Türk Kadın Sağlığı ve Neonatoloji Dergisi

To cite this article: Ulubas Isik D, Kavurt S, Aydemir O, Bas AY, Demirel N. Serum ischemia-modified albumin levels in neonatal sepsis and septic shock. Turk J Womens Health Neonatol 2020; 2(1): 7-12

Original Article

Serum ischemia-modified albumin levels in neonatal sepsis and septic shock

Neonatal sepsis ve septik şokta serum iskemi modifiye albümin düzeyleri

Dilek Ulubaş Işık*[1], Sumru Kavurt[1], Özge Aydemir[2], Ahmet Yağmur Baş[3], Nihal Demirel[3]

[1]Department of Neonatology, Etlik Zubeyde Hanim Women's Health Teaching and Research Hospital, University of Health Sciences,Ankara

[2]Department of Neonatology, Osmangazi University Faculty of Medicine, Eskisehir,

[3]Department of Neonatology, Yildirim Beyazit University Faculty of Medicine, Ankara

Abstract

Aim: Neonatal sepsis is the most common cause of morbidity and mortality. Serum ischemia-modified albumin (IMA) is a specific and sensitive marker for ischemic conditions. We aimed to investigate IMA levels in neonatal sepsis and its relation to disease severity.

Material and Method: A prospective controlled study was conducted in a tertiary neonatal intensive care unit (NICU) between March 2012 and December 2012. Neonates diagnosed with sepsis younger than 28 days' postnatal age were enrolled. Serum IMA levels with blood culture, C- reactive protein (CRP) complete blood count, and peripheral smear were obtained at the time of diagnosis. Clinical data, clinical risk index for babies (CRIB), and pediatric logistic organ dysfunction score (PELOD), septic shock, and prognosis were recorded.

Results: 39 patients and 22 healthy controls were enrolled. Mean gestational age (GA) and birth weight (BW) of patients were 30.1 ± 4.2 weeks and 1257 ± 474 g, respectively. Serum IMA levels were significantly higher in patients compared to controls (p=0.04). Serum IMA levels were higher in patients with septic shock (n=8) compared to patients without shock (n=31), but the difference was not statistically significant (p=0.348). Serum IMA levels were correlated CRIB score (p=0.008, rho=0.337), white blood count (WBC) (p=0.008, rho=0.419) and absolute neutrophil count (ANC) (p=0.006, rho=0.429).

Conclusion: Serum IMA levels were significantly higher in septic neonates. However, there was no significant difference between neonates with septic shock and without shock. Serum IMA levels may be useful in neonatal sepsis at the time of diagnosis. Further studies are needed for predicting disease severity in a larger group of septic neonates.

Key words: ischemia-modified albumin; newborn; sepsis

Corresponding author*: Dilek Ulubaş Işık, University of Health Sciences Etlik Zubeyde Hanim Women's Health Training and Research Hospital, Neonatal Intensive Care Unit, Yeni Etlik Caddesi 55, Etlik, 06010, Ankara, TURKEY
e-mail: dilekulubas@yahoo.com
ORCID: 0000-0001-9937-4624
Received: 22.02.2020 Accepted: 25.03.2020

Öz

Amaç: Yenidoğan sepsisi en sık görülen morbidite ve mortalite nedenidir. Serum iskemi modifiye albümin (IMA), iskemik durumlar için spesifik ve hassas bir belirteçtir. Bu çalışmada yenidoğan sepsisinde IMA düzeylerini ve hastalık şiddeti ile ilişkisini araştırmayı amaçladık.

Gereç ve Yöntem: Mart 2012 ile Aralık 2012 tarihleri arasında üçüncü basamak yenidoğan yoğun bakım ünitesinde (NICU) prospektif kontrollü bir çalışma yapılmıştır. Postnatal 28 günden küçük sepsis tanısı alan bebekler çalışmaya dahil edildi. Sepsis tanısında kan kültürü, C-reaktif protein (CRP) tam kan sayımı ve periferik yayma ile birlikte serum İMA düzeylerine bakıldı. Klinik veriler, bebekler için klinik risk indeksi (CRIB) ve pediyatrik lojistik organ disfonksiyon skoru (PELOD), septik şok ve prognoz kaydedildi.

Bulgular: Çalışmaya 39 hasta ve 22 sağlıklı kontrol dahil edildi. Hastaların ortalama gebelik haftası ve doğum ağırlığı sırasıyla 30.1 ± 4.2 hafta ve 1257 ± 474 gramdı. Hastalarda serum IMA düzeyleri kontrollere göre anlamlı olarak yüksekti (p=0.04). Septik şok tanısı alan hastalarda (n=8) serum IMA düzeyleri şok olmayan hastalara göre daha yüksekti (n =31), ancak fark istatistiksel olarak anlamlı değildi (p=0.348). Serum İMA düzeyleri, beyaz hücre sayısı (p=0.008, rho=0.419), mutlak nötrofil sayısı (p=0.006, rho=0.429) ve CRIB skoru (p=0.008, rho=0.337) ile korelasyon gösterdi.

Sonuç: Sepsisli yenidoğanlarda serum İMA düzeyleri anlamlı olarak yüksek bulundu. Bununla birlikte, septik şoku olan ve olmayan yenidoğanlar arasında anlamlı bir fark yoktu. Serum İMA düzeyleri yenidoğan sepsis tanısında yararlı olabilir. Hastalığın şiddetini tahmin etmede kullanılabilmesi için sepsis tanısı olan daha çok sayıda yenidoğanda yapılan çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: İskemi modifiye albumin; yenidoğan; sepsis

Introduction

Neonatal sepsis is a systemic inflammatory response syndrome that is secondary to infection. Sepsis is a significant cause of morbidity and mortality in newborns (1). While the mortality rate among full-term infants is approximately 3%, the mortality rate in preterm infants is as high as 30% to 54% (2, 3). The presence of acute organ dysfunction characterizes severe sepsis. Cardiac failure and hypoperfusion are observed in nearly half of the infants with sepsis. Inadequate tissue perfusion is the most important event leading to morbidity and mortality in sepsis (4). Progressive tissue hypoperfusion associated with generalized inflammation and endothelial activation can occur before the development of hypotension (5).

Ischemia-modified albumin (IMA) is generated due to the modification of the N-terminus cobalt binding sites of the albumin by the effect of released free radicals from ischemic tissues. IMA is a specific and sensitive marker for an ischemic process (6). It is well known that IMA rises within minutes from the onset of the ischemic event and remains elevated for several hours after cessation of ischemia. It was first described as a new biomarker in myocardial ischemia (7). However, current studies suggest it as a marker for the early diagnosis of oxidative stress in different clinical conditions such as chronic kidney disease, hyperlipidemia, and diabetes (8-10). The high serum IMA levels have been detected in newborns with perinatal asphyxia, necrotizing enterocolitis, severe fetal hypoxia, neonatal sepsis, anemia of prematurity, and transient tachypnea (11-16). The inflammation reduces the binding capacity of albumin to cobalt, resulting in higher IMA levels (8, 17). We hypothesized that septic neonates had elevated IMA levels associated with inflammation and perfusion failure. This study aims to investigate IMA levels in neonatal sepsis and their relation to severe sepsis and prognosis.

Material and method

A prospective controlled study was conducted in a tertiary neonatal intensive care unit between March 2012 and December 2012. Term and preterm infants diagnosed with sepsis younger than 28 days' postnatal age were enrolled. Postnatal age-matched healthy infants were taken as controls. Patients and controls were enrolled in the same period. Exclusion criteria were determined as major congenital anomalies, perinatal asphyxia, hemodynamically significant patent ductus arteriosus, and surgery last week. The local Ethics Committee approved the study. Informed consent was obtained from the parents.

i. Definitions

Neonates with two or more of the following clinical features were evaluated for sepsis: a) Respiratory deterioration (tachypnea, apnea, increased ventilatory support); b) Cardiovascular deterioration (bradycardia, pallor, decreased perfusion or hypotension); c) Metabolic disturbances (hypoglycemia, hyperglycemia, metabolic acidosis); d) Temperature irregularities (hypothermia, hyperthermia); e) Feeding intolerance; f) Neurologic deterioration (lethargy, hypotonia, decreased activity). All infants with suspected sepsis were evaluated with laboratory tests, including complete blood count (CBC), peripheral blood smear, C-reactive protein (CRP), and blood culture. Laboratory criteria used as indicators of sepsis were as following: a) White blood cell (WBC) count >34.000/ mm^3 or <5000 /mm^3; b) Absolute neutrophil count (ANC) <1500/ mm^3or >14.500/ mm^3; c) Immature /total neutrophil ratio >0.2; e) Platelet count <100.000/ mm^3; f) CRP >10 mg/dl. In addition to clinical criteria, if two or more laboratory abnormalities were present, the infant was diagnosed as sepsis. The proven sepsis in patients with positive blood culture was considered. Patients with negative cultures were considered as clinical sepsis.

Severe sepsis with septic shock and organ dysfunction was defined according to the criteria described in the 2005 International Consensus Conference on Pediatric Sepsis (18). Septic shock was defined as sepsis with cardiovascular dysfunction despite the administration of isotonic intravenous fluid bolus >40 mL/kg in 1 hour. Cardiovascular dysfunction was described as the presence of hypotension (<5th percentile for age or systolic blood pressure <2 SD below normal for age) or need for a vasoactive drug to maintain blood pressure in the normal range or at least two of the following conditions: unexplained metabolic acidosis (base deficit> 5 mEq/L), elevated arterial lactate (>2 times upper limit of normal), oliguria (urine output <0.5 mL/kg/h), prolonged capillary refill (>5 sec.), core to peripheral temperature gap >3°C. Multiorgan dysfunction syndrome (MODS) was defined as more than two organ dysfunctions.

ii. Measurements

Venous blood samples for IMA were obtained within 24 h of sepsis diagnosis. Samples were centrifuged at 5000 rpm for 10 min and stored at -80 °C until analysis. Serum IMA levels were measured by a colorimetric assay developed by Bar-Or et al. (19) based on the measurement of unbound cobalt after incubation with the patient's serum. Increased amounts of IMA results in less cobalt binding and more residual unbound cobalt available for complex with a chromogen (dithiothretiol-DDT), which can be measured photometrically. The procedure was as follows: 50 µL of 0.1% cobalt chlorides was added to 200 µL of serum, gently mixed, and waited for 10 min for adequate cobalt-albumin binding. Then, 50 µL of DDT, at a concentration of 1.5 mg/ml, was added as a colorizing agent, and the reaction was stopped 2 min later by adding 1.0 mL of 0.9% NaCl. The colored product was measured at 470 nm and compared to a serum–cobalt blank without DTT and reported in absorbance units (ABSU).

Adjusted IMA was calculated as (individual serum albumin concentration/median serum albumin concentration of the population) x IMA value. The correct IMA values for serum albumin (median serum albumin concentration of each group of the subjects were used separately) were obtained by this formula (20).

iii. Clinical data and outcome measures

Clinical data, clinical risk index for babies (CRIB) score, pediatric logistic organ dysfunction score (PELOD), presence of septic shock, MODS, and death were recorded. Laboratory data, including blood gases, WBC, CRP, and culture results, were also recorded. The primary outcome was the difference in serum IMA levels between infants with sepsis and healthy controls. Secondary outcomes were the association of IMA with CRIB and PELOD score, measures of organ dysfunction, markers of inflammation, and clinical outcome.

iv. Statistical analysis

Statistical analyses were conducted using SPSS version 17.0 (SPSS Inc., Chicago, IL). Data are expressed as numbers (n), frequencies (%), medians with minimum-maximum values, and mean ± standard deviation. Student t-test and Mann-Whitney u test were used to compare continuous parametric and nonparametric variables. The chi-square ($\chi 2$) test was used to compare categorical variables. Spearman and Pearson's correlation coefficients were used for nonparametric and parametric data, respectively. Differences were considered significant at a probability level of $p<0.05$.

Results

Thirty–nine neonates with sepsis and 22 healthy controls were enrolled. There were no statistical differences regarding demographic characteristics between the groups (**Table 1**). Mean gestational age and birth weight of the study group patients were 30.1 ± 4.2 weeks and 1257 ± 474 g, respectively. Three patients had MODS. Six of the patients with sepsis died.

Table 1. Demographic, clinical characteristics and IMA levels of the study and control groups

	Sepsis (n=39)	Control (n=22)	p values
Gestational age (week)*	30.1± 4.2	29.6 ± 2.4	0.75
Birth weight (g)*	1257 ± 474	1514 ± 818	0.764
APGAR **	8 (5-9)	8 (6-9)	0.912
Gender (F/M)	23/16	11/11	0.595
Cesarean section, n (%)	30 (76)	17 (77)	0.163
Postnatal age (days) **	9 (1-25)	12 (1-28)	0.099
Length of stay in NICU (days)**	25 (1-98)	34 (1-75)	0.121
RDS, n (%)	24 (%6.5)	13 (%59.5)	0.852
PDA, n (%)	10 (%25.6)	2 (%9.1)	0.182
IVH (n, %)	2(%5.1)	1(%4.5)	0.92
CRIB**	3 (0-12)	1 (0-4)	**0.021**
IMA (ABSU)*	0.89 ± 0.62	0.54 ± 0.37	**0.04**
Adjusted IMA (ABSU)*	0.87 ± 0.63	0.55 ± 0.42	**0.031**

NICU: Neonatal intensive care unit, RDS: respiratory distress syndrome, PDA: Patent ductus arteriosus, IVH: Intraventricular hemorrhage, CRIB: clinical risk index for babies, IMA: ischemia modified albumin, ABSU: absorbance units, *The values are presented as mean ± Standard Deviation, **The values are presented as median (minimum-maximum), P<0.05: Statistically significant

Ten of patients (25%) were diagnosed as early-onset of neonatal sepsis, while 29 patients (75%) with sepsis were diagnosed late-onset of neonatal sepsis. Blood cultures were positive in 24 (61%) infants with sepsis, and cerebrospinal fluid (CSF) cultures were positive in two of them. Causative microorganisms were Gram-positives in eleven patients, namely Staphylococcus aureus (n=4), coagulase-negative Staphylococcus spp. (n=5), group B streptococcus (n=2), and Gram-negatives for 13 patients, namely Escherichia coli (n=5), Pseudomonas aeruginosa (n=2), Klebsiella spp. (n=3), Enterobacter aerogenes (n=2), and Citrobacter spp. (n=1).

Ischemia-modified albumin, and adjusted IMA levels were significantly higher in neonates with sepsis compared to controls (p=0.04, p=0.031) **(Table 1)**. The IMA levels were similar among patients with clinical and proven sepsis. Patients with Gram-positive sepsis and Gram-negative sepsis also had similar IMA levels.

There was no statistical difference for laboratory findings, including WBC, ANC, immature/total neutrophil ratio, and CRP in septic infants with shock (n=8) and without shock (n=31) (**Table 2**). Median platelet count was lower in septic infants with shock compared to septic infants without shock, and the difference was statistically significant (p=0.003). Clinical data for CRIB and PELOD scores were compared in the septic patients with shock and without shock. The PELOD clinical score was significantly higher in patients with septic shock compared to patients without septic shock (p=0.001). Serum IMA and adjusted IMA levels were similar in patients with and without septic shock (p=0.348, p=0.646). Serum IMA and adjusted IMA levels were higher in patients with late-onset sepsis compared to patients with early neonatal sepsis, the results were not statistically significant (p=0.459). Moreover, the IMA levels were similar in patients with early neonatal sepsis and controls (p=0.329).

Table 2: Clinical data, IMA levels and laboratory findings in infants with and without septic shock

	Infants without septic shock (n=31)	Infants with septic shock (n=8)	p values
WBC (/mm³)*	13,900 (740-67,600)	15,000 (2750-54,000)	0.728
ANC (/mm³)*	8000 (150-41,550)	4505 (360-32,100)	0.543
Immature/total neutrophil count**	0.22 ± 0.1	0.26 ± 0.09	0.196
Platelet count (/mm³)*	234,000 (12,000-420,000)	37,500 (12,000-189,000)	**0.003**
CRP (mg/dl)**	43.6 ± 31.8	45.3 ± 39.7	0.222
CRIB score**	3.48 ± 4.04	5.8 ± 3.4	0.06
PELOD score**	5.5 ± 6.6	23.5 ± 14.8	**0.001**
IMA (ABSU) **	0.81 ± 0.56	1.15 ± 0.82	0.348
Adjusted IMA (ABSU)**	0.83 ± 0.59	1.03 ± 0.79	0.317

WBC: White blood cells, ANC: Absolute neutrophil count, CRP: C- reactive protein, CRIB: clinical risk index for babies, PELOD: pediatric logistic organ dysfunction, IMA: ischemia modified albumin, ABSU: absorbance units, *Values were presented as median (minimum-maximum), **Values were presented as mean ±SD, P<0.05: Statistically significant

The IMA levels were similar in male and female infants and not correlated with GA, BW, postnatal age, and laboratory findings, including CRP, WBC, immature/total ratio, and PELOD score. IMA levels were correlated with the CRIB score (p=0.008, rho=0.337), WBC (p=0.008, rho=0.419) and ANC (p=0.006, rho=0.429).

The ROC (Receiver operating characteristic) analysis was performed for the confirmation of neonatal sepsis. IMA levels with a cutoff point of 0.45 ABSU seems to be an appropriate tool for the diagnosis of neonatal sepsis with a sensitivity of 71%, and specificity of 50% (AUC [area under the curve] =0.659; p=0.04 [asymptomatic 95%confidence interval = 0.520-0.798]).

Discussion

Albumin is the most abundant serum protein and is a powerful extracellular antioxidant. Ischemia-modified albumin is a modification of serum albumin that results from oxidative stress and concurrently produced superoxide radicals that appear during ischemic events. Oxidative stress plays a vital role in the pathogenesis of sepsis. In septic patients, inflammation and tissue hypoxia is the primary source to produce reactive oxygen species (15).

Initially, IMA has been reported as a marker for cardiac ischemia (7). Recent studies have demonstrated that IMA levels were also associated with other ischemic conditions such as liver cirrhosis, sepsis, brain ischemia, end-stage renal disease, and mesenteric ischemia in adult patients (21, 22).

Elevated cord blood levels of IMA have been determined in complicated deliveries with hypoxic-ischemic stress (12). Iacovidou et al. reported that cord blood IMA levels at term newborns did not differ between healthy and intrauterine growth-restricted infants. In this study, it was also reported that IMA levels were higher in cases of cesarean section compared to vaginal delivery. IMA levels of cord blood were not found to be correlated with gestational age or gender in the same study (23). In our study, male and female newborns had similar serum IMA levels, which were not correlated with GA and BW.

Recently, a few studies are reporting IMA levels in neonates associated with diseases causing ischemic-hypoxic events. In a study including neonates with necrotizing enterocolitis, higher serum IMA levels were reported. Besides, they reported that IMA levels were found to be superior to CRP and IL-6 in both diagnosis and follow-up (13). Elevated IMA levels were also determined in neonates with severe transient tachypnea (14). Yerlikaya et al. reported that serum IMA levels were increased in patients with late-onset neonatal sepsis and a decrease of IMA levels after treatment (15). Furthermore, it was reported that serum IMA level is a useful marker in neonatal sepsis at the time of diagnosis (24). Similar to these findings, in the present study, we demonstrated higher serum IMA levels in patients with neonatal sepsis compared to controls, but we did not find any significance in patients with early neonatal sepsis. However, this is the first study comparing the IMA levels according to the severity of sepsis in the neonatal period. Serum IMA levels were higher in neonatal sepsis with septic shock, but the difference was not statistically significant. A small number of cases with septic shock can explain this finding.

Early neonatal morbidity and mortality are greatly affected by neonatal sepsis and the following septic shock. Sepsis is the cause of 30-50% of total neonatal mortality every year in developing countries (25). Early recognition and treatment of neonatal sepsis are essential for prognosis. The diagnosis of sepsis may be delayed in newborns due to the absence of specific clinical signs and symptoms (26). In addition to blood culture, typical diagnostic parameters include conventional laboratory tests that are routinely serum-based, such as WBC, ANC, I/T ratio, and CRP (27, 28). The other acute-phase proteins for diagnostic accuracy in neonatal sepsis had also been demonstrated, including serum amyloid A, procalcitonin, lipopolysaccharide-binding protein, mannose-binding lectin, and hepcidin. The serum IL-6, IL-8, IL-10, and TNF-α concentrations elevated before those of acute-phase reactants were detected in infants with sepsis. Biomarkers should assist in the prediction of disease of severity at the onset of infection and predict later prognosis with the therapy of neonatal sepsis (29). The present study demonstrated elevated IMA levels at the onset of sepsis, similar to previous studies.

There were several limitations in our study. Firstly, the blood samples were taken only on the first day of diagnosis, and the course of IMA levels during sepsis and after treatment were not evaluated. Secondly, the number of patients with septic shock and non-survivors was small, which might lead to type II statistical error. These may explain why we could not show a relation between IMA levels and the severity of the disease.

In conclusion, the results suggest that serum IMA levels might be a useful biomarker in neonatal sepsis at diagnosis. However, further studies are needed for predicting disease severity in a larger group of septic neonates.

Declaration of Interest

The authors report no conflict of interest.

References

1. Ethan G. Leonard, Katherine Dobbs. Postnatal Bacterial Infections. In: Martin RJ, Fanaroff AA, Walsh MC, editors. Fanaroff and Martin's neonatal-perinatal medicine: diseases of the fetus and infant. 10th ed. St. Louis (MO): Elsevier Mosby; 2015. 734-750.

2. Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928-2003. Pediatrics 2005; 116:595-602.
3. Stoll BJ, Hansen NI, Sánchez PJ, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. Pediatrics 2011; 127:817-826.
4. Kermorvant-Duchemin E, Laborie S, Rabilloud M, Lapillonne A, Claris O. Outcome and prognostic factors in neonates with septic shock. Pediatr Crit Care Med 2008; 9:186-191.
5. Nguyen HB, Rivers EP, Abrahamian FM, et al. Severe sepsis and septic shock: review of the literature and emergency department management guidelines. Ann Emerg Med 2006; 48:28-54.
6. Dominguez-Rodriguez A, Abreu-Gonzalez P. Current role of ischemia-modified albumin in routine clinical practice. Biomarkers 2010; 15:655-662.
7. Sinha MK, Roy D, Gaze DC, Collinson PO, Kaski JC. Role of "Ischemia modified albumin", a new biochemical marker of myocardial ischaemia, in the early diagnosis of acute coronary syndromes. Emerg Med J 2004; 21:29-34.
8. Kaefer M, Piva SJ, De Carvalho JA, et al. Association between ischemia modified albumin, inflammation and hyperglycemia in type 2 diabetes mellitus. Clin Biochem 2010; 43:450-454.
9. Kotani K, Caccavello R, Sakane N, Miyamoto M, Gugliucci A. Influence of ezetimibe monotherapy on ischemia-modified albumin levels in hypercholesterolemic patients. Pharmacol Rep 2011; 63:1248-1251.
10. Mehmetoglu I, Yerlikaya FH, Kurban S, Erdem SS, Tonbul Z. Oxidative stress markers in hemodialysis and peritoneal dialysis patients, including coenzyme Q10 and ischemia-modified albumin. Int J Artif Organs 2012; 35:226-232.
11. Dursun A, Okumus N, Zenciroglu A. Ischemia-modified albumin (IMA): could it be useful to predict perinatal asphyxia? J Matern Fetal Neonatal Med 2012; 25:2401-2405.
12. Gugliucci A, Hermo R, Monroy C, Numaguchi M, Kimura S. Ischemia-modified albumin levels in cord blood: a case-control study in uncomplicated and complicated deliveries. Clin Chim Acta 2005; 362:155-160.
13. Yakut I, Tayman C, Oztekin O, Namuslu M, Karaca F, Kosus A. Ischemia-modified albumin may be a novel marker for the diagnosis and follow-up of necrotizing enterocolitis. J Clin Lab Anal 2014; 28:170-177.
14. Oztekin O, Kalay S, Tayman C, Namuslu M, Celik HT. Levels of ischemia-modified albumin in transient tachypnea of the newborn. Am J Perinatol 2015; 30:193-198.
15. Yerlikaya FH, Kurban S, Mehmetoglu I, et al. Serum ischemia-modified albumin levels at diagnosis and during treatment of late-onset neonatal sepsis. J Matern Fetal Neonatal Med 2014; 27:1723-1727.
16. Erol S, Unal S, Demirel N, et al. Evaluation of serum ischemia-modified albumin levels in anemia of prematurity. J Matern Fetal Neonatal Med 2018; 31:3133-3138.
17. Zuwala-Jagiello J1, Warwas M, Pazgan-Simon M. Ischemia-modified albumin (IMA) is increased in patients with chronic hepatitis C infection and related to markers of oxidative stress and inflammation. Acta Biochim Pol 2012; 59:661-667.
18. Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005; 6:2-8.
19. Bar-Or D, Lau E, Winkler JV. A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia-a preliminary report. J Emerg Med 2000; 19:311-315.
20. Lippi G, Montagnana M, Salvagno GL, Guidi GC. Standardization of ischemia-modified albumin testing: adjustment for serum albumin. Clin Chem Lab Med 2007; 45:261-262.
21. Sbarouni E, Georgiadou P, Voudris V. Ischemia modified albumin changes-review and clinical implications. Clin Chem Lab Med 2011; 49:177-184.
22. Erdem SS, Yerlikaya FH, Çiçekler H, Gül M. Association between ischemia-modified albumin, homocysteine, vitamin B(12) and folic acid in patients with severe sepsis. Clin Chem Lab Med 2012; 50:1417-1421.
23. Iacovidou N, Briana DD, Boutsikou M, et al. Cord blood ischemia-modified albumin levels in normal and intrauterine growth restricted pregnancies. Mediators Inflamm 2008; 2008:523081.
24. Khashana A, Ayoub A, Younes S, Abdelrahman A. Ischemia modified albumin in early neonatal sepsis. Infect Dis (Lond) 2016; 48:488-489.
25. Silveira RD, Giacomini C, Procianoy RS. Neonatal sepsis and septic shock: concepts update and review. Rev Bras Ter Intensiva 2010; 22:280-290.
26. Lever A, Mackenzie I. Sepsis: definition, epidemiology, and diagnosis. BMJ 2007; 335:879-883.
27. Buttery JP. Blood cultures in newborns and children: optimising an everyday test. Arch Dis Child Fetal Neonatal Ed 2002; 87:F25-28.
28. Chiesa C, Natale F, Pascone R, Osborn JF, Pacifico L, Bonci E, et al. C reactive protein and procalcitonin: reference intervals for preterm and term newborns during the early neonatal period. Clin Chim Acta 2011; 412:1053-1059.
29. Bhandari V. Effective Biomarkers for Diagnosis of Neonatal Sepsis. J Pediatric Infect Dis Soc 2014; 3:234-245.