Risk Factors and Short-term Prognosis of Severe Neonatal Asphyxia Complicated with Acute Kidney Injury: A Post-print

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Abstract

Background: Early diagnosis of neonatal acute kidney injury (AKI) is difficult, with high mortality rates, and current research on severe asphyxia complicated by neonatal AKI is relatively scarce.

Objective: To investigate the risk factors and short-term prognosis of neonatal severe asphyxia complicated by AKI, and to analyze the predictive value of relevant factors, in order to take measures to reduce the incidence of AKI and improve outcomes for such infants.

Methods: A total of 172 neonates with severe asphyxia hospitalized in the Neonatal Intensive Care Unit of the First Affiliated Hospital of Bengbu Medical College from January 2016 to January 2023 were enrolled as study subjects. According to whether the infants developed AKI, they were divided into an AKI group (n=43) and a non-AKI group (n=129). Clinical data and laboratory test results were collected, and the short-term prognosis of AKI infants (survival or death during hospitalization) was recorded. Multivariate Logistic regression analysis was used to explore the influencing factors of neonatal severe asphyxia complicated by AKI, and receiver operating characteristic (ROC) curve analysis was used to investigate the predictive value of relevant indicators for neonatal severe asphyxia complicated by AKI.

Results: Gestational age, birth weight, 5-min Apgar score, and platelet count in the AKI group were lower than those in the non-AKI group, while the incidence of coma, invasive mechanical ventilation, respiratory failure, and serum cystatin C (Cys C) levels were higher than those in the non-AKI group, with statistically significant differences ($P<0.05$). Multivariate Logistic regression analysis showed that 5-min Apgar score [OR=1.553, 95%CI=(1.193~2.021), P=0.001], invasive mechanical ventilation [OR=2.965, 95%CI=(1.021~8.611), P=0.046],

and serum Cys C level [OR=0.231, 95%CI=(0.109~0.487), P<0.001] were influencing factors for neonatal severe asphyxia complicated by AKI. ROC curve analysis showed that the AUC of serum Cys C for predicting AKI was 0.777 (95%CI=0.701~0.854, P<0.05). The in-hospital mortality rate in the AKI group was 51.2% (22/43), while that in the non-AKI group was 21.7% (28/129). The mortality rate in the AKI group was significantly higher than that in the non-AKI group, with a statistically significant difference (2=13.572, P<0.001).

Conclusion: Low 5-min Apgar score, invasive mechanical ventilation, and high postnatal serum Cys C increase the risk of AKI in neonates with severe asphyxia. Postnatal serum Cys C is a reliable indicator for predicting neonatal severe asphyxia complicated by AKI.

Full Text

Risk Factors and Short-Term Prognosis of Severe Neonatal Asphyxia Complicated with Acute Kidney Injury

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Abstract

Background: Early diagnosis of acute kidney injury (AKI) in neonates is difficult and associated with high mortality, yet research on severe neonatal asphyxia complicated with AKI remains limited.

Objective: To investigate the risk factors and short-term prognosis of AKI in neonates with severe asphyxia, and to evaluate the predictive value of relevant factors to inform interventions that reduce AKI incidence and improve resuscitation outcomes.

Methods: We enrolled 172 neonates with severe asphyxia admitted to the Neonatal Intensive Care Unit of the First Affiliated Hospital of Bengbu Medical College between January 2016 and January 2023. Participants were divided into an AKI group (n=43) and a non-AKI group (n=129) based on AKI status. Clinical data and laboratory findings were collected, and short-term prognosis (survival or death during hospitalization) was recorded. Multivariate logistic regression analysis identified factors influencing AKI development in severe neonatal asphyxia, while receiver operating characteristic (ROC) curves assessed the predictive value of relevant indicators.

Results: The AKI group exhibited significantly lower gestational age, birth weight, 5-minute Apgar scores, and platelet counts compared to the non-AKI

group (P<0.05). The AKI group also had higher proportions of coma, invasive mechanical ventilation, respiratory failure, and elevated serum cystatin C (Cys C) levels (P<0.05). Multivariate logistic regression revealed that 5-minute Apgar score [OR=1.553, 95%CI=(1.193-2.021), P=0.001], invasive mechanical ventilation [OR=2.965, 95%CI=(1.021-8.611), P=0.046], and serum Cys C [OR=0.231, 95%CI=(0.109-0.487), P<0.001] were independent risk factors. ROC analysis demonstrated that serum Cys C predicted AKI with an AUC of 0.777 (95%CI=0.701-0.854, P<0.05). The in-hospital mortality rate was 51.2% (22/43) in the AKI group versus 21.7% (28/129) in the non-AKI group, a statistically significant difference (^{2}=13.572, P<0.001).

Conclusions: Low 5-minute Apgar score, invasive mechanical ventilation, and elevated postnatal serum Cys C increase AKI risk in neonates with severe asphyxia. Postnatal serum Cys C represents a reliable predictor for AKI in this population.

Keywords: Acute kidney injury; Neonatal asphyxia; Respiratory insufficiency; Apgar score; Risk factors; Prognosis

Introduction

Neonatal asphyxia refers to a pathophysiological condition characterized by hypoxemia, hypercapnia, and acidosis resulting from failure to establish normal breathing after birth due to various prenatal, intrapartum, or postpartum causes [1]. The hypoxia and acidosis trigger compensatory blood redistribution to maintain perfusion of the heart, brain, and adrenal glands while reducing renal blood flow, leading to hypoxic-ischemic kidney injury. Clinically, asphyxiated neonates often exhibit transient oliguria and temporary elevations in serum creatinine (Scr), with severe cases progressing to acute kidney injury (AKI) [2].

AKI is a critical clinical syndrome characterized by abrupt deterioration or loss of renal function, manifesting as oliguria or anuria, fluid and electrolyte disturbances, acid-base imbalances, and elevated levels of nitrogenous waste products such as blood urea nitrogen (BUN) and Scr, with mortality rates approaching 50% [1]. Neonatal renal parenchymal cells have limited anaerobic metabolic capacity and poor tolerance to hypoxia, making them vulnerable to AKI following asphyxia [3]. Previous studies report renal injury rates of 36.2% and 26.7% in severe and mild asphyxia cases, respectively [4], with severe asphyxia carrying particularly high AKI risk. However, early AKI symptoms in neonates are often atypical and easily overlooked, delaying treatment and compromising outcomes [5]. Early risk assessment is therefore crucial for improving prognosis. Despite this, research specifically examining severe asphyxia complicated by AKI remains scarce. Investigating the risk factors for AKI in severely asphyxiated neonates and implementing early interventions could significantly reduce AKI incidence and improve survival.

This study analyzed clinical data from neonates with severe asphyxia to identify risk factors for AKI development, evaluate short-term prognosis, and assess the predictive value of relevant indicators to enable early recognition and proactive management, thereby reducing mortality and improving outcomes.

Methods

1.1 Study Subjects We retrospectively reviewed 181 neonates with severe asphyxia admitted to our Neonatal Intensive Care Unit between January 2016 and January 2023. Inclusion criteria followed the 2016 Expert Consensus on Neonatal Asphyxia Diagnosis [6]: 1-minute Apgar score $ $3 or 5-minute Apgar score $ $5, plus umbilical artery pH <7.0. AKI diagnosis was based on neonatal AKI guidelines [7], defined by any of the following: (1) Scr increase $ $26.5 mol/L within 48 hours; (2) Scr increase to $ $1.5 times baseline within 7 days; or (3) urine output $< 0.5 mL \cdot kg^{\{-1\} \cdot h}\{-1\}$ for 6-12 hours. Exclusion criteria included: (1) failure to meet diagnostic criteria for severe asphyxia or AKI; (2) incomplete laboratory data or death within 24 hours; (3) severe congenital anomalies; or (4) missing clinical data. The final cohort comprised 172 neonates, divided into an AKI group (n=43) and non-AKI group (n=129). This study was approved by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College (2022KY086). Patient data were anonymized prior to analysis, and informed consent was waived.

1.2 Data Collection We collected clinical and laboratory data including gestational age, birth weight, age at admission, sex, delivery mode, 1-minute and 5-minute Apgar scores, coma status, invasive mechanical ventilation, respiratory failure, maternal age, gestational diabetes, hypertension, perinatal complications (intrauterine distress, placental abruption, premature rupture of membranes, amniotic fluid contamination, umbilical cord abnormalities), and initial laboratory results within 24 hours (blood pH, white blood cell count, platelet count, sodium, potassium, calcium, Scr, BUN, and serum cystatin C [Cys C]). Short-term prognosis (survival or death during hospitalization) was recorded for AKI patients. Survival was defined as stable vital signs, improving organ function, and progressive weight gain; death included both in-hospital mortality and deaths following family withdrawal of care due to irreversible critical illness.

1.3 Statistical Analysis Data were analyzed using SPSS 26.0. Normally distributed continuous variables were expressed as mean±standard deviation and compared using independent samples t-tests; non-normally distributed variables were presented as median (P25, P75) and compared using Mann-Whitney U tests. Categorical variables were expressed as frequencies and compared using ^{2} tests. Multivariate logistic regression identified factors influencing AKI development, while ROC curves assessed predictive value. Statistical significance was set at P<0.05.

Results

2.1 General Characteristics Among 181 neonates with severe asphyxia, 5 died within 24 hours before complete evaluation, 3 had missing laboratory data, and 1 had severe congenital anomalies, leaving 172 for analysis. AKI occurred in 43 cases (25.0% incidence), with 9.3% (4/43) developing AKI within 24 hours, 32.5% (14/43) within 48 hours, 41.9% (18/43) within 72 hours, and 16.3% (7/43) within 7 days.

The AKI group had significantly lower gestational age, birth weight, 5-minute Apgar scores, and platelet counts compared to the non-AKI group ($P<0.05$). The AKI group also showed higher proportions of coma, invasive mechanical ventilation, respiratory failure, and elevated serum Cys C ($P<0.05$). No significant differences were observed in age at admission, sex, delivery mode, 1-minute Apgar score, maternal age, gestational diabetes, hypertension, or perinatal complications including intrauterine distress, placental abruption, premature rupture of membranes, amniotic fluid contamination, and umbilical cord abnormalities. Laboratory parameters including blood pH, white blood cell count, sodium, potassium, calcium, Scr, and BUN were also comparable between groups .

2.2 Multivariate Logistic Regression Analysis Using AKI occurrence as the dependent variable (no=0, yes=1) and significant univariate factors as independent variables (gestational age, birth weight, 5-minute Apgar score, platelet count, serum Cys C [continuous], coma [no=0, yes=1], invasive mechanical ventilation [no=0, yes=1], respiratory failure [no=0, yes=1]), multivariate logistic regression identified three independent risk factors: 5-minute Apgar score [OR=1.553, 95%CI=(1.193-2.021), P=0.001], invasive mechanical ventilation [OR=2.965, 95%CI=(1.021-8.611), P=0.046], and serum Cys C [OR=0.231, 95%CI=(0.109-0.487), P<0.001] .

2.3 ROC Curve Analysis ROC analysis of 5-minute Apgar score and serum Cys C revealed that serum Cys C predicted AKI with an AUC of 0.777 (95%CI=0.701-0.854, P<0.05), sensitivity of 88.4%, and specificity of 58.1% at a cutoff value of 1.44 mg/L [Figure 1: see original paper].

2.4 Short-term Prognosis The in-hospital mortality rate was significantly higher in the AKI group at 51.2% (22/43) compared to 21.7% (28/129) in the non-AKI group (^{2}=13.572, P<0.001).

Discussion

The pathophysiology of neonatal asphyxia centers on hypoxia. Neonatal renal tubular epithelial cells have robust metabolic activity and high sensitivity to hypoxia, rendering them susceptible to injury under hypoxic conditions [8]. Asphyxia-induced acidosis causes renal vasoconstriction and impaired perfusion, reducing renal blood flow. As asphyxia severity increases, cardiac output declines due to myocardial hypoxia, further compromising renal perfusion and

exacerbating kidney injury [9]. Consequently, both AKI incidence and mortality increase with asphyxia severity.

Current diagnostic criteria for neonatal AKI lack standardization. Physiologic increases in renal blood flow and perfusion pressure after birth can be disrupted by perinatal asphyxia, increasing AKI susceptibility [10]. These physiological characteristics, combined with diagnostic uncertainty, contribute to missed diagnoses and poor outcomes. However, early AKI is often reversible, and timely intervention improves prognosis. Identifying risk factors for AKI in severely asphyxiated neonates is therefore crucial for implementing preventive strategies and reducing mortality.

Our findings align with previous research demonstrating associations between AKI and low gestational age, low Apgar scores, mechanical ventilation, and low birth weight [11]. Preterm and low-birth-weight neonates have immature kidneys vulnerable to hypoxic-ischemic injury. Hu et al. [12] identified 5-minute Apgar score as a risk factor for AKI in critically ill neonates, consistent with our results showing that low 5-minute Apgar score independently predicts AKI in severe asphyxia. Prolonged or severe asphyxia leads to circulatory failure and cerebral hypoxia, causing brain damage—the most severe complication of neonatal asphyxia [14]. Coma indicates severe brain injury and correlates with high mortality. Neonates, particularly those in deep coma or with critical illness, have poor glomerular filtration and tubular concentration capacity, predisposing them to prerenal injury [10]. Our study confirmed a higher proportion of comatose patients in the AKI group.

Mechanical ventilation increases intrathoracic pressure, compressing mediastinal structures and pulmonary vessels, reducing venous return and cardiac output, ultimately decreasing renal perfusion and glomerular filtration rate [15]. Meta-analyses have identified mechanical ventilation as an AKI risk factor in critically ill neonates [12], and Chen et al. [16] demonstrated that invasive mechanical ventilation significantly increases AKI risk in very low birth weight infants. Our results corroborate these findings, showing high invasive mechanical ventilation rates in the AKI group and establishing it as an independent risk factor.

Respiratory failure causes hypoxemia or hypercapnia, affecting hemodynamics through vasoactive mediators and precipitating AKI. Hemodynamic instability represents a recognized AKI risk factor in very low birth weight infants [17]. While Bozkurt and Yucesoy [3] identified placental abruption and cardiac arrest at birth as independent AKI risk factors in asphyxiated neonates receiving therapeutic hypothermia, our study did not find placental abruption to be a significant factor, possibly due to small sample size. We observed lower platelet counts in the AKI group, though other electrolyte disturbances (sodium, potassium) showed no correlation with AKI development.

Cys C, a cysteine protease inhibitor freely filtered at the glomerulus and rapidly catabolized after proximal tubular reabsorption, serves as an excellent glomerular filtration rate marker [10]. Chen et al. [18] demonstrated its importance for

early diagnosis of renal impairment after neonatal asphyxia, and Zhang et al. [19] confirmed its predictive value for AKI in asphyxiated term neonates. Our ROC analysis identified a Cys C cutoff of 1.44 mg/L (AUC=0.777, 95%CI=0.701-0.854, P<0.05) with 88.4% sensitivity and 58.1% specificity, establishing elevated Cys C as an independent AKI risk factor with good clinical predictive value. Unlike Scr, which changes belatedly after 48-72 hours and indicates 25-50% renal function loss [20-21], Cys C elevations precede overt metabolic derangements, enabling earlier intervention.

Reported AKI incidence in severe neonatal asphyxia ranges from 17.65% [22] to 50-70% [4]; our 25.0% incidence may be underestimated as some patients may have died before meeting diagnostic criteria. Mortality rates for AKI in critically ill neonates range from 10-61% [23]; our AKI group mortality of 51.2% (22/43) significantly exceeded the 21.7% (28/129) rate in the non-AKI group, consistent with previous findings.

Our study utilized readily available 24-hour postnatal laboratory results to identify early injury markers and raise AKI alerts. However, as a retrospective single-center study, these findings require validation through larger prospective multicenter studies.

Conclusion

Low 5-minute Apgar score, invasive mechanical ventilation, and elevated postnatal serum Cys C constitute independent risk factors for AKI in neonates with severe asphyxia. Serum Cys C serves as a reliable predictive biomarker. Close monitoring of 5-minute Apgar scores and serum Cys C values, along with meticulous management of invasively ventilated patients, may reduce AKI incidence and improve outcomes in this vulnerable population.

Author Contributions

Pei Xuejing: study conception and design, manuscript writing. Shen Huaiyun: manuscript review and revision, final approval, overall responsibility. Xu Qianqian: participant selection and sample collection. Liu Binbin and Wang Huihui: data collection and organization.

Conflict of Interest

The authors declare no conflict of interest.

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