41	> 1.9mg/L	0.723~0.860	0.045
NGAL	0.806	97.37	55.17	> 97.4μg/L	0.732~0.868	0.050
United	0.847	84.21	75.86	-	0.777~0.901	0.046

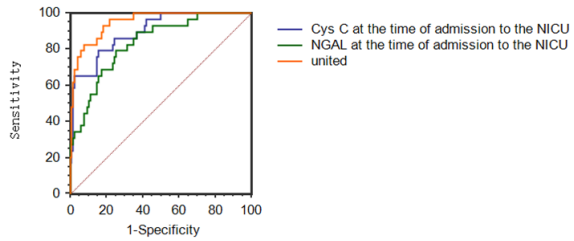

Figure1 The CysC and NGAL levels at NICU admission predict the ROC of AKI in critically ill neonates

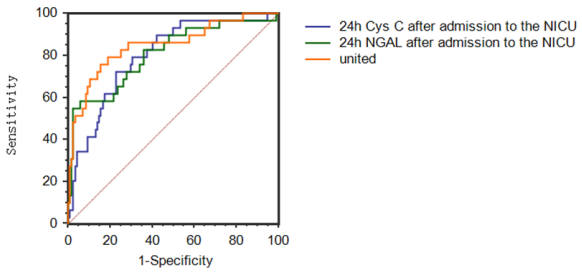

Figure2 ROC at 24h CysC, NGAL levels after NICU admission predicted AKI in critically ill neonates

2.4 Comparison of prognosis of critically ill newborns between non-AKI group and AKI group

There were 5 in-hospital deaths in the AKI group and 9 in-hospital deaths in the non-AKI group. There was no significant difference in mortality between the two groups x2=2.287, P=0.130),the total hospital stay of AKI group was 20-37 (28.72±4.24) d, and that of non-AKI group was 17-30 (22.35±3.46) d, the total hospital stay of AKI group was longer than that of non-AKI group (t=7.476, P < 0.001).

3. Discussion

With the in-depth analysis of pathophysiological mechanisms and the innovation of molecular diagnostic technologies, significant pro-

gress has been made in the etiology classification, molecular diagnostic strategies and clinical management plans of neonatal AKI. However, the key challenge in the current diagnostic field is to screen highly sensitive biological indicators and identify their clinical interfering factors. Previous experience has shown that neonatal AKI is significantly time-specific, and most cases occur within 7 days after birth. Therefore, critical newborns have a high need to assess the risk of AKI early for later management. Blood creatinine, a traditional predictor of AKI, may lead to deviations between the detection level and the actual renal function of the newborn due to the interference of transplacental metabolism and the slow change of concentration in the newborn mother [7], thus reducing the predictive efficacy of early AKI. Based on the above limitations, the research focus of the international academic community has shifted to exploring upstream molecular markers of blood creatinine. Previous evidence has shown that NGAL and CysC, as AKI warning markers, have shown good early diagnosis efficiency in adult patients [8], but they have been less verified in predicting the risk of AK in severe newborns. In view of the unique developmental biological characteristics of neonatal kidneys such as imperfect differentiation of nephron structure and immature hemodynamic regulation mechanisms, their AKI pathophysiological characteristics are significantly different from those of other age groups. Therefore, it is necessary to re-verify the predictive value of NGAL and CysC.

CysC is a low molecular weight cationic protein with a molecular weight of 13.3kDa. It is synthesized and secreted into the circulatory system by all nucleated cells at a constant rate. Its metabolism relies almost entirely on glomerular filtration clearance and is not affected by renal tubular reabsorption or secretion. This characteristic makes it have a higher value in reflecting the glomerular filtration rate than serum creatinine [9]. Some scholars have shown that in children, the correlation coefficient between CysC and glomerular filtration rate is significantly higher than that of blood creatinine, and its concentration is not affected by anthropometric parameters such as height and body mass [10]. In addition, CysC has its advantageous biological characteristics, that is, it cannot pass through the blood-placental barrier, which means that neonatal CysC is entirely produced from the fetus, effectively eliminating maternal interference. The results of this study showed that at admission to NICU and 24 hours after admission to NICU, the CysC level in the AKI group was higher than that in the non-AKI group, and the ROC curve verified that this indicator can be used as a predictor of AKI in critically ill newborns. Xu et al.[11] believed that Cys-C≥ 2.2 mg/L can be used as a predictive criterion for AKI in newborns. Compared with its cutoff value, this study has a lower cutoff value. Combined with the specificity and sensitivity results, it was considered to be consistent with the reference urine volume diagnosis of AKI in this study and the use of plasma samples for testing, so there are differences in the results.

NGAL is quickly expressed and secreted by renal tubular epithelial cells after human kidney injury. Its concentration usually increases significantly within 2 to 6 hours after renal injury occurs. It can be detected in the plasma of early AKI, and its change is earlier than that of blood creatinine. Studies have further confirmed that NGAL can not only predict the occurrence of AKI, but also assess its severity, and has high clinical application value [12]. The results of this study showed that at admission to NICU and 24 hours after admission to NICU, NGAL levels in the AKI group were higher than those in the non-AKI group, and the ROC curve verified that this indicator can be used as a predictor of AKI in critically ill newborns. It is worth mentioning that the results show that NGAL and Cys-C have a better effect in predicting AKI in critically ill newborns. Compared with the test results 24 hours after admission to the NICU, the combined effect of the two is higher when admission to the NICU. The reasons are still unclear. It is necessary to conduct in-depth research in the future, and at the same time remind that when using NGAL and Cys-C to predict AKI in critically ill newborns, it is necessary to diagnose the test time and analyze the results specifically. From the prognosis results, it can be seen that critically ill children with AKI have higher mortality and hospital stay, which once again reminds them of the need to be admitted to the NICU to assess the risk of AKI early.

To sum up, CysC and NGAL have the value of predicting AKI in critically ill newborns. Compared with testing after admission to the NICU, the combined testing of CysC and NGAL when first admitted to the NICU has a better predictive effect on AKI.

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