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Correlation of serum albumin with the clinical features and prognosis of preterm neonates in the neonatal intensive care unit

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Summary

Objective: To evaluate the clinical significance of serum albumin (ALB) levels in the early evaluation and prognosis of preterm infants in the neonatal intensive care units (NICUs). *Materials and Methods:* The authors collected and retrospectively analyzed complete clinical records of preterm infants admitted to the NICU from July 2012 to March 2013. The cases were divided into three groups according to their ALB levels: ≥30 g/L, 25–30 g/L, and ≤25 g/L. *Results* The mean gestational age in the ≤25 g/L ALB group was significantly higher than that in the ≥30 g/L ALB group [(33.41 ± 2.15) weeks] ($p < 0.05$). The prealbumin, blood platelet, and blood urea nitrogen in the ≤ 25 g/L ALB group were significantly lower than those in the > 30 g/L ALB group ($p < 0.05$). In addition, serum lactate in the ≤ 25 g/L ALB group was significantly higher than that in the ≥ 30 g/L ALB group ($p < 0.05$). *Conclusion* Serum ALB level increased with increasing gestational age. Lower ALB levels were associated with more perinatal complications, damage to multiple organs, more severe cases, and mechanical ventilation, which resulted in longer hospital stays and poorer prognoses.

Key words: Preterm infant; Serum albumin; Clinical performance; Prognosis.

Introduction

Advances in perinatal care have improved the survival rate of very low birth weight (VLBW) preterm neonates, and even extremely low birth weight (ELBW) preterm neonates, as well as the high morbidity of severe infections. Hepatic protein synthesis in preterm neonates is less than that in full-term neonates; thus, serum protein levels are indicators for evaluating fetal and preterm protein nutrition. Serum albumin (ALB) is a negative acute-phase protein; thus, the degree of hypoalbuminemia of critically ill patients is correlated with the intensity of the inflammatory response triggered by infections [1]. Nevertheless, ALB levels should be considered an indicator for severity and a reliable indicator for frailty, a physiological condition characterized by low functional reserve, high susceptibility to stressors, and unstable homeostasis. However, research on protein levels and clinically relevant indicators in preterm neonates are limited. The whole clinical data regarding the preterm neonates were analyzed retrospectively from the cases admitted in the present neonate intensive care unit (NICU) between July 2012 and March 2013. The authors explored the clinical significance of different ALB levels during the early assessment and prognosis of preterm neonates to provide a basis for clinical therapy and medication. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Liaocheng Peoples Hospital. Written informed consent was obtained from all participants.

Materials and Methods

Patient selection

The preterm neonates were recruited in the retrospective observational study were admitted into the present NICU from July 2012 to March 2013. The inclusion criteria were as follows: 1) gestational age < 37 weeks; 2) the patients were admitted within 24 hours; and 3) the patients did not receive any serum or blood products before the blood samples were collected. The exclusion criteria were as follows: 1) age > 24 hours when blood was collected; 2) maternal and fetal blood antigen groups were incompatible; and the mother received plasmapheresis during pregnancy; 3) neonates with associated congenital malformations, chromosomal disorders, and suspected genetic metabolic diseases; and 4) incomplete clinical data.

Methods

All subjects underwent routine physical examination and laboratory tests after admission. An additional sample was drawn from the same arterial sampling point using lithium heparin vacutainer tubes. The samples were sent to the central laboratory of the present hospital. Plasma and serum were subjected to multicomponent analyses.

Laboratory tests: arterial and venous blood samples were collected within 24 hours after birth. The following laboratory variables were determined: serum albumin (ALB), prealbumin (PA), urea nitrogen (BUN), creatinine (Cr), creatine kinase (CK), isoenzyme (CKMB), high-sensitivity C-reactive protein (CRP), white blood cell, blood platelets, lactate (Lac), and so on. The other indicators included neonatal critical illness score (NCIS): the most abnormal values within 24 hours were considered the first score. The authors also recorded gestational age, birth weight, sex, mode of delivery, duration of hospitalization, complications, prognosis, and other complications during pregnancy.

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Table 1. — *Population characteristics (n=339).*

	≤25g/L	25-30 g/L	≥30 g/L	F	*p*
Cases, n.	168	87	84		
Male gender, n.	99	54	51	0.149[a]	0.928
Caesarean section, n.	90	40	75	13.771	0.000
ALB, g/L	23.11±1.90	27.45±1.18	31.93±2.26	218.442	0.000
Gestational age, mean ± SD, wk	32.47±2.22*	32.85±2.22	33.41±2.15	1.176	0.185
Birth weight, mean ± SD, kg	1.76±0.48	1.73±0.44	1.83±0.58	0.285	0.753

*Compared with group ≥ 30 g/L, $p < 0.05$.

Table 2. — *Perinatal factors, n. (n=339).*

	≤ 25g/L	25-30 g/L	≥30 g/L	X^2	*p*
Gestational hypertension	36	18	42	12.441	0.000
Gestational diabetes	9	0	3	1.178	0.312
PROM	30	29	7	6.230	0.003
Fetal distress	12	1	9	7.539	0.001
Twin/multiple births	13	3	0	4.613	0.012
Fetal death	3	0	0	1.028	0.361
Infection	10	0	3	0.793	0.455
Placenta	9	3	3	0.112	0.895
Umbilical cord	10	0	8	0.523	0.594
Abdominal discomfort or social reason	12	10	2	1.361	0.261
Congenital heart disease	4	5	3	0.276	0.760
Other organ dysfunction	8	6	5	0.002	0.998

The study was approved by the medical ethics committee of the hospital.

All newborns who were admitted into the NICU were divided into three groups according to the ALB level: ≥ 30 g/L, 25 g/L to 30 g/L, and ≤ 25 g/L.

Statistical analysis

The data are presented as the mean ± standard deviation (SD) if they followed a normal distribution. Differences among groups were tested using an ANOVA. The number of cases and percentages were used for the count data, and R was determined using two chi-square tests. However, if the data did not meet the requirements of the chi-square test, a Fisher exact test was performed. Differences with $p < 0.05$ were considered statistically significant.

Results

General information

A total of 339 preterm neonates were recruited into the study: 201 boys and 138 girls; eight cases were twins and one case involved triplets, 135 deliveries were natural childbirth and 204 were via cesarean section. The subjects were divided into three groups: ≤ 25 g/L (168 cases), 25 g/L to 30 g/L (87 cases), and ≥ 30 g/L (84 cases). The mean ALB level for the ≤ 25 g/L group was (23.11 ± 1.90) g/L, that for the 25 g/L to 30 g/L group it was (27.45±1.18) g/L, and that for the ≥ 30 g/L group it was (31.93±2.26) g/L ($p = 0.000$). The mean gestational age for the 25 g/L to 30 g/L group was (32.47 ± 2.22) weeks and that for the ≥30 g/L group was (33.41 ± 2.15) weeks ($p < 0.05$). The three groups did not significantly differ in terms of birth weight ($p = 0.753$; Table 1).

Table 3. — *Laboratory test results, mean ± SD (n=339).*

	≤25 g/L	25-30 g/L	≥30 g/L	F	*p*
PA, g/L	68.90±33.83	78.62±32.25	87.25±23.40	3.383	0.038
WBC, $\times 10^9$/L	14.18±8.10	14.91±6.84	11.79±6.03	1.464	0.236
PLT, $\times 10^9$/L	223.02±85.19	247.42±58.34	264.79±77.45	3.120	0.048
rCRP, mg/L	2.64±4.08	2.34±5.88	1.11±1.66	1.241	0.293
BUN, mmol/L	4.54±3.17	4.35±3.00	6.86±3.85	4.927	0.009
Cr, mmol/L	72.66±34.49	65.18±22.59	75.57±19.54	1.010	0.368
CK, mmol/L	362.48± 314.45*	335.07± 327.34	217.64± 141.68	2.456	0.09
CKMB, mmol/L	117.39± 167.70	130.10± 206.33	90.89± 78.93	0.437	0.647
Lac, mmol/L	4.60±3.19*	3.41±1.97	3.38±2.29	2.086	0.130

Perinatal information

In the ≤ 25 g/L ALB group, 36 cases (21.4%) developed gestational hypertension, 30 cases (17.9%) developed premature rupture of membranes, 12 cases (7.1%) developed fetal distress, and 13 cases (7.7%) developed superfetation. In the 25 g/L−30 g/L ALB group, 18 cases (20.7%) developed gestational hypertension, 29 cases (33.3%) developed premature rupture of membranes, 1 case (1.2%) developed fetal distress, and 3 cases (3.4%) developed superfetation. However, in the ≥30 g/L ALB group, 42 cases (50%) developed gestational hypertension, 7 cases (8.3%) developed premature rupture of membranes, 9 cases (10.7%) developed fetal distress, and 0 cases (0%) developed superfetation. The disease incidence was higher in the ≤25 g/L ALB group than the other groups ($\chi^2 = 12.441, 6.230, 7.539, 4.613$; $P = 0.000, 0.003, 0.001, 0.012$) (Table 2).

Laboratory result

The prealbumin level in the ≤25 g/L ALB group was (68.90 ± 33.83) g/L, that in the 25 g/L to 30 g/L group was (78.62 ± 32.25) g/L, and that in the ≥ 30 g/L ALB group was (87.25 ± 23.40) g/L, and the F value among the three groups was 3.383 ($p = 0.038$). The platelet count was (223.02 ± 85.19) in the ≤ 25 g/L ALB group, (247.42 ± 58.34) in the 25 g/L to 30 g/L group, and (264.79 ± 77.45) in the ≥30 g/L ALB group ($F = 3.120$, $p = 0.048$). The blood urea nitrogen (BUN) was (4.54 ± 3.17) mmol/L in the ≤ 25 g/L ALB group, (4.35 ± 3.00) mmol/L in the 25 g/L to 30 g/L ALB group, and (6.86 ± 3.85) mmol/L in the ≥ 30 g/L ALB group ($F = 4.927$, $p = 0.009$). The BUN in the ≤ 25 g/L ALB group significantly differed from that in the 30 g/L ALB group ($p < 0.05$; Table 3).

Table 4. — *Severe infections, organ damage, NCIS (n=339).*

	≤25g/L	25-30g/L	≥30 g/L	F or X^2	*p*
Severe infection, n.	30	10	9	0.371	0.691
Organ damage, n.					
< 4	135	66	69		
≥ 4	33	21	15	12.000	0.035
NCIS					
Individual, n.	108	36	39	4.078	0.037
Non-individual, mean ± SD	94.70±6.10	95.41±4.94	97.07±3.92	0.917	0.407
Mechanical ventilation (invasive/non-invasive)	39	12	16	3.299	0.041

Table 5. — *Outcomes and length of stay (n=339).*

	≤25g/L	25-30g/L	≥30 g/L	F or X^2	*p*
Outcomes					
Survival, n.	150	87	84	4.885	0.027
Death, n.	12	0	0		
Length of stay, mean ± SD, d	24.38±11.17	22.51±13.31	17.07±10.24	3.002	0.049

Severe infection complications, organ damage, and NCIS

The incidence rates of severe infection did not significantly differ among the three groups (17.9%, 11.5%, and 10.7%, $p > 0.05$). Up to 33 patients in the ≤ 25 g/L ALB group, 21 patients in the 25 g/L to 30 g/L, and 15 cases in the ≥ 30 g/L ALB group developed functional damage to ≥ four organs (F = 12.000, P = 0.035). A total of 108 cases (64.3%) in the ≤25 g/L ALB group, 36 cases (41.4%) in the 25 g/L to 30 g/L ALB group, and 39 cases (46.4%) in the ≥30 g/L ALB group had single critical illness scores (sugar levels less than 1.0 mmol/L) ($\chi^2 = 4.078$, P = 0.037; Table 4).

Outcomes and length of stay

The length of stay in each group was (24.38 ± 11.17), (22.51±13.31), and (17.07 ± 10.24) days, respectively (F = 3.002, $p = 0.049$). The ≤ 25 g/L ALB group had 12 deaths, whereas the other two groups had no deaths ($\chi^2 = 4.885$, $p = 0.027$; Table 5).

Discussion

ALB is the most abundant plasma protein and it is synthesized exclusively in the liver. ALB maintains the colloid osmotic pressure of the blood (accounting for 80%), acts as a buffer, and it transports bilirubin, uremic toxins, porphyrins, fatty acids, metals, cortisol, thyroxine, endotoxins, medications, and endogenous nitric oxide. Furthermore, ALB may be an important antioxidant; thus, it may contribute to neuronal survival during development. These functions are of vital importance to critically ill preterm neonates [2]. Human ALB 4% prolongs the survival of endotoxemic mice. Human ALB 4% activates endothelial nitric oxide synthase and restores lipopoly- saccharide-impaired flow-dependent endothelial dilation of mesenteric arteries. This finding is associated with downregulation of nuclear factor κB and upregulation of nuclear respiratory factor-2 and heme oxygenase-1 [3]. Low ALB levels are common in critically ill patients, with incidences rates as high as 40% to 50% [4]. In a study with a large number of critically ill preterm neonates, Iacobelli *et al.* [5] reported that hypoproteinemia (total protein levels less than 40 g/L) on day 1 of life is an independent factor associated with severe adverse outcome (SAO), defined as in-hospital death or severe neurologic injury on cranial ultrasound). Thus, the present authors designed the study to explore the clinical significance of different ALB levels on the early assessment and prognosis of preterm neonates to provide a basis for clinical therapy and medication.

The premature infants were delivered preterm because of various reasons, and have incomplete liver development, especially in VLBW and ELBW neonates. Preterm neonates have lower levels of ALB and prealbumin because of decreased synthesis and inadequate reserves [6-8]. In recent years, more studies have evaluated fetal nutrition. Artero *et al.* suggested that albumin levels are closely related to the severity of the disease and prognosis. However, ALB infusion has not been investigated clinically [9]. Therefore, understanding the actual serum protein levels and clinically relevant indicators will help us better assess clinical conditions of patients to provide a reliable basis for drug therapy.

The average gestational age was (32.47 ± 2.22) weeks in the ≤ 25 g/L ALB group and (33.41 ± 2.15) weeks in the ≥ 30 g/L ALB group ($p < 0.05$). Up to 36 cases (21.4%) in the ≤ 25 ALB group, 18 cases (20.7%) in the 25 g/L to 30 g/L ALB group, and 42 cases (50%) in the > 30 g/L ALB group developed pregnancy-induced hypertension. The present authors found that low economic level and poor awareness of antenatal care resulted in more obstetric diseases; for example severe gestational hypertension and preeclampsia (70%). Severe pre-eclampsia causes significant mortality and morbidity to both the mother and the child [10]. Organ damage is common during early preeclampsia, especially to the placenta and the liver. The reduced ALB synthesis after IUGR reflects low intrauterine ALB synthesis because of the lower availability of amino acids in utero. The data suggest that a low supply of intrauterine nutrients restricts the growth and potentially reduces the postnatal protein turnover, including ALB turnover [11-13]. The mean weight of the neonates in the ≤ 25 g/L ALB group ≤ 25 g/L was (1.68 ± 0.46) kg and that in the > 30 g/L ALB group was (2.07 ± 0.48) kg ($p = 0.000$).

Sharma *et al.* [14] found platelet count is negatively correlated with the incidence of neonatal sepsis. Torkaman [15] *et al.* showed that thrombocytopenia is negatively correlated with the incidence of neonatal sepsis. In the present study, the platelet count in the ≤ 25 g/L ALB group was

lower than those in the other two groups (223.02 ± 85.19, 247.42 ± 58.34, 264.79 ± 77.45; $p < 0.05$). In the ≤ 25 g/L ALB group, 30 cases developed premature rupture of membranes (PROM) (17.9%), which indicates that ALB level is an indirect indicator for inflammation. Thus, we need to observe the associated clinical manifestations to control the infection in time [1]. BUN and creatinine are indicators of renal function and indirect indicators of nutritional state. In the present study, the BUN level was higher in the > 30 g/L ALB group than in the ≤ 25 g/L ALB group. However, the renal blood flow and glomerular filtration rate after birth increased rapidly with decreasing renal vascular resistance and increased systemic blood pressure. Thus, we should observe clinical changes to diagnose the pathology promptly.

Blood Lac level is a sensitive biochemical marker for tissue perfusion and oxygen delivery that can be used to assess disease severity and outcome. Some studies have shown that blood Lac levels are negatively correlated with the neonatal critical illness score [16-19]. In the present study, the Lac level was (4.60 ± 3.19) mmol/L in the ≤ 25 g/L ALB group, which is higher than the (3.38 ± 2.29) mmol/L in the ≥ 30 g/L ALB group. Therefore, ALB level and serum Lac complement each other when used for evaluating the condition of preterm neonates [20-22].

NCIS is commonly used in the clinical assessment of neonates. The scores accurately reflect the severity of illness, with lower scores indicating higher chances of the mortality [23-25]. In the ≤ 25 g/L ALB group, 108 cases were subjected to single NCIS (64.3%) and 39 cases required mechanical ventilation [invasive and non-invasive mechanical ventilation (23.2%)]. Logistic multivariate analysis revealed that NCIS and mechanical ventilatory support are independent risk factors for neonatal outcome. However, non-invasive mechanical ventilation, NCPAP, and NIPPV may be preferred for clinical assisted ventilation.

The study by Vincent *et al.* [26] indicated that the severity of disease increases by 89% and the mortality rate increases by 137% when ALB is as low as 10 g/L. Higher mortality rates were also correlated with damage to more than four organs. In the present study, 33 cases (19.6%) in the ≤ 25 g/L ALB group developed damage to at least four organs, which is significantly higher than in the other groups. Twelve patients died in the ≤ 25 g/L ALB group, whereas no patients died in the other two groups ($p < 0.05$). The mean length stay was (24.38 ± 11.17) days in the ≤ 25 g/L ALB group, which is longer than the (24.38±11.17) days in the ≥ 30 g/L ALB group. Furthermore, the cost of hospitalization was high, which aggravated the economic burden.

Iacobelli *et al*. showed that low plasma protein concentrations within the first day of life is strongly predictive of a negative outcome in VLBW [5]. Logistic and multiple regression analysis confirmed that the association of hypoproteinemia-SAO remained significant after adjusting for other major predictors of outcome at baseline (odds ratio, 3.4; 95% confidence interval, 2.1–5.4; $p < 0.0001$). Hypoproteinemia was highly associated with SAO in this cohort of critically ill preterm infants [5]. The increased capillary permeability in critical cases was sufficient to sequester ALB into the interstitium. Vincent *et al.* showed that hypoalbuminemia at discharge is correlated with ICU readmission and unexpected deaths [26].

Therefore, searching for new indicators in sick preterm infants should include markers that can be used to assess the condition. In conclusion, ALB is a sensitive indicator for predicting the early condition and prognosis of preterm neonates. The present analysis only included a small sample size. Therefore, further studies are needed to understand the actual ALB levels, particularly in a large sample of preterm neonates, especially VLBW and ELBW. Moreover, understanding the connection between ALB and prognosis is important for determining whether human blood ALB should be administered intravenously.

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