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Association of Cord Blood Total Protein and Albumin Levels with Respiratory Distress Syndrome

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ABSTRACT

Background: Respiratory distress syndrome (RDS) is one of the major causes of morbidity and mortality in preterm newborns. The severity and treatment of RDS affect the outcomes of premature neonates in neonatal intensive care units. Some studies have claimed that hypoalbuminemia and hypoproteinemia are associated with poorer outcomes in preterm neonates. The current study aimed to assess the association of serum total protein and albumin with the presentation of RDS among this group of newborns.

Methods: This cross-sectional study was carried out on a total of 100 preterm newborns. The study population included a control group of healthy neonates (n=50) and case group of newborns diagnosed with RDS (n=50). For each neonate, a 2 ml sample of the arterial blood was taken from the umbilical artery, and laboratory indices, including total serum protein and albumin, were measured. Statistical analysis was conducted to compare potential variations between the samples of the healthy and RDS groups.

Results: According to the obtained findings, no statistical difference was observed between the healthy and RDS preterm neonates regarding total protein (P=0.16) and serum albumin (P=0.27) levels. Total serum protein and albumin were not affected by the newborn's birth weight and gender (P>0.05) among both the healthy preterm neonates and those with RDS. However, a significant association was observed regarding gestational age (P<0.05) for both the healthy and RDS neonates and maternal age for the healthy neonates only (P<0.05).

Conclusion: No difference was observed in total serum protein and albumin levels between the healthy preterm neonates and those with RDS. Furthermore, total serum protein and albumin levels were not affected by gender, birth weight, and maternal age among the RDS patients. However, they were directly associated with the gestational age at the time of birth in both the RDS and healthy groups.

Keywords: Newborn, Prematurity, Respiratory distress syndrome, Serum albumin, Total protein

Introduction

Hyaline membrane disease also known as respiratory distress syndrome (RDS) with more popularity has remained a significant neonatal healthcare matter for preterm neonates worldwide (1). Although, as a result of recent progress in management schedules, the number of survivors has dramatically increased, RDS is still a significant underlying cause of morbidity and mortality due to prematurity (2). The RDS is inversely associated with gestational age and birth weight. It has been demonstrated that the risk of RDS progression diminishes from 92% at 24-25 weeks of gestation to 57% at 31-32 weeks of gestation (1).

Prematurity is the main factor leading to the RDS presentation. This syndrome clinically presents with early respiratory distress following birth by the signs, including cyanosis, tachypnea, grunting, nasal flaring, and intercostal and subcostal retractions. The symptoms usually show progression, and supplemental oxygen may be required. The rapid progression of the disease may

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cause respiratory failure. The initial chest X-ray may appear to be normal. However, the typical radiographic pattern developing during the first day includes a diffuse reticulogranular pattern, giving the classic ground-glass appearance in both lung fields, low lung volume, and air bronchograms.

The diagnosis of RDS is based on a combination of the previously described clinical features, evidence of prematurity, exclusion of other causes of respiratory distress, and characteristic radiographic appearance. Early diagnosis and disciplined medical management are required as RDS can cause hypoxia, hypercapnia, and acidosis and quickly leads to irrecoverable complications, such as asphyxia, hypoxic-ischemic encephalopathy, and multi-organ damage (2-4). Mortality can result from the severe impairment of gas exchange, alveolar air leaks, pulmonary hemorrhage, or intraventricular hemorrhage (4). Impaired gas exchange due to the reduced compliance of the lungs and alveolar collapse is the basis of RDS pathophysiology occurring because of surfactant secretion deficiency. In addition, disrupted alveolocapillary membrane leads to pulmonary edema and eventually lung injury (1).

Surfactant is a complex mixture of lipids and proteins reducing surface tension (5, 6). The alveolar fluid of the lungs contains phospholipid, which is combined with a number of proteins. These proteins reduce lung inflammation in preterm neonates, and their normal structure and function maintain normal bronchoalveolar fluid homeostasis (7, 8).

Clara cell 10-kD protein (CC10) is one of those proteins that have anti-inflammatory properties and inhibit secretory phospholipase A2 from surfactant destruction. The CC10 has been observed in the tracheal aspirate fluid of ventilated premature newborns and circulates in the blood. The concentrations of CC10 have been demonstrated to negatively correlate with the concentration of inspired oxygen required by preterm neonates with RDS (9).

It has been demonstrated that hypoproteinemia (10) and hypoalbuminemia (11) are associated with adverse outcomes in adults struggling with acute respiratory distress syndrome. However, there have been studies representing the adverse effects of hypoproteinemia on the outcomes of premature neonates (12). Recent studies have raised the hypothesis that hypoproteinemia in prematurity may be a risk factor for RDS (13). This is based on the potential role of oncotic pressure by serum proteins and their effect on the alveolar-capillary membrane and lung compliance (9, 10). The results of studies in this regard are uncertain and further investigations are required. Therefore, this study aimed to investigate the relationship between the cord blood levels of albumin and total protein with the presentation of RDS.

Methods

The current cross-sectional study was carried out on 100 preterm neonates born at Shahid Beheshti and Alzahra hospitals affiliated to Isfahan University of Medical Sciences, Isfahan, Iran, within the 1st December 2018 and 31st June 2019. The preterm neonates with a gestational age of 28-37 weeks born at the aforementioned hospitals were included in the study. Major congenital anomalies and asphyxia were considered the unmet criteria. The parents' reluctance to participate in the study, diagnosis of chorioamnionitis in the mother, failure in sampling, and other diagnoses for the respiratory distress other than RDS, such as early sepsis or congenital pneumonia, were the exclusion criteria of this study.

The Ethics Committee of Isfahan University of Medical Sciences primarily approved the study protocol based on the code number of IR.MUI.MED.REC.1397.280. The research process was entirely explained for the legal guardians of the neonates, and they were requested to sign the written form of participation in the study. By the consideration of the inclusion and exclusion criteria and based on the study protocol, immediately after giving birth, a 2 ml sample of the arterial blood was taken from the umbilical artery following the sterilization of the clamped umbilical cord using a 22-gauge needle. The methodology for data collection is illustrated in Figure 1.

The blood samples were sent to a laboratory in order to measure serum total protein and albumin levels. The preterm neonates were followed, and those admitted at the neonatal intensive care unit (NICU) with clinical and laboratory manifestations of RDS were identified and entered the case group. The preterm neonates who did not show the symptoms were considered the controls. The neonates with diagnoses other than RDS were excluded from the study. Sampling continued until the study subjects in each group reached 50.

The demographic information of the neonates, including mother's age, gestational age, maternal medical history during pregnancy, type of the delivery (i.e., cesarean section or normal vaginal delivery), newborn's birth weight, gender, Apgar

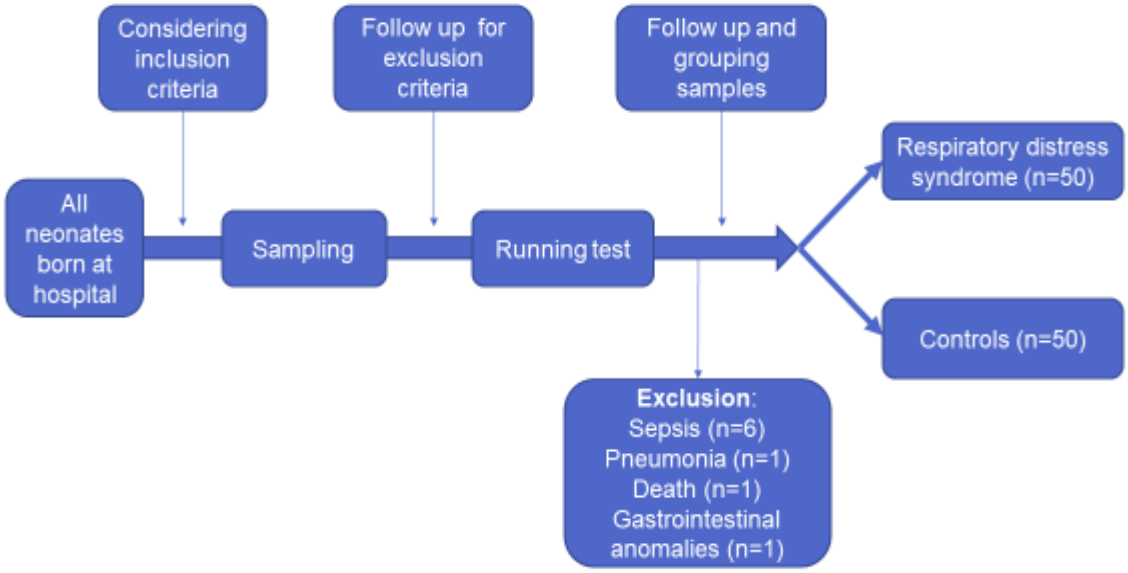

Figure 1. Methodology for data collection

score at birth, and underlying reason for NICU admission, were entered into the study checklist. The information was obtained from the newborn's medical record or by asking mothers.

In order to minimize the inter observer bias, the measurement was performed at the target laboratory of the Alzahra Hospital by trained independent technicians. All of the measurements were automatically carried out and presented. SPSS statistical software (version 25) was used for data analysis. The collected data were presented in the measured value, mean, percentage, and standard deviation. For statistical analysis, independent T-test, ANOVA, and Pearson's correlation coefficient were used. P-value of less than 0.05 was considered as a significant level.

Results

The present study was carried out on a total of 100 preterm neonates with a mean gestational age of 237.98±16.33 days and mean birth weight of 2106.25±600.41 g. The mean values of gestational age were 33±2 and 34±3 weeks in the case and control groups, respectively. Most (54%) of the studied population were males and delivered through cesarean section (96%). The serum protein and albumin levels of the total population were 4.83±0.67 and 3.24±0.34 gr/dl, respectively. Table 1 tabulates the demographic information of the studied population.

As shown in Table 2, there was a slight difference between the case and control groups regarding the average total protein and serum albumin. Both values were lower for the case group with an RDS diagnosis. However, statistical analysis did not indicate any significant differences between the control and case groups (Table 2) with p-values of higher than 0.05.

Table 1. Demographic information of study population

Variable		Frequency (n)	%
Gender	Female	46	46.0
	Male	54	54.0
Delivery type	Cesarean section	96	96.0
	Normal vaginal delivery	4	4.0
		Mean	Standard deviation
Total protein		4.83	0.67
Albumin		3.24	0.34
Gestational age (day)		237.98	16.33
Weight (g)		2106.25	600.41

The total serum protein and albumin levels were not statistically different between the females and males and healthy preterm newborns and RDS newborns (P>0.05). We observed that maternal age affected both total serum protein (P<0.001) and albumin (P=0.003) levels among the healthy preterm newborns. The neonates born from over 31-year-old mothers had significantly higher levels of total serum protein and albumin. Similar patterns were not observed for the newborns with the diagnosis of RDS (P>0.05; Table 3).

Pearson's correlation test showed a significant correlation between the neonatal age at birth and levels of both total protein and albumin. In this regard, by the increase in age, both measured

Table 2. Comparison of total protein and albumin levels in case and control groups

	Group	n	Mean	Standard deviation	Standard error of mean	P-value
Total protein	Normal	50	4.92	0.65	0.09	0.16
	RDS	50	4.73	0.67	0.09	
Albumin	Normal	50	3.27	0.36	0.05	0.27
	RDS	50	3.20	0.32	0.05	

RDS: Respiratory distress syndrome

Table 3. Comparison of total serum protein and albumin levels between case and control groups considering gender and maternal age

Group	Variable	Group	n	Mean	Standard deviation	Standard error of mean	P-value
Normal	Total protein	Male	24	4.97	0.81	0.17	0.63
		Female	26	4.88	0.46	0.09	
	Albumin	Male	24	3.33	0.43	0.09	0.27
		Female	26	3.22	0.28	0.05	
RDS	Total protein	Male	22	4.74	0.69	0.15	0.98
		Female	28	4.73	0.67	0.13	
	Albumin	Male	22	3.22	0.35	0.07	0.64
		Female	28	3.18	0.31	0.06	
Normal	Total protein	Maternal age<30 years	14	4.34	0.55	0.14	<0.001*
		Maternal age≥30 years	36	5.15	0.53	0.09	
	Albumin	Maternal age<30 years	14	3.04	0.39	0.10	0.003*
		Maternal age≥30 years	36	3.37	0.31	0.05	
RDS	Total protein	Maternal age<30 years	21	4.63	0.74	0.16	0.37
		Maternal age≥30 years	29	4.81	0.62	0.12	
	Albumin	Maternal age<30 years	21	3.20	0.35	0.08	0.90
		Maternal age≥30 years	29	3.19	0.32	0.06	

RDS: Respiratory distress syndrome
*P-value of less than 0.05

Table 4. Assessment of correlation of neonatal gestational age with total serum protein and albumin levels

Group			Total protein	Albumin
Healthy	Gestational age (week)	Pearson's correlation coefficient	0.49	0.40
		P-value	<0.001**	0.004**
	Birth weight (g)	Pearson's correlation coefficient	0.19	0.12
		P-value	0.18	0.41
	Maternal age (year)	Pearson's correlation coefficient	0.52**	0.32*
		P-value	<0.001*	0.03*
RDS	Gestational age (week)	Pearson's correlation coefficient	0.53	0.47
		P-value	<0.001**	0.001**
	Birth weight (g)	Pearson's correlation coefficient	0.25	0.26
		P-value	0.08	0.06
	Maternal age (year)	Pearson's correlation coefficient	0.18	-0.01
		P-value	0.21	0.95

RDS: Respiratory distress syndrome
* Significant at level of 0.05 (two-tailed)
** Significant at level of 0.01 (two-tailed)

indices increased; however, the correlation was more significant in the RDS group. The correlation between the total protein and albumin levels with the birth weight was also investigated. No statistically significant correlation was observed between the control and case groups (P>0.05). Further analysis of the correlation between maternal age and aforementioned indices represented a significant direct correlation among the healthy neonate; nevertheless, no relation was observed between maternal age with total protein and albumin levels among the RDS neonates as shown in Table 4.

Discussion

In the present study, there was no statistical difference regarding the total serum protein and albumin levels between the preterm neonates admitted with the diagnosis of RDS and healthy newborns. We also described the direct

association of measured indices with the gestational age in both the case and control groups. However, maternal age and birth weight did not affect the mentioned indices among the preterm RDS neonates.

Various studies have shown that hypoalbuminemia is associated with poor outcomes, such as mortality, morbidity, and prolonged intensive care unit (ICU) and hospital stay of critically ill adult patients (14). The number of studies assessing the values of albumin levels in pediatrics is limited, and the results were often contradictory. The results of some studies indicated that hypoalbuminemia is a common condition among children admitted to pediatric ICU but not associated with poor outcomes (15, 16). In contrast, other studies showed that albumin can be used as a predictive indicator of poor outcomes in critically sick children (17-20).

There have been studies assessing the association of albumin with several indices related to the prematurity. One study carried out on neonates with a birth weight of less than 1500 g showed a significant association between low serum albumin level and mortality in very low birth weight newborns but no association with morbidity, measured by intraventricular hemorrhage and necrotizing enterocolitis In the aforementioned study, the recorded albumin measurements were not realized at standardized times, with some measurements performed on the neonates with the gestational age of 1 week (21). Another study conducted on very preterm infants (24-31 weeks) showed a significant association between hypoproteinemia and severe adverse outcomes, such as mortality or severe neurological injury, on cranial ultrasound (12).

Cai et al. conducted a study on the 364 premature neonates and measured their albumin levels. They divided albumin levels into three categories of low, medium, and high. Their assessments showed significantly higher rates of RDS incidence among those with low levels of albumin than those reported for two other groups. Multiple logistic regression showed that albumin concentration on the first day of life was an independent predictor of mortality. They even presented that in the first day of life, an albumin level of 22.8 g/dl had 72% and 85% of sensitivity and specificity, respectively, for the prediction of neonatal mortality (22).

To confirm the findings of a study carried out by Cai et al., Tourer et al. conducted another study in Baskent University Hospital in Ankara, Turkey, on 199 preterm neonates under 32 weeks of gestation. They divided the newborns into three groups based on serum albumin levels. The mean serum albumin levels were 25.5±3.8, 30.1±2.7, and 35.3±3.7 g/l for < 25, 25-75, and > 75 percentile groups, respectively. They claimed that the prevalence of neonatal RDS, prevalence of neonatal sepsis, and mortality were significantly higher in the < 25 percentile group.

The albumin concentrations of lower than 27.2 g/l were associated with mortality, with 71% of sensitivity and 86% of specificity. They concluded that an increase in the permeability of alveolar capillaries and protein leakage in the alveolar space is responsible for a low level of proteinemia among the RDS neonates (13). Bland et al. presented the predictive values of cord proteins for the early diagnosis of RDS (23). Another investigation showed significant improvement in the serum albumin levels of those preterm neonates with RDS that recovered from respiratory distress (24).

In contrast to the results of the above-mentioned studies, in the present study, no significant correlation was observed between serum albumin and total protein among the two groups. This can be due to the fact that we obtained the samples immediately after birth from the cord blood, and they were influenced by the maternal condition or serum albumin level. In addition, the number of samples in the current study was limited to 50. However, considering the measurement of albumin and protein levels as a prediction method, it is required to perform similar investigations with a larger sample size.

The direct correlation of gestational age with the serum levels of proteins was identified in the present study. Similar observations have been reported by Li et al. (25) and Morris et al. (21). This can be due to hepatic maturity among the older neonates. The association of serum albumin with gestational age was demonstrated by Torer et al. in a study observing a significant relationship between the serum levels of albumin and mortality of preterm neonates (13). Confirmatory results were indicated by Yang et al. who assessed the value of albumin and prognosis of prematurity (26).

The present study identified a direct correlation between maternal age with serum total protein and albumin among the preterm newborns healthy at birth; however, this association was not observed for the RDS neonates. To the best of our knowledge, this issue has not been previously reported in other studies.

In summary, there were no statistical differences between the serum total protein and albumin of premature healthy newborns and those with RDS. Nevertheless, some studies have presented the significant role of albumin in prematurity complications. It is recommended to carry out further investigations in this regard. Furthermore, these measurements were not affected by gender and body weight at birth in both groups, while it was directly associated with the gestational age at the time of birth in both the RDS and normal cases.

Limitations

One of the limitations of this study was related to the sample size and insufficient number of patients for each week of gestational age which was too small to be generalized to the whole community. Other limitations included the difficulty in defining the accurate normal ranges of serum albumin and total protein in preterm neonates, lack of measuring total protein level in pregnant women to identify its effect on cord blood albumin, and limited access to patients for the follow-up to determine the outcomes. In this regard, it is required to perform further studies to investigate the factors potentially affecting the results.

Conclusion

No statistically significant difference was observed in total serum protein and albumin levels between the healthy preterm neonates and those diagnosed with RDS. The total serum protein and albumin levels were not affected by gender, birth weight, and maternal age among the RDS patients. However, they were directly associated with the gestational age at the time of birth in both the RDS and healthy neonates. A direct correlation was observed between maternal age with serum total protein and albumin among the healthy preterm newborns which was reported for the first time in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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