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Relationship Between Serum Albumin Levels and Infections in Newborn Late Preterm Infants

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Background: We aimed to evaluate the clinical value of serum albumin levels for the evaluation and prognosis of late preterm infants with infections.

Material/Methods: This was a retrospective study performed in late preterm infants admitted at the neonatal intensive care unit (NICU) of the Liaocheng People's Hospital between July 2012 and March 2013. Data, including laboratory test results, neonatal critical illness score (NCIS), perinatal complications and prognosis, were analyzed. The newborn infants were divided into 3 groups according to their serum albumin levels, (≥30 g/L, 25–30 g/L and ≤25 g/L for high, moderate, and low, respectively).

Results: Among 257 patients, birth weight was 2003±348 g, gestational age was 35.7±2.3 weeks, and 59.1% were male. In addition, 127 (49.4%) were in the low albumin group. There were 32 patients with sepsis, 190 with infections, and 35 without infection, and their rates of hypoalbuminemia were 86.0%, 50.5%, and 30.7%, respectively (P<0.05). Albumin levels of the patients who survived were higher than those of the patients who died. In the low albumin group, the number of individual-event-critical NCIS cases and the frequency of multiple organs injuries were 63.8% and 28.3%, respectively, and were higher than in the 2 other groups. Mortality was higher in patients with sepsis. Hypoalbuminemia was associated with severe adverse outcomes (odds ratio=6.3, 95% confidence interval: 3.7–10.9, P<0.001).

Conclusions: Hypoalbuminemia was frequent among neonates with sepsis. Lower albumin levels might be associated with a poorer prognosis. Albumin levels could be appropriate for the diagnosis and prognosis of late preterm neonates with infections.

MeSH Keywords: Intensive Care Units • Neonatal Abstinence Syndrome • Serum Albumin, Radio-Iodinated

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Background

New knowledge in perinatal care has resulted in improved survival of newborn infants with very low weight at birth and in decreased complication and disability rates in these surviving newborn infants treated in neonatal intensive care units (NICUs) [1–3]. However, due to the immaturity of the innate immune system, preterm neonates are susceptible to bacterial infections [4]. Indeed, neonatal sepsis remains a leading cause of morbidity and mortality among preterm infants, with mortality rates of 3–50% (depending upon series), especially with Gram-negative pathogens [3,5,6].

Sepsis is a systemic inflammatory response to infections, and the isolation of bacteria from the blood is considered the criterion standard for the diagnosis of sepsis [7,8]. However, it takes 24–48 h to obtain culture results. Inoculation of small amounts of blood decreases its sensitivity, as approximately 60–70% of infants have a low level of bacteremia [9]. In addition, if the results come back negative after 48–72 h, clinicians still have to make a decision about how to proceed, and precious time was lost.

There have been many studies on various markers, such as hematological indices, acute-phase reactants, C-reactive protein, procalcitonin, cytokines, and cell surface markers [10–14]. Recently, serum albumin has been suggested as being an important marker for short- and long-term prognosis of neonatal sepsis [15], supported by a meta-analysis [16]. Indeed, serum albumin levels are decreased in the acute phase of infections [17]. Low serum albumin levels in critically ill patients are associated with the inflammatory response intensity to infections [18]. Hypoalbuminemia and the severity of disease are closely associated both in adults and in newborn infants [19,20]. Reduced albumin levels are due to redistribution, increased catabolism, or both [21]. In sepsis, increased vascular permeability leads to increased albumin levels in the interstitial compartment [15,21,22]. Iacobelli et al. [23,24] reported that hypoproteinemia on day 1 of life was independently associated with in-hospital death or severe neurological impairments. Hypoalbuminemia has been shown to predispose newborn infants to necrotizing enterocolitis [25]. Albumin injection has been suggested to improve outcomes in neonates and adults, but there are few evidence-based guidelines [16,26–30].

There are still very few reports about the relationship between hypoalbuminemia and illness severity and prognosis in preterm neonates with infections. The aim of this retrospective study was to evaluate the clinical value of serum albumin levels for the evaluation and prognosis of late preterm infants with infections.

Material and Methods

Patients

This was a retrospective study of prospectively collected data from all consecutive late preterm infants (34 and 36^{+6} weeks of gestational age (GA)) admitted within 24 hours of life to the tertiary NICU of the Liaocheng People's Hospital between July 2012 and July 2013. The newborn infants did not receive any serum or blood products before the blood samples were collected. Exclusion criteria were: 1) aged >24 h when the blood was sampled; 2) maternal fetal blood group was incompatible and the mother received plasmapheresis during pregnancy; 3) congenital malformations, chromosomal disorders or suspected genetic metabolic diseases; 4) unavailable first-day plasma albumin values; or 5) incomplete clinical data.

This study was approved by the institutional medical research ethics committee of the Liaocheng People's Hospital. The need for individual consent was waived by the committee due to the retrospective nature of the study.

Data collection

Data were extracted from the prospectively maintained electronic database of our hospital. In this database, data are collected at delivery and hospital discharge. Appropriately trained staff audit this database regularly. Records were validated and anonymized for the purpose of this study. The dataset included pre-existing clinical and gynecological diseases, obstetric history and illnesses, baby's gender, GA, birth weight, cord blood lactate concentration, mode of delivery, complications, prognosis, neonatal morbidities and neonatal death. The neonatal critical illness score (NCIS) was assessed using the most abnormal values within 24 hour by the same physician.

Laboratory data

Blood samples were collected and analyzed at the central laboratory of the Liaocheng People's Hospital. Arterial blood gas, lactate, albumin, prealbumin (PA), white blood cell count (WBC), platelet counts, C-reactive protein (CRP) and procalcitonin (PCT) were assessed at admission.

Albumin measurements were performed using the bromocresol green method. Albumin levels <25 g/L was the criteria used to define hypoproteinemia.

Sepsis

The diagnosis of sepsis was made according to the 2005 international standards of neonatal sepsis [7]. The systemic inflammatory response syndrome (SIRS) refers to newborn infants

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with a core temperature >38.5°C (or <36°C) or increased leukocyte counts (or immature neutrophils >10%) or secondary to chemotherapy-decreased WBC count, and the presence of the following two criteria: 1) non-external factors or other causes resulting from ongoing tachycardia or bradycardia; and 2) average respiratory rate significantly faster or requiring mechanical ventilation for acute course in the absence of neuromuscular disease and without association with general anesthesia. Sepsis was defined as the presence of SIRS accompanied by an infection. In the presence of one or more vital organ dysfunction, severe sepsis was diagnosed.

Grouping

Patients were grouped according to two grouping schemes: 1) according to serum albumin levels (≥30 g/L, 25-30 g/L or ≤25 g/L, for high, moderate or low, respectively); or 2) according to the final diagnosis (sepsis, neonatal infection other than sepsis or no infection).

Statistical analysis

Normally distributed continuous data are presented as means ± standard deviation (SD) and were analyzed using ANOVA with the Tukey's post hoc test. Categorical data are presented as proportions and were analyzed using the chi-square or the Fisher's exact test, as appropriate. A Cox multivariate analysis was used to determine the odds ratio (OR) and 95% confidence intervals (95%CI) for developing severe outcomes (death or disability). SPSS 19.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Two-sided P-values <0.05 were considered statistically significant.

Results

Characteristics of the patients

Clinical data were missing or incomplete for 26 infants, and albumin values were not available for 51 infants. Therefore, 257 infants were included. Table 1 presents the characteristics of the included infants. There were 152 boys and 105 girls, including 8 sets of twins and 1 set of triplets. Infants were delivered vaginally for 102 and by C-section for 155. There were 139 (54.1%) cases of significant NCIS. Neonatal sepsis was diagnosed in 32 cases (including 8 with severe sepsis); neonatal pneumonia in 125 cases (including pneumonia with neonate inspiratory distress syndrome in 30 cases); purulent meningitis in 10 cases; urinary tract infections in 5 cases; enteritis in 5 cases; and neonatal necrotizing enterocolitis in 15 cases. Thirty-five infants were without infection. Six infants died. Hypoproteinemia (albumin <25 g/L) was observed in 127 cases (49.4%); 66 infants had moderate albumin levels; and 64 infants had high albumin levels.

Table 1. Characteristics of the newborn infants (N=257).

Variable	Observation
Maternal age, mean±SD, y	27.8±7.6
Preeclampsia, n (%)	72 (28.0)
Gestational diabetes, n (%)	15 (5.8)
Antenatal steroids, n (%)	91 (35.6)
Singleton pregnancy, n (%)	238 (92.6)
Birth weight, mean±SD, g	2003±348
Gestational age, mean±SD, wk	35.7±2.3
Male gender, n (%)	152 (59.1)
Caesarean section, n (%)	155 (60.3)
Cord blood lactate, mean±SD, mmol/L	4.60±2.29
Hypoproteinemia, n (%)	127 (49.4)
Requiring invasive mechanical ventilation, n (%)	67 (26.0)
Discharge diagnosis	
Neonatal sepsis, n (%)	32 (12.5)
Neonatal pneumonia, n (%)	125 (48.6)
Purulent meningitis, n (%)	10 (3.9)
Enteritis, n (%)	5 (1.9)
Neonatal necrotizing enterocolitis, n (%)	15 (5.8)
Non-neonatal infection, n (%)	35 (13.6)
Urinary tract infections, n (%)	5 (1.9)

Maternal complications

Maternal complications occurred for 82% (210/257) of infants, including 102 cases of perinatal infections (39.6%), 72 of preeclampsia (28.0%), 15 of gestational diabetes (5.8%) and 25 of fetal distress (10.0%).

Laboratory result

Table 2 presents the laboratory results according to the albumin level groups. Compared with the moderate and high albumin groups, patients in the low albumin group had low prealbumin levels (P=0.04), low platelets (P=0.048) and high PCT levels (P<0.001).

Infections, hypoalbuminemia and mortality

Thirty-two infants were diagnosed with neonatal sepsis including 27 (86.0%) with hypoalbuminemia; 190 infants were diagnosed with neonatal infection including 95 (50.5%) with

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Table 2. Laboratory test results.

	Albumin groups			P-values
	≤25 g/L N=127	25–30 g/L N=66	≥30 g/L N=64	
PA, g/L	68.90±33.83	78.62±32.25*	87.25±23. 40*	0.038
WBC, ×10^9/L	14.18±8.10	14.91±6.84	11.79±6.03	0.236
PLT, ×10^9/L	223.02±85.19	247.42±58.34	264.79±77.45*	0.048
CRP, mg/L	2.64±4.08	2.34±5.88	1.11±1.66	0.293
PCT, ng/ml	19.64±9.73	16.34±9.88*	6.62±6.68*	<0.001

OR – odds ratio; 95%CI – 95% confidence interval; PCT – procalcitonin; PLT – platelets, CRP – C-reactive protein; WBC – white blood cell count. * P<0.05 *vs.* the ≤25 g/L group.

Table 3. Infections and mortality.

	Albumin (g/L)	Hypoalbuminemia (%)	Mortality (%)
Neonatal sepsis	21.11±3.90	86.0	15.6 (5/32)
Neonatal infection	27.45±1.18*	50.5*	0.01 (1/190)*
neonatal noninfection	31.93±2.26*	30.7*	0 (0/35)*
P-values	<0.001	<0.001	<0.001

* P<0.05 *vs.* the neonatal sepsis.

hypoalbuminemia; and 35 infants were without infection including 10 (30.7%) with hypoalbuminemia (Table 3). Serum albumin levels were significantly different between the three groups (P<0.001). The mortality was higher in the neonatal sepsis group compared with the other two groups (P<0.001).

Albumin levels was 29.6±7.5 g/L in the patients who survived, but were 20.4±6.9 g/L in the patients who died (P<0.001). In the low albumin group, 36 infants had more than four organs damaged (P<0.001), and 81 had a single NCIS (P<0.001). More infants required mechanical ventilation in the low albumin group compared with the other two groups (P=0.04) (Table 4).

Multivariate analysis

Table 5 shows that hypoalbuminemia (OR=6.3, 95%CI: 3.7–10.9, P<0.001), PCT (OR=3.8, 95%CI=1.8–7.6, P<0.001), platelets (OR=3.1, 95%CI: 1.8–5.1, P<0.001), CRP levels (OR=1.9, 95%CI: 1.1–3.1, P=0.01) and white blood cell counts (OR=2.5, 95%CI: 1.4–4.8, P=0.003) were independently associated with detrimental outcomes (death or disability).

Discussion

The aim of the present study was to evaluate the clinical value of serum albumin levels for the evaluation and prognosis of late preterm infants with infections. Results showed that among the 257 patients, there were 32 patients with sepsis, 190 with infections and 35 without infection, and their rates of hypoalbuminemia were 86.0%, 50.5% and 30.7%. Albumin levels of the patients who survived were higher than those of the patients who died. In the low albumin group, the number of individual-event-critical NCIS cases and the frequency of multiple organs injuries were 63.8% and 28.3%, respectively, higher than in the two other groups. Mortality was higher in patients with sepsis. Hypoalbuminemia was associated with severe adverse outcomes (odds ratio=6.3, 95% confidence interval: 3.7–10.9). These preliminary data suggest that late preterm infants need more examination to clarify the treatment of hypoalbuminemia together with infection.

Sepsis can contribute to neonatal chronic lung diseases, retinopathy, coagulation functions and periventricular white matter lesions. Indeed, Mitha et al. [31] have found that the frequency of cerebral palsy was higher in infants with sepsis than in uninfected infants, and that early treatment affected the outcomes. However, the lack of specificity of the early signs and symptoms of infections poses a problem for diagnosis. In order to avoid the spread of the infection and complications, doctors often use antibiotics for premature infants with high risk factors. However, the overuse of antibiotics may affect the normal intestinal flora, and induce fungal infections and drug resistance. In the era of multidrug resistance, it is mandatory

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Table 4. Organ damage and NCIS.

	≤25 g/L	25–30 g/L	≥30 g/L	P-values
Cases, n	127	66	64	
Organ damage, n (%)				<0.001
<4	91 (71.7)	50 (75.8)	56 (87.5)	
≥4	36 (28.3)	16 (24.2)	8 (12.5)	
NCIS				
Single, n (%)	81 (63.8)	29 (43.9)	27 (42.2)	<0.001
Score	94.70±6.10	95.41±4.94	97.07±3.92	0.407
Ventilation, n (%)	39 (30.7)	12 (18.2)	16 (25.0)	0.041

Table 5. Variables associated with severe adverse outcome.

	OR	95%CI	P-values
Hypoproteinemia	6.3	3.7–10.9	<0.001
PCT	3.8	1.8–7.6	<0.001
PLT	3.1	1.8–5.1	<0.001
CRP	1.9	1.1–3.1	0.01
WBC	2.5	1.4–4.8	0.003

OR – odds ratio; 95%CI – 95% confidence interval; PCT – procalcitonin; PLT – platelets, CRP – C-reactive protein; WBC – white blood cell count. Severe adverse outcomes included death and disability.

to avoid the unnecessary use of antibiotics to treat non-infected infants. However, the main problem is that blood cultures need 24–48 h to produce a result, and the infants cannot be left untreated for this length of time.

Serum albumin levels are decreased in the acute phase of infections. Therefore, low serum albumin levels in critically ill patients are associated with the inflammatory response intensity to infections [18,32]. Low serum albumin levels are very common in critically ill patients, with reported incidences as high as 40–50% [33]. A previous study has shown that human serum albumin may activate the endothelial nitric oxide synthase and restore the lipopolysaccharide-impaired flow-dependent endothelial dilation in mesenteric arteries [34]. This was associated with downregulation of nuclear factor κB and upregulation of nuclear respiratory factor-2 and heme oxygenase-1 [34]. In the present study, a multivariate analysis revealed that the association between hypoalbuminemia and adverse outcomes was independent from other factors, which is supported by previous studies using different methodologies [35,36]. In addition, measuring serum albumin levels is easy, and the results can be obtained very fast, allowing the physician to adjust in treatment approach in a timely manner.

Some studies have shown that low birth weight, premature birth, maternal bacterial infection, chorioamnionitis, premature rupture of membranes, maternal GBS carriers, checking the vagina over three times, prolonged labor, severe preeclampsia, gestational diabetes, Apgar score <4 were risk factors for adverse outcomes of sepsis [37]. A study has shown that the premature rupture of membranes and chorioamnionitis could increase the risk of sepsis by about eight folds [38]. Subclinical intrauterine infection is a major cause of premature birth [39]. In the present study, perinatal complications and maternal risk factors accounted for 82%, of which 39.6% was perinatal infections.

CRP is an acute phase protein secreted by the liver, but its levels often cannot increase accordingly to the bacterial infection present in neonates because of the immature immune status [40]. In the present study, CRP was not significantly different between groups. PCT is proven to be a good marker of severe invasive bacterial infections in newborn infants [41]. Serum PCT has high sensitivity and positive predictive value for the diagnosis of neonatal bacterial infection [42]. In the present study, PCT levels were indeed different between the albumin groups, and PCT levels were an independent marker of poor outcomes.

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The NCIS is commonly used for assessing the critical condition of newborn infants [43]. In the low albumin group, the cases of significant NCIS newborn infants were higher than in the two other groups, more newborn infants needed assisted ventilation and more newborn infants had multi-organ dysfunction (≥4). Low early blood protein levels may impair adequate intravascular volume and blow flow to vital organs in preterm infants [23]. Therefore, hypoalbuminemia may induce serious damage to the structure and function of many organs. In the present study, the albumin levels in the survival group were significantly lower than in the dead group. Indeed, a previous study has shown that there was close relation between hypoproteinemia and disease severity and prognosis [44].

In critical care, the evaluation of mortality and morbidity shortly after sepsis may not be sufficient for epidemiological and clinical studies; and the prognosis and eventual impacts on the long-term after a critical illness is a pivotal topic of interest [45]. Previous studies suggest that serum albumin levels should be used to assess the severity of infections and critical illnesses [46]. Injecting albumin has been tried as a potential therapy, but studies so far failed to indicate any real benefit [44]. Further studies are necessary to establish better treatments in neonates with low albumin levels.

The present study is not without limitations. Indeed, the sample size was relatively small and was from a single center. In addition, due to its retrospective nature, we were limited in the variables that we could assess. Additional studies including more patients from multiple centers should be carried out to reach firmer conclusions.

Conclusions

Hypoalbuminemia was frequent among neonates with sepsis. Lower serum albumin levels might be associated with a poorer prognosis. Serum albumin levels could be appropriate for the prognosis of late preterm neonates with infections.

Conflict of interest

The authors declare that they have no conflict of interest.

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