Original article

Value of Serum Albumin Level in Assessment of Severity of Acute Bronchiolitis Assessed by Modified Tal Score

Mohamed M. Rashad [a], Yasser M. Ismail [b], Yahia T. Alshafie [a], Heba R. Abdelbaset [a]

[a] Department of Pediatrics, Faculty of Medicine Benha University, Egypt. [b] Department of Clinical and Chemical Pathology, Faculty of Medicine Benha University, Egypt.

Corresponding to: Yahia T. Alshafie, Department of Pediatrics, Faculty of Medicine Benha University, Egypt.

Email:
01202988762y@gmail.com

Abstract

Background: Acute bronchiolitis is the inflammation of the bronchioles, which is most typically caused by a virus and is common in children under the age of two. The aim of this study was to evaluate if serum albumin levels on admission are associated with severity of illness in infants with Acute bronchiolitis according to their Modified Tal score. **Methods:** This single-center, case control observational study included 50 infants with acute bronchiolitis and 50 healthy infants as a control group. All cases were subjected to full history taking, complete clinical examination, modified Tal score and laboratory investigations as complete blood count, arterial blood gases, C reactive protein and serum albumin level. **Results:** Bronchiolitis group included 26 females and 24 males; their mean age was 7.5±4.8 months. There was no statistical difference between cases and control regarding their age, sex, gestational age, nutritional history or age of weaning. Most cases (42%) had mild disease, 38% of cases had moderate disease and 20% of cases had severe disease. Bronchiolitis group had statistically higher serum albumin compared to control group. Cases with severe bronchiolitis had statistically lower albumin level compared with moderate and mild cases. Serum albumin could detect cases with acute bronchiolitis from controls; AUC was 0.724 (CI: 0.626-0.822), p<0.001 and detect severe cases with acute bronchiolitis; AUC was 1, p<0.001. **Conclusion:** Serum albumin levels can be an objective, inexpensive and widely available biomarker to use in conjunction with the current clinical scores to diagnose and to assess severity of the disease

Key words: Serum Albumin; Acute Bronchiolitis; Modified Tal Score; severity

Introduction

Acute bronchiolitis is the inflammation of the bronchioles, which is most typically caused by a virus and is common in children under the age of two. The disease is distinguished by its regularity of incidence, which is highest during the winter months of November to March (1). A subcommittee of the American Academy of Pediatrics 2006 together with the European Respiratory Society (ERS) defined acute bronchiolitis

693

(AB) as a constellation of clinical symptoms and signs including a viral respiratory prodrome followed by increased lower respiratory effort and wheezing in infants <2 years of age with a peak in infants aged 3-6 months. It is a self-limiting condition but may be severe and life-threatening (2).

Bronchiolitis is the most common lower respiratory tract infection in children less than 1 year of age and is usually of viral etiology (3). It is the most common cause of hospital admission for infants beyond the neonatal period (4).

Bronchiolitis is characterized clinically by expiratory breathing difficulties in babies, while cough, tachypnea, hyperinflation, chest retraction, broad crackles, and wheezing are several untypical symptoms. The disease has a diverse and complex clinical course, whose symptoms can range from mild to severe and quickly lead to respiratory failure. Therefore, pediatric patients need to be diagnosed early and treated promptly to avoid mortality (5).

Albumin is a 69kDa protein that is mainly synthesized by the liver and plays an important role in several physiological mechanisms. It has long been well established that hypoalbuminemia is a powerful prognostic marker in the general population and many pathological settings, mainly as a result of malnutrition and inflammation (6).

During severe AB a reduced energetic intake, impaired nutritional status and an inflammation with a cytokine-mediated acute phase response can coexist, leading to lowered levels of serum albumin. However, the association between albumin and AB severity has been little investigated in this setting (7).

The aim of this study was to evaluate if serum albumin levels on admission are associated with severity of illness in infants with Acute bronchiolitis according to their Modified Tal score.

Methods

This single-centre, case control observational study included 50 infants with acute bronchiolitis admitted to the Pediatric Department of Benha University Hospital and 50 age and sex matched, healthy control infants were selected from the outpatient clinic of Benha University Hospital from August 2021 to August 2022.

Inclusion criteria:

- All infants aged 2 - 24 months admitted in the Pediatric Department with acute bronchiolitis.

- The diagnosis of AB was based on medical history, physical exam and chest radiography.

Exclusion criteria:

- Infants aged <2 months and >24 months.

- Patients previously diagnosed with malnutrition.

- Bacterial superinfection (based on CBC, CRB and chest radiography).

- Patients that received any intravenous fluids including albumin before the intervention.

Study groups;

- **Bronchiolitis group:** included 50 children and they were further divided according to their severity (assesses by modified Tal score (MTS)):

    1) **Severe bronchiolitis group**: included 10 patients with conditions deemed by the attending pediatrician and intensivist to merit pediatric intensive care unit (PICU) admission, MTS $\geq$ 11.

    2) **Moderate bronchiolitis group**: included 19 patients admitted in the classic hospital words, with MTS from 6-10

    3) **Mild bronchiolitis group**: included 21 patients admitted in the classic hospital words, with MTS $\leq$ 5.

- **Control group:** included 50 apparently healthy children matching the patient's groups for age & sex.

The study was approved by Ethical committee of Benha University. And an informed written consent was taken from parents or caregivers of enrolled children, after full explanation of the aim of the study.

All the infants were subjected to full medical and demographic history taking, complete clinical examination with assessment of modified Tal Score (8)**,** and laboratory Investigations: Complete blood count, Arterial blood gases, C reactive protein, serum albumin level and chest X-ray.

The Research Ethics Committee at Faculty of Medicine Banha University (REC-FOMBU) is independent organized committee operating according t

Approval code: **Ms - 10-8-2021**

<u>Statistical Analysis</u>

The collected data was revised, coded, tabulated using Statistical package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Data were presented and suitable analysis was done according to the type of data obtained for each parameter. Normality of data; Shapiro test was done to test the normality of data distribution. Descriptive statistics: Mean, Standard deviation ($\pm$ SD) for parametric numerical data, while Median and range for non-parametric numerical data. Frequency and percentage of non-numerical data. Analytical statistics: Student T Test was used to assess the statistical significance of the difference between two study group means. For the comparison of more than two groups' means, one way analysis of variance (ANOVA) was used. Chi-Square test was used to examine the relationship between two qualitative variables. Fisher's exact test was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells. Correlation analysis: To assess the strength of association between two quantitative variables. The correlation coefficient defines the strength and direction of the linear relationship between two variables. The ROC Curve (receiver operating characteristic) provides a useful way to evaluate the sensitivity and specificity for quantitative diagnostic measures that categorize cases into one of

two groups. The optimum cut off point was defined as that which maximized the AUC value. The area under the ROC curve (AUC) results were considered excellent for AUC values between 0.9-1, good for AUC values between 0.8-0.9, fair for AUC values between 0.7-0.8, poor for AUC values between 0.6-0.7 and failed for AUC values between 0.5-0.6.

Results

This study included 50 children with acute bronchiolitis and 50 healthy children as a control group.

Bronchiolitis group included 26 females and 24 males, their mean age was 7.5±4.8 months, there was no statistical difference between cases and control regarding their age, sex, gestational age, nutritional history or age of weaning. Table 1

Bronchiolitis group had statistically higher TLC, lymphocytes, C reactive protein and statistically lower neutrophils and serum albumin compared to control group. Table 2

Most cases (42%) had mild disease, 38% of cases had moderate disease and 20% of cases had severe disease, figure 1.

There was no statistical difference between mild, moderate or severe bronchiolitis as regarding to their age, sex, weight or nutritional history. Table 3

Severe cases had statistically higher C reactive protein, PCo2, and statistically lower PH, PO2 and serum albumin compared to mild and moderate cases. Table 4

Serum albumin correlates negatively with total leucocyte count, C reactive protein and PCo2, and correlates positively with Ph and PO2. While there were no statistical correlations between serum albumin and other parameters. Table 5

ROC analysis was done to assess the performance of serum albumin to detect cases with acute bronchiolitis from controls; AUC was 0.724 (CI: 0.626-0.822), p<0.001. At a cutoff point <3.8 g/dL, the sensitivity was 90% and specificity was 95%. Figure 2

ROC analysis was done to assess the performance of serum albumin to detect severe cases with acute bronchiolitis; AUC was 1, p<0.001. At a cutoff point <3.8 g/dL, the sensitivity was 100% and specificity was 95%. Figure 3

Table 1: Sociodemographic data of the studied groups

		Bronchiolitis group N=50	%	Control group N=50	%	Test	P value
Sex	**Female**	26	52.0%	22	44.0%	X^2=0.64	0.42
	Male	24	48.0%	28	56.0%		
Age (months)	**Mean ±SD**	7.5±4.8		8.5±4.1		t=1.9	0.063
	Range	2-22		2-24			
Gestational age (weeks)	**Mean ±SD**	37.5±1.1		37.7±1.1		t=0.45	0.58
	Range	36-40		36-40			
Weight (kg)	**Mean ±SD**	7.7±2.4		8.1±2.5		t=2.01	0.059
	Range	4.4-13		4.6-13.2			
Nutritional history	**Breast feeding**	25	50.0%	28	56.0%	X^2=0.37	0.83
	Artificial feeding	1	2.0%	1	2.0%		
	Breast + artificial	24	48.0%	21	42.0%		
Age of weaning (months)	**Mean ±SD**	5.1±0.8		4.9±0.9		t=1.5	0.13
	Range	4-6		4-6			

X^2: Chi-square test, t: student t-test,

Table 2: Laboratory investigations of the studied groups

		Bronchiolitis group N=50	%	Control group N=50	%	Test	P value
Hemoglobin (g/dl)	**Mean ±SD**	10.8±1.3		10.9±1.2		t=0.27	0.87
	Range	8.4-13.6		8.5-13.8			
TLC (10^3/uL)	**Mean ±SD**	11.9±2.8		9.7±2.5		t=3.9	**<0.001***
	Range	6.6-16.7		5.8-14.6			
Neutrophils (%)	**Mean ±SD**	32.8±6.9		38.5±6.7		t=4.1	**<0.001***
	Range	18.7-52.3		25.4-59.3			
Lymphocytes (%)	**Mean ±SD**	59.8±7.5		53.6±7.2		t=4.2	**<0.001***
	Range	41.6-74.4		33.6-69.1			
Platelets (10^3/uL)	**Mean ±SD**	350±112		344±102		t=0.29	0.77
	Range	156-609		168-565			
C-reactive protein (mg/dl)	**Mean ±SD**	24.6±12.3		7.5±2.4		t=5.1	**<0.001***
	Range	0-24		0-12			
C-reactive protein	**Negative**	20	40.0%	42	84.0%	X^2=26.4	**<0.001***
	Positive	30	60.0%	8	16.0%		
Serum albumin (g/dl)	**Mean ±SD**	4.2±0.69		4.7±0.4		t=5.1	**<0.001***
	Range	2.9-5.3		3.9-5.4			

X2; Chi-square test, t: student t-test, *: significant, TLC: Total leucocyte count

Table 3: Sociodemographic data according to disease severity

		Severity						Test	P value
		Mild		Moderate		Severe			
		N=21	%	N=19	%	N=10	%		
Sex	Female	11	52.4%	10	52.6%	5	50.0%	X^2=0.34	0.78
	Male	10	47.6%	9	47.4%	5	50.0%		
Age (months)	Mean ±SD	7±5		9±6		5±2		F=1.8	0.17
Weight (kg)	Mean ±SD	7.69±2.35		8.31±2.74		6.83±1.64		F=1.2	0.29
Gestational age (weeks)	Mean ±SD	38±1		38±1		38±1		F=0.44	0.64
Nutritional history	Breast feeding	10	47.6%	10	52.6%	5	50.0%	X^2=4.2	0.37
	Artificial feeding	0	0.0%	0	0.0%	1	10.0%		
	Breast + artificial	11	52.4%	9	47.4%	4	40.0%		

X^2: Chi-square test, F: F value of one-way ANOVA

Table 4: Laboratory investigations according to disease severity

	Severity			Test	P value
	Mild Mean±SD	Moderate Mean±SD	Severe Mean±SD		
HB (g/dl)	11.31±1.23	10.78±1.48	10.46±1.34	F=1.5	0.22
TLC (10^3/uL)	11.82±3.12	11.35±2.43	13.17±2.60	F=1.4	0.24
PLT (10^3/uL)	379±118	317±95	352±122	F=1.3	0.27
Neutrophils (%)	31.3±5.8	34.8±7.7	32.1±6.8	F=1.08	0.37
Lymphocytes (%)	61.3±7.5	58.1±7.6	60.2±7.3	F=1.1	0.34
C-reactive protein(mg/dl)	5±3	7±4	17±7	F=21.3	**<0.001***
PH	7.38±0.02	7.34±0.02	7.21±0.03	F=17.6	**<0.001***
PO2 (mmHg)	47±5	45±4	32±1	F=53.9	**<0.001***
PCo2 (mmHg)	40±2	45±2	57±5	F=136.5	**<0.001***
HCO3 (mmol/L)	19.0±1.8	19.6±1.7	18.6±2.0	F=1.3	0.28
Serum Albumin level (g/dl)	4.85±0.21	4.12±0.22	3.08±0.12	F=274.2	**<0.001***

F: F value of one-way ANOVA, *: significant

Table 5: Correlations between serum albumin and other clinical parameters

	Serum Albumin level (g/dL)	
	r	P value
Age (months)	0.137	0.173
Weight (kg)	0.168	0.094
Gestational age (weeks)	0.035	0.732
Age of weaning (months)	-0.103	0.403
Hemoglobin (mg/dl)	0.117	0.250
Total leucocyte count (10^3/uL)	-0.200	**0.046***
Neutrophils (%)	0.119	0.238
Lymphocytes (%)	-0.135	0.179
Platelets (10^3/uL)	0.026	0.797
C-reactive protein (mg/dl)	-0.580	**<0.001***
PH	0.696	**<0.001***
PO2 (mmHg)	0.609	**<0.001***
PCo2 (mmHg)	-0.809	**<0.001***
HCO3 (mmol/L)	0.174	0.085
Total score	-0.738	<0.001*

r: Correlation coefficient, *: significant
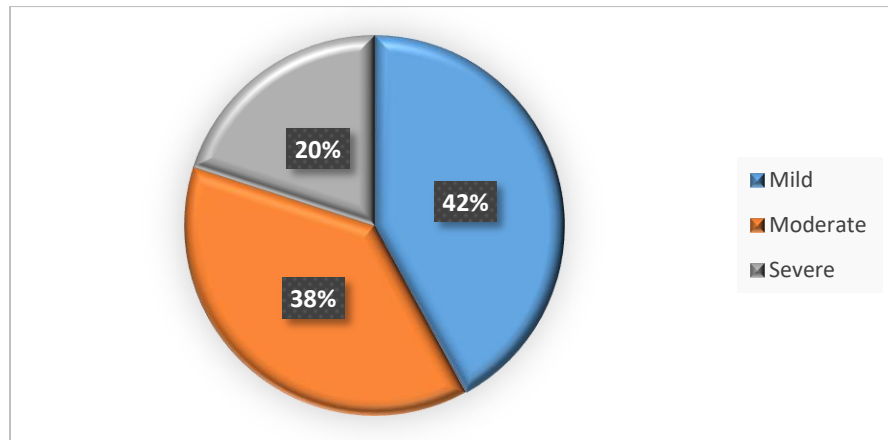
Figure 1: Disease severity in the bronchiolitis group
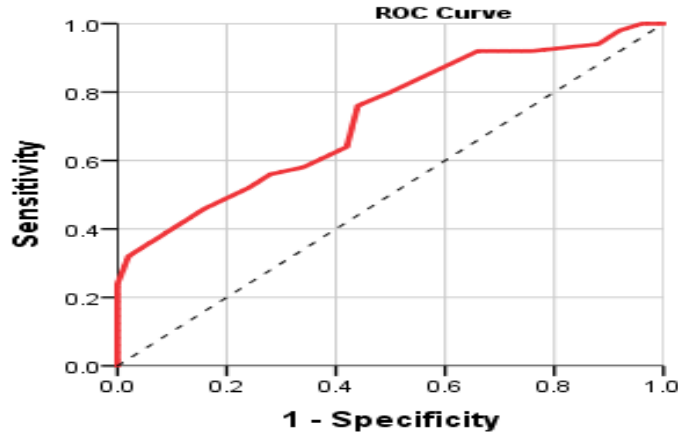
Figure 2: ROC curve of the performance of serum albumin to detect cases with acute bronchiolitis.
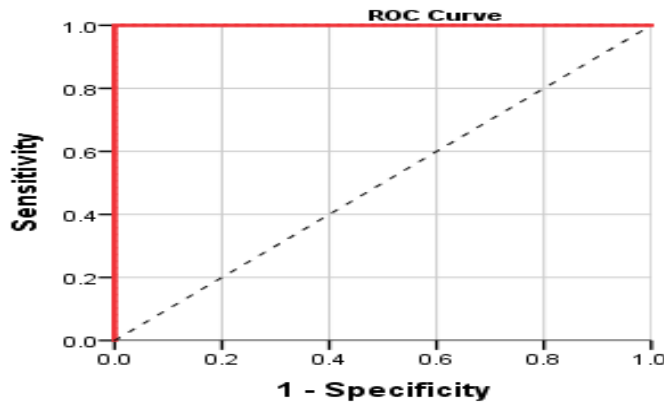

Figure 3: ROC curve of the performance of serum albumin to detect severe cases with acute bronchiolitis.

Discussion

In the current study, the bronchiolitis group had significantly lower pH, PO_2, HCO_3 and higher PCO_2 compared to the control group. In addition, the bronchiolitis group had significantly higher TLC, lymphocytic count, C-reactive protein and significantly lower neutrophil count and serum albumin compared to the control group.

Our results were in the same line with a study reported that in bronchiolitis, levels of pH, PO_2, HCO_3 and O_2 saturation were significantly decreased (p<0.0001), while

PCO_2 was increased as compared to normal group (9).

In the present study, there was no statistical difference between mild, moderate or severe bronchiolitis as regarding to their age, sex, weight or nutritional history.

Our results were in agreement with a study, where patients were divided into two groups, severe bronchiolitis (85 patients) and mild-moderate bronchiolitis (355 patients) (10). No difference was determined between the two groups

regarding their sex. In contrast to a study found that 61% of the patients assessed as severe bronchiolitis and given respiratory support with CPAP or MV were boys, and 39% were girls (11). Similarly, another study investigated risk factors for severe bronchiolitis in the emergency department and observed that 60.5% of severe bronchiolitis patients were boys (12).

Regarding age; Our results were agreed with a study, as the mean age of the patients with severe bronchiolitis was 6.50 months, and that of the mild-moderate bronchiolitis cases was 6.07 months, but the difference not statistically significant (10). Similarly, a study reported a mean age of 6.60 months in the patients of severe bronchiolitis, but with no significant difference compared to the control group (12).

However, a study found a significantly higher requirement for mechanical ventilation in the first six months, especially in patients younger than two months, compared to the control group (11). In a study of risk factors for respiratory decompensation, it was reported that a mean age of 4.2 months in a group developing respiratory failure and 7.2 months in a group with no respiratory failure. The difference was statistically significant. The authors also identified age less than six months as a significant predictor of respiratory decompensation (13).

Regarding weight; Our results were matched with a study that found no statistically significant difference in weight-for-age z-scores between groups developing and not developing respiratory failure (13).

Regarding history of breast feeding; our results were consistent with a study which reported that the history of breastfeeding was present only in 74.1% of the severe bronchiolitis group, and in 75.2% of the mild-moderate group with no statistically significant difference were between the two groups (10). Similarly, a research found history of breastfeeding in 57% of the patients of severe bronchiolitis and in 61% of the control group, but the difference was not statistically significant (11). However, In a study of the severity of respiratory syncytial virus (RSV) infection and breastfeeding, it was determined that a more severe clinical course among non-breastfed young infants, and reported that breastfeeding exhibited a protective effect (14).

Regarding gestational age; our results were consistent with a study which reported that mean gestation in the severe bronchiolitis group in the present study was 38.2 weeks, compared to 38.3 weeks in the mild-moderate bronchiolitis group (10). The difference was not significant (p=0.602). Similarly, another study investigated that risk factors for intensive care requirements among children with bronchiolitis and determined a mean gestation period of 37.9 weeks in a group followed-up in intensive care and of 38.2 weeks in a control group, the difference not being significant (15). However, a study reported a mean gestation time of 35.8 weeks in cases requiring mechanical ventilation support compared to 38 weeks in a control group, the difference being statistically significant (16).

In the current study, cases with severe bronchiolitis had statistically lower

albumin level compared with moderate and mild cases.

Our results were comparable with a study reported that the patients with severe AB presented lower serum albumin levels at admission than those without severe illness (3.7 (0.11) g/dl vs 4 (0.5) g/dl; p=0.034). The patients with serum albumin <3.5 g/dl presented a five-fold risk of PICU admission (OR 5.5 (CI95% 1-55-19); p =0.008). After adjusting for potential confounders (age, weight for age, presence of comorbidity, BROSJOD score, respiratory acidosis and CRP) in a multivariate logistic regression analysis, serum albumin level less than 3.5 g/dl remained independently associated with a higher risk of severe AB (a OR 4.1 (1.2-24); p = 0.032) (7).

In the same way, a study reported that low serum albumin level appeared to be associated with increased risk of apnea in patients with acute bronchiolitis after adjustment for known apnea risk factors (young age, preterm birth, and weight-for-age z score) (11).

The mechanism leading to low albumin levels in bronchiolitis is uncertain. One possibility is decreased synthesis of albumin. Although poor nutrition is commonly considered the main origin of hypoalbuminemia, not all malnourished individuals had low albumin levels. Another possible mechanism of low serum albumin would be increased losses in urine or stool, or increased breakdown of albumin. Another potential mechanism for the low serum albumin levels is the inflammatory process associated with viral infections, specifically neurogenic inflammation(6).

In the present study, serum albumin level showed significant positive correlations with pH and PO_2 and significant negative correlations with total leucocyte count, CRP and PCO_2. In addition, serum albumin correlated negatively with the total modified Tal score and all its parameters. However, there were no significant correlations between serum albumin and other parameters.

Our results were partially agreed with a study which reported that serum albumin displayed a significant correlation with CRP (r_s=-0.27; p =0.008), PCO2 (r_s=-0.32; p=0.003), and HCO3 (r=-0.24; p=0.029) levels. However, in contrast to our results they observed that serum albumin level had significant negative correlations with age (r_s=0.50; p <0.001) and weight for age percentile (r_s=0.33; p= 0.002) (7).

The positive correlation observed between the age and the serum albumin level has been previously recognized in neonates and small infants (17), Malnutrition and inflammation are considered to play a major role in occurrence of hypoalbuminemia (18).

Although hypoalbuminemia has traditionally been linked to malnutrition, we observed that body weight didn't correlate with the serum albumin level. So, hypoalbuminemia is not considered a specific nutritional marker in our patients. Moreover, patients previously diagnosed with malnutrition were excluded from our study. We think that inflammation could play a key role in the occurrence of hypoalbuminemia in AB.

Decreased serum albumin develops usually late during malnutrition. Serum albumin concentration is influenced by

various non-nutritional factors, impairing its validity as a nutritional parameter in patients who have acute-phase response and metabolic stress. Also, albumin is assumed to be a negative acute phase protein. Inflammation mediated by cytokines leads to decreased synthesis of albumin and causes albumin redistribution associated with increased capillary permeability (18). We think that the negative correlation between CRP and serum albumin level observed in our study suggests that hypoalbuminemia in AB is due to the acute inflammatory response.

The association of low serum albumin levels with high concentrations of inflammatory markers such as CRP, or IL-6 has been previously demonstrated in adults (19). Of note, among the inflammatory mediators that have been described to play an essential role in the Respiratory Syncytial Virus pathology are cytokines (20). Among these, the pro-inflammatory cytokine IL-6 is has been described to be critical for regulating disease severity during RSV infection in mice models, and has been related with the development of neurologic alterations in infants (21). Thus, it could be possible that the increase of inflammatory mediators such as IL-6 during AB leads to an increase in the hepatic production of positive acute phase reactants, such as CRP, while conversely decreasing the production of negative acute phase reactants such as albumin.

In the present study, ROC analysis was done to assess the performance of serum albumin in detecting cases with acute bronchiolitis. The AUC was 0.724 (CI: 0.626-0.822), p<0.001. At a cutoff point <3.8 g/dL, the sensitivity was 90% and

specificity was 95%. Also, ROC analysis was done to assess the performance of serum albumin in detecting severe cases with acute bronchiolitis. The AUC was 1, p<0.001. At a cutoff point <3.8 g/dL, the sensitivity was 100% and specificity was 95%.

Our results were in agreement with a study revealed that the ROC curve for serum albumin in predicting severe AB was generated, yielding an AUC of 0.70 (95% CI 0.59-0.79). A cut-off point of 3.5 g/dl presented a sensitivity of 71%, specificity of 68%, positive predictive value of 0.29, and negative predictive value of 0.92 (7).

Our study has some limitations; It was an observational relatively small sized and single centre study. Therefore, it may not be representative of the outcomes at other sites because of special circumstances such as physician quality, hospital features, different resources or hospitalization/PICU admission criteria. We did not investigate the trends in serum albumin level which could reveal more kinetic information and should be a subject of the further research.

However, this study approved the advantage of using serum albumin level for predicting bronchiolitis severity; it would be an objective, inexpensive and widely available biomarker to use in conjunction with current clinical scores to assess the disease severity.

Conclusion

Serum albumin decreases significantly in acute bronchiolitis. In addition, patients with severe bronchiolitis have statistically significant lower albumin levels compared with those having moderate or mild

disease. Serum albumin significantly correlates positively with blood pH and PO_2 concentration and negatively with the total leukocyte count, C-reactive protein and PCO_2. Serum albumin levels can be an objective, inexpensive and widely available biomarker to use in conjunction with the current clinical scores to diagnose and to assess severity of the disease.

References

1. Nguyen SN, Nguyen TNT, Vu LT, Nguyen TD. Clinical Epidemiological Characteristics and Risk Factors for Severe Bronchiolitis Caused by Respiratory Syncytial Virus in Vietnamese Children. Int J Pediatr. 2021;2021.

2. Abdel Baky A, Fouda EM, Hussein SM, Sobeih AA, Abd Al Razek AM, Hassanain AI, et al. Bronchiolitis diagnosis, treatment, and prevention in children: an evidence-based clinical practice guideline adapted for the use in Egypt based on the 'Adapted ADAPTE'Methodology. Egypt Pediatr Assoc Gaz. 2022;70(1):1–9.

3. Silver AH, Nazif JM. Bronchiolitis. Pediatrics in review. 2019;40:568-76.

4. Chung A, Reeves RM, Nair H, Campbell H. Hospital admission trends for bronchiolitis in Scotland, 2001–2016: a national retrospective observational study. J Infect Dis. 2020;222(Supplement_7):S592–8.

5. Bem RA, Bont LJ, van Woensel JBM. Life-threatening bronchiolitis in children: eight decades of critical care. Lancet Respir Med. 2020;8(2):142–4.

6. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: pathogenesis and clinical significance. J Parenter Enter Nutr. 2019;43(2):181–93.

7. Rodríguez-González M, Rodríguez-Campoy P, Estalella-Mendoza A, Estepa-Pedregosa L, Flores-González JC. Association of serum albumin levels with inflammation and clinical outcomes in children with acute bronchiolitis. Authorea Prepr. 2020

8. McCallum GB, Morris PS, Wilson CC, Versteegh LA, Ward LM, Chatfield MD, et al. Severity scoring systems: are they internally valid, reliable and predictive of oxygen use in children with acute bronchiolitis? Pediatr Pulmonol. 2013;48(8):797–803.

9. Mohamed MAE-G, Zayed KM. Impact of acute bronchiolitis on cardiac functions and serum microRNA-122 and 499. Am J Infect Dis. 2016;12(1):11–9.

10. Caliskan MN, Tekin M, Konca C. Determination of predictive risk factors for severe bronchiolitis. Int J Clin Pract. 2021;75(11):e14760.

11. Mansbach JM, Geller RJ, Hasegawa K, Espinola JA, Stevenson MD, Sullivan AF, et al. Association of serum albumin with apnea in infants with bronchiolitis: A secondary analysis of data from the MARC-35 study. JAMA Netw Open. 2019;2(7):e197100–e197100.

12. Robledo-Aceves M, de Jesús Moreno-Peregrina M, Velarde-Rivera F, Ascencio-Esparza E, Preciado-Figueroa FM, Caniza MA, et al. Risk factors for severe bronchiolitis caused by respiratory virus infections among Mexican children in an emergency department. Medicine (Baltimore). 2018;97(9).

13. Dadlez NM, Esteban-Cruciani N, Khan A, Douglas LC, Shi Y, Southern WN. Risk factors for respiratory decompensation among healthy infants with bronchiolitis. Hosp Pediatr. 2017;7(9):530–5.

14. Nishimura T, Suzue J, Kaji H. Breastfeeding reduces the severity of respiratory syncytial virus infection among young infants: A multi-center prospective study. Pediatr Int. 2009;51(6):812–6.

15. Coskun Y, Saglam Yarimcan F, Mamal-Torun M, Akman İ. Risk factors for intensive care need in children with bronchiolitis: A case-control study. 2017;

16. Semple MG, Taylor-Robinson DC, Lane S, Smyth RL. Household tobacco smoke and admission weight predict severe bronchiolitis in infants independent of deprivation: prospective cohort study. PLoS One. 2011;6(7):e22425.

17. Torer B, Hanta D, Yapakci E, Gokmen Z,

Parlakgumus A, Gulcan H, et al. Association of serum albumin level and mortality in premature infants. J Clin Lab Anal. 2016;30(6):867–72.

18. Eckart A, Struja T, Kutz A, Baumgartner A, Baumgartner T, Zurfluh S, et al. Relationship of nutritional status, inflammation, and serum albumin levels during acute illness: a prospective study. Am J Med. 2020;133(6):713–22.

19. Aksu U, Gulcu O, Aksakal E, Kalkan K, Öztürk M, Korkmaz AF, et al. The association between CRP/Albumin ratio and in-stent restenosis development in patients with ST-segment elevation myocardial infarction. J Clin Lab Anal. 2019;33(4):e22848.

20. Bohmwald K, Gálvez NMS, Canedo-Marroquín G, Pizarro-Ortega MS, Andrade-Parra C, Gómez-Santander F, et al. Contribution of cytokines to tissue damage during human respiratory syncytial virus infection. Front Immunol. 2019;10:452.

21. Vázquez Y, González L, Noguera L, González PA, Riedel CA, Bertrand P, et al. Cytokines in the respiratory airway as biomarkers of severity and prognosis for respiratory syncytial virus infection: an update. Front Immunol. 2019;10:1154.