

Decrease of HC and Hypoproteinemia: Possible Predictors of Complication of Neonatal Sepsis in a Developing Country?

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Research article

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Abstract

Background: The main purpose of our study was to determine the predictors of the complications of neonatal sepsis.

Methods: This was a retrospective cohort study conducted in neonatal intensive care unit between June 2016 to February 2020. Neonates with late-onset sepsis (Age > 3 days old) were enrolled in this study. According to whether merged complication after sepsis, children were divided into complication group and non-complication group. The demographic data, perinatal conditions, blood cell count analysis, blood culture, hypoproteinemia within 1 week after the onset and treatment measures were compared.

Results: A total of 87 infants with late-onset sepsis were enrolled in this study. (1) Significant differences were observed between the complication and non-complication group with regard to hemoglobin concentration (HC), decrease of HC, hypoproteinemia and red blood cell transfusion ($P < 0.05$). (2) Further comparison found that children with sepsis who had moderate and more severe anemia at the time of onset were more likely to have complications than those with mild or no anemia. (3) The results of binomial stepwise logistic regression suggested that significant decrease of HC (OR = 1.113, $P = 0.000 < 0.05$) and hypoproteinemia (OR = 3.953, $P = 0.012 < 0.05$) were independent risk factors for complication in infants with sepsis. (4) A receiver operating characteristic analysis showed that the AUC was 0.807 for decrease of HC.

Conclusions: Significant decrease of HC and hypoproteinemia were independent risk factors for complication and may predict the occurrence of complication in infants with late-onset sepsis in the early stage.

1. Background

Neonatal sepsis is one of the most common infectious diseases in newborns with high morbidity and mortality, and remains as the third major cause of neonatal death, especially in developing countries^[1-2]. Sepsis can cause many diseases, such as septic shock, neonatal necrotizing enterocolitis, meningitis, osteomyelitis, etc^[3]. The occurrence of these diseases not only increases the mortality of newborns, and also cause short-term and long-term sequelae, such as intestinal stenosis, short bowel syndrome, neurological and skeletal system sequelae, etc^[4-6], Seriously affect the quality of newborns's life. Therefore, exploring the predictors of complications of neonatal sepsis will help to take targeted prevention measures to reduce the incidence of complications and mortality. Up to now, there are many studies on the severity and prognosis of sepsis all over the world, but very few studies on the predictors of complications of neonatal sepsis, especially quantitative indicators. Hence, we hope that through this study, we can obtain quantitative indicators which are easy to obtain in clinical practice to predict the occurrence of complications, with a view to reducing the incidence of complications, and provide new clues for optimizing the treatment strategy in the early clinical stage.

2. Methods

2.1 Study subjects

This was a retrospective cohort study conducted in neonatal intensive care unit (NICU). Neonates with late-onset sepsis (age > 3d) diagnosed by a neonatal specialist at the Southwest Hospital of the First Hospital Affiliated to Army Medical University, China between June 2016 to February 2020. According to whether merged complications after sepsis, infants were divided into complication and non-complications group. Exclude: (1) Intrauterine infection leads to early-onset sepsis (Age \leq 3d), meconium aspiration syndrome; (2) Those with genetic metabolic diseases and congenital deformity; (3) Anemia caused by intracranial hemorrhage, gastrointestinal hemorrhage, pulmonary hemorrhage, etc; (4) Incomplete case data.

2.2 Clinical definitions

The diagnostic criteria for sepsis refer to the Guidelines for the Diagnosis and Treatment of Neonatal Sepsis (2003) revised by the Chinese Medical Association^[7]. Diagnostic criteria for sepsis: infants have fever or low body temperature, less crying, poor response and feeding and other clinical manifestations. At the same time, blood culture or sterile body cavity cultured pathogenic bacteria. Or have the above clinical manifestations and have at least the following two: \square Blood cell count analysis: the white blood cell (WBC) count $< 5 \times 10^9/L$, or increased (when the age \leq 3d, WBC $> 25 \times 10^9/L$; the age $>$ 3d, WBC $> 20 \times 10^9/L$); \square Cell classification: immature neutrophils / total neutrophils (I/T) ≥ 0.16 ; \square Platelet count (PLT) $< 100 \times 10^9/L$; \square C-reactive protein (CRP) ≥ 8 mg/L. Complications caused by sepsis include septic shock, neonatal necrotizing enterocolitis (NEC), meningitis, osteomyelitis, Diffuse intravascular coagulation, etc. For the diagnosis of complications, refer to the fourth edition of Practical Neonatology^[3]. Hemoglobin concentration (HC) in the neonatal period < 145 g/L is anemia, 144 - 120 g/L is mild, - 90 g/L is moderate, - 60g/L is severe, and < 60 g/L is extremely severe^[8]. Diagnostic criteria for hypoproteinemia: serum albumin (Alb) $< 25g/L$ ^[9].

2.3 Data collection

Demographic data were obtained from the electronic medical records and included mother's prenatal condition, such as whether there was premature rupture of membranes, amniotic fluid meconium pollution, maternal hypertension and diabetes, etc. At the same time, the information of children, such as gender, gestational age, birth weight, age of onset, comorbidities, blood cell count analysis, blood culture, albumin within 1 week after the onset and treatment measures (after the occurrence of sepsis and before the occurrence of complications) was also recorded. When patients first showed the symptoms of sepsis (such as fever, poor response and feeding), the blood samples collected for the first time would be examined. Laboratory parameters such as WBC, PLT, HC, the decrease of HC, blood culture and albumin were measured. The decrease of HC was the result of comparing the most recent HC before sepsis with HC at the time of sepsis.

2.4 Statistical analysis

SPSS 20.0 was used for statistical analysis. The measurement data was expressed as mean \pm standard deviation ($x \pm s$), Categorical variables were presented as absolute number and percentage, and were compared using Chi-square test and Fisher's Exact test. Multivariate logistic regression analysis was used to assess the risk factors of complication in neonatal sepsis. The sensitivity and specificity were compared by analyzing the area under the ROC curve. $P < 0.05$ was considered significant. In the upper right corner of P value: '§' is the representative of Fisher's Exact test.

3. Results

3.1 Baseline characteristics

Total 87 children with sepsis were included, 56 in the non-complication group and 31 in the complication group, including 14 cases of NEC, 6 of septic shock, 8 of meningitis, 2 of osteomyelitis, and 1 of DIC. Demographic characteristics of the two groups were presented in Table 1, including their gender, gestational age, birth weight, age of onset, perinatal situation, comorbidities, et al. The table showed that there were no significant differences were observed regarding these data among the complication group and non-complication group ($P > 0.05$).

3.2 significant differences in HC, decrease of HC, hypoproteinemia and red blood cell transfusion

Significant differences were observed between the complication and non-complication group with regard to HC, decrease of HC, hypoproteinemia within 1 week after the onset and red blood cell transfusion ($P < 0.05$). No significant difference in WBC, PLT, HC, blood culture and mechanical ventilation was observed among the two groups ($P > 0.05$, Table 2). Further analysis of the impact of different degrees of anemia on the incidence of complication suggested that children with moderate or more severe anemia were more likely to had complications than those with mild or no anemia ($P < 0.05$, Table 3).

3.3 Significant decrease of HC and hypoproteinemia were independent risk factors for complication in infants with sepsis

Binomial stepwise logistic regression was used with whether complication occurred as the dependent variable, and the above statistically significant indicators, including HC, decrease of HC, hypoproteinemia and red blood cell transfusion were used as independent variables to test whether each factor had a significant effect on complication. The results suggested that significant decrease of HC (OR = 1.113, $P = 0.000 < 0.05$) and hypoproteinemia (OR = 3.953, $P = 0.012 < 0.05$) were independent risk factors for complication in infants with sepsis. (Table 4).

3.4 The high predictive value of decrease of HC for complication in infants with sepsis

The receiver operating characteristic (ROC) analysis of sepsis showed that area under the curve (AUC) was 0.807, suggesting that decrease of HC may predict the occurrence of complication in infants with

sepsis (Table 5, Figure 1).

4. Discussion

The neonatal immune system is immature, highly susceptible to many microorganisms and prone to sepsis, especially premature infants and low birth weight infants. Long-term use of invasive procedures and intravenous nutrition increase the incidence of sepsis. Due to the low immunity and weak resistance of the newborn, sepsis often develops rapidly from subclinical symptoms to severe systemic infection symptoms, causing damage to systemic organs and the occurrence of diseases, such as NEC, meningitis, septic shock, DIC, etc, making sepsis become an important cause of neonatal death^[10]. Therefore, it is great significance to analyze the specific risk factors of complications and death of sepsis, taking active control measures to reduce the incidence of complications and mortality. Our study found that there was significant difference in HC, decrease of HC, hypoproteinemia within 1 week after the onset and red blood cell transfusion between the complication group and non-complication group. Further logistic regression showed that significant decrease of HC and hypoproteinemia were independent risk factors for complication in infants with sepsis.

4.1 The effect of anemia and decrease of HC on the complications and prognosis of children with sepsis

Sepsis is often accompanied by anemia or a decrease in hemoglobin concentration. Many causes can lead anemia, such as iatrogenic blood loss, reduced serum iron levels, shortened red blood cell life and increased destruction, etc. In addition, vascular endothelial glycocalyx shedding and intravenous fluid administration lead to blood thinning^[11-13], which is also manifested by a decrease in HC, causing thinning 'anemia'. But in the early stage of sepsis, the decrease of HC is mostly caused by increased destruction of red blood cells and damage to the glycocalyx layer. In severe infection, a large number of inflammatory factors are released, on the one hand, directly destroying red blood cells, causing a decrease in HC. On the other hand, a large number of inflammatory factors destroy the glycocalyx layer of the vascular endothelium, causing dilution anemia. Therefore, we speculate that the decrease of HC may reflect the level of inflammation in the body, the more obvious the decrease in HC, the more severe the inflammation. After the occurrence of sepsis, the body may have microcirculation disturbances, leading to tissue ischemia and hypoxia. When severe infection occurs, a large amount of inflammatory factors are secreted in the body, which leads to true anemia or dilute 'anemia' through various mechanisms. The significantly reduced HC further causes ischemia and hypoxia, and redistribution of blood in the body, causing or aggravating the microcirculation disorder. Eventually, sepsis and significantly reduced HC complement each other and cause adverse effects on tissue organs. Studies have shown that anemia is a high-risk factor of NEC^[14-18], and the incidence of NEC in children with moderate or above anemia is higher than that without anemia or mild anemia^[19]. Jung SM^[20] found that low hemoglobin levels (< 9.0 g/dL) were observed in approximately 20% of patients with septic shock, and the severity of decrease in these levels correlated with mortality, the lower the HC, the higher the mortality rate. Loftus TJ^[21] found that reducing anemia may improve the prognosis of sepsis patients. This study found that the incidence

of complications in children with sepsis was closely related to the severity of anemia and the degree of HC reduction at the onset. Moderate or above anemia and significantly reduced HC are more likely to have complications. At the same time, this study found that after the occurrence of sepsis and before the occurrence of complications, the transfusion of red blood cells may increase the incidence of complications. Many studies have also shown that the transfusion of red blood cells can lead to the occurrence of NEC [22-23], and increase the chance of surgery in children with NEC and reduce the survival rate [24]. A foreign study on blood transfusion after sepsis in children showed that after sepsis-related anemia, compared to the restrictive strategy group, there had a significantly higher incidence of acute respiratory distress syndrome and acute lung injury in the liberal transfusion group. Moreover, mortality was significantly higher, and liberal transfusion might be associated with a worse outcome [25]. In addition, other studies found that the transfusion of red blood cells may increase the mortality of critically ill patients [26-27]. It should be pointed out that the anemia associated with sepsis is not all true anemia, and sometimes it may be caused by blood dilution related to fluid load [28-29]. Therefore, after the occurrence of sepsis, even if the HC is reduced, it is necessary to strictly grasp the blood transfusion pointer and carefully infuse red blood cells.

Further logistic regression showed that decrease of HC was an independent predictors for complication in infants with sepsis. By comparing the ROC curves of the decrease of HC, the results showed that the AUC was 0.807 for the decrease of HC, which suggests that decrease of HC (cut-off value: 14.5) may predicted the occurrence of complication in infants with sepsis.

4.2 The effect of hypoproteinemia on the complications and prognosis of children with sepsis

This study found that the incidence of hypoproteinemia in the complication group was significantly higher than that in the non-complication group. Logistic regression showed that hypoproteinemia was an independent risk factor for complication in infants with sepsis. Hypoproteinemia is a common complication of sepsis and albumin can be reduced by about 10–15 g/L within 1 week after sepsis. After infection, a large number of inflammatory mediators such as interleukin - 1 (IL - 1), IL - 6 and tumor necrosis factor - α (TNF - α) are released, which can inhibit albumin synthesis. In addition, when the children have sepsis, the body will have fever, stress and inflammation. These symptoms will accelerate metabolism, a large amount of albumin in the body quickly synthesizes acute-phase protein, causing the albumin level to drop [30]. At the same time, increased permeability and destruction of vascular endothelial integrity can also lead to hypoalbuminemia [9]. Hypoproteinemia can cause the plasma colloid osmotic pressure to drop and a large amount of fluid remains in the tissue gap, which reduces the effective blood volume of the body and causes damage to multiple organ functions. In addition, albumin can clear free radicals in the body and inhibit the production of oxygen free radicals by multinuclear cells. But when sepsis occurs, a large number of inflammatory factors are secreted, leading to proinflammatory and anti-inflammatory imbalances in the body, the activity of free radicals is out of control, and a large number of free radicals are produced. The occurrence of hypoalbuminemia leads to a weakening of the body's ability to scavenge free radicals and promote the development of sepsis. Therefore, it is necessary

to pay attention to children with hypoalbuminemia after the occurrence of infection. For those with sepsis complicated with hypoalbuminemia, the hypoalbuminemia should be actively corrected to reduce the incidence of complications.

This study has some limitations. This study investigated the relationship between complications among infants with late-onset sepsis and decrease of HC and hypoalbuminemia. The incidence of complications in infants with sepsis in our hospital is not high, so the sample size of the complication group is small, conclusions must be further validated with larger sample sizes. In addition, the retrospective nature of the study is a limitation, as only blood cell count analysis and blood culture at the initial stage of the disease were counted, and the results of other onset times were not recorded. Finally, we only report on the situation in a developing country. Our results may not correlate with those of other countries on the grounds of racial differences, as well as different healthcare systems and medical technologies.

Conclusion

A careful analysis of the decrease of HC and hypoproteinemia within 1 week after sepsis, which is easily accessible and affordable, represents a valuable tool to predict the occurrence of complication in infants with late-onset sepsis in the early stage.

Declarations

Ethical statement

This study was approved by the Ethics Committee of the First Hospital Affiliated of Army Medical University (Chongqing, China. KY2020065). All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

The informed consent for participation in the study was obtained from legal guardians.

Availability of data and materials

The data analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no conflicts of interest to declare.

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No funding has been received.

Authors' contributions

W.L conceived and designed this study and revised the manuscripts. N.C, W.T.F, M.T collected the samples. N.C analyzed the data and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Tables

Table 1
The baseline clinical characteristics of the complication and non-complication group

	Complication (n = 31)	Non-Complication (n = 56)	P
Gender(Male,n%)	13(41.9%)	31(55.4%)	0.230
Gestational Age (Week)	31.96 ± 2.79	32.67 ± 3.39	0.325
Birth Weight(g)	1659.19 ± 562.10	1753.57 ± 647.40	0.497
Age of Onset(d)	18.61 ± 11.33	19.09 ± 9.80	0.838
Breastfeeding(n%)	25(80.6%)	49(87.5%)	0.531 [§]
Cesarean section(n%)	19(61.3%)	39(69.6%)	0.429
PROM > 18h(n%)	5(16.1%)	11(19.6%)	0.685
Meconium pollution of amniotic fluid(n%)	1(3.2%)	2(3.6%)	1.000 [§]
Pregnancy hypertension(n%)	5(16.1%)	14(25.0%)	0.337
Maternal diabetes(n%)	3(9.7%)	11(19.6%)	0.361 [§]
Asphyxia(n%)	2(6.5%)	4(7.1%)	1.000 [§]
Small for gestational age(n%)	7(22.6%)	21(37.5%)	0.153
NRDS(n%)	11(35.5%)	13(23.2%)	0.220
Apnea(n%)	7(22.6)	12(21.4%)	0.901
Pulmonary hemorrhage(n%)	3(9.7%)	5(8.9%)	1.000 [§]

PROM > 18 h indicates Premature rupture of membranes > 18 hours, NRDS indicates neonatal respiratory distress syndrome. Measurement presented as mean ± SD. Categorical variables were presented as absolute number and percentage, and were compared using Chi-square test and Fisher's Exact test. P < 0.05 was considered significant. In the upper right corner of P value: '§' is the representative of Fisher's Exact test.

Table 2
Comparison of laboratory indicators and treatment measures between the two groups

	Complication (n = 31)	Non-Complication (n = 56)	P
WBC ($\times 10^9/L$)	9.76 \pm 5.91	11.32 \pm 8.96	0.387
PLT ($\times 10^9/L$)	187.65 \pm 104.20	202.77 \pm 137.53	0.596
HC(g/L)	111.74 \pm 11.59	123.71 \pm 21.65	0.001
Decrease of HC(g/L)	17.87 \pm 15.80	9.71 \pm 10.37	0.013
Blood culture (positive,n%)	13(41.9%)	25(44.6%)	0.807
Hypoproteinemia(n%)	20(64.5%)	14(21.5%)	0.000
Mechanical ventilation(n%)	10(32.3%)	12(21.4%)	0.266
Red blood bell infusion(n%)	17(54.8%)	16(28.6%)	0.016
WBC indicates white blood cell, PLT indicates Platelets and HC indicates hemoglobin concentration. Measurement presented as mean \pm SD. Categorical variables were presented as absolute number and percentage, and were compared using Chi-square test and Fisher's Exact test. P < 0.05 was considered significant.			

Table 3
Comparison of the severity of anemia between the two groups

	Complication (n = 31)	Non-Complication (n = 56)	P
No Anemia or Mild Anemia (n%)	7(22.6%)	30(53.6%)	
Moderate or Above Degree Anemia (n%)	24(77.4%)	26(46.4%)	0.005

Table 4
Logistic regression analysis results

	b	SE(b)	Walds	P	OR	95% CI for OR
Decrease of HC	0.107	0.028	14.224	0.000	1.113	(1.053–1.176)
Hypoproteinemia	1.375	0.545	6.354	0.012	3.953	(1.358–11.510)
HC indicates Hemoglobin concentration.						

Table 5
The ROC curve of the decrease of HC for predicting complication in sepsis

	Cut-off value	Sensitivity	Specificity	Youden index
Decrease of HC (g/L) AUC = 0.807 (0.703–0.912)	14.5	0.81	0.73	0.54
	13.5	0.84	0.68	0.52
	16.5	0.71	0.80	0.51
	15.5	0.74	0.75	0.50
	17.5	0.65	0.84	0.49

Figures

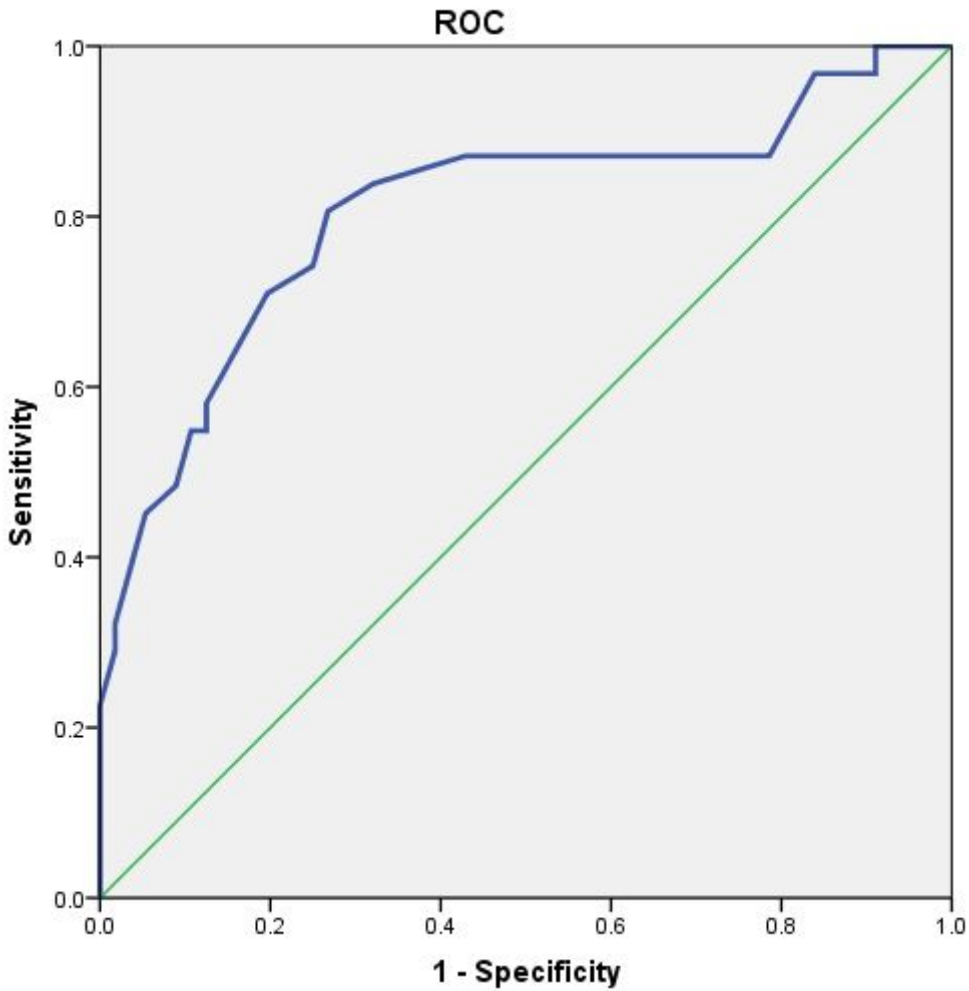


Figure 1

The ROC curve of decrease of HC for predicting complication in infants with sepsis.