Kerman University of Medical Sciences and Health Services
Scientific Research Journal
Journal of Kerman University of Medical Sciences
JKMU
Journal of Kerman University of Medical Sciences, 2019; 26 (1): 12-21

The Cut-off Point of Ferritin, Procalcitonin, and Serum CRP Levels in the Peripheral Blood of Neonates Suffering from Sepsis

Zahra Kamiab, M.D.[1], Mohammad Reza Mohammadi Hassan, M.D.[2], Gholamhossein Hassanshahi, Ph.D.[3], Gholamreza Bazmandegan, M.D.[4], Shokoofeh Darakhshan, M.D.[5]

1- Assistant Professor, Clinical Research Development Unit, Ali-Ibn Abi-Talib Hospital, & Social Medicine Department, Medical School, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
2- General physician, Clinical Research Development Unit, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
3- Professor, Molecular Medicine Research Centre, Institute of Basics Medical Sciences, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
4- Assistant Professor, Non-communicable Diseases Research Center, & Clinical Research Development Unit, Ali-Ibn Abi-Talib Hospital, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
5- Assistant Professor, Neonates Department, Ali-Ibn Abi-Talib Hospital, Rafsanjan University of Medical Sciences, Rafsanjan, Iran (Corresponding author; E-mail: clinresearch85@gmail.com)
Received: 2 January, 2019 Accepted: 16 January, 2019

ARTICLE INFO

Article type:
Original Article

Keywords:
Sepsis
Neonate
Ferritin
Procalcitonin
CRP
Rafsanjan

Abstract

Background: Sepsis is regarded as a critical clinical status in neonates. Since blood culture is a time-consuming method, the present study was conducted to investigate the serum level of Ferritin, Procalcitonin, and CRP in the peripheral blood of term neonates suspected with sepsis to have a quicker diagnosis for the disease.

Methods: In the present cross-sectional study, a total of 60 neonates suspected with sepsis who had been hospitalized in Ali ibn Abi Talib Hospital of Rafsanjan/ Iran in 2015-2016 were randomly selected. Before conducting the treatment processes, blood samples were taken from all neonates and sent for blood culture. The intended markers were measured both before and after the treatments and the results were recorded in special forms for each neonate. Data were analyzed through SPSS20 and using chi-squared test, Paired t-test, and drawing a ROC curve for determining the best cut-off point and measuring the sensitivity and specificity.

Results: In this study, 70% of the neonates suspected with sepsis were male, 56.7% were younger than 7 days old and 96.7% had natural weight. The most common symptoms were poor feeding and reduced sucking reflexes. Data analysis of the markers indicate that they reduced significantly after the treatment ($p<0.001$). The sensitivity, specificity, and the best cut-off point were respectively 64.3%, 43.5%, and 257.8 for Ferritin, 78.6%, 50%, and 23 for Procalcitonin and 85.7%, 65.2%, and 21.5 for CRP.

Conclusion: According to the obtained findings, applying these markers can be of a great use in diagnosing neonatal sepsis. However, given the low sensitivity and specificity of Ferritin, Procalcitonin and CRP in the present study, further studies need to be conducted to obtain more definite results.

Citation: Kamiab Z, Mohammadi Hassan M.R, Hassanshahi GH.H, Bazmandegan GH.R, Darakhshan SH. The Cut-off Point of Ferritin, Procalcitonin, and Serum CRP Levels in the Peripheral Blood of Neonates Suffering from Sepsis. *Journal of Kerman University of Medical Sciences*, 2019; 26 (1): 12-21.

Introduction

Neonatal sepsis is a clinical syndrome within the first months of neonatal life associated with systemic symptoms and bacterial infection (1). Sepsis is the most common cause of mortality among neonates and in the developing countries, it accounts for 30-50% of neonatal mortality every year (2). The prevalence of this disease in the developed countries is 1-4 cases in every 1000 births. However, in the developing countries, it has been reported to be 10 times higher (3).

One of the main factors in neonatal sepsis management is accurate diagnosis; a large number of mortality arising from sepsis can be prevented by early diagnosis (4). There are no accurate diagnostic tests. Moreover, the interpretation of the findings of such tests is difficult in neonates (5). As a result, a set of clinical symptoms and laboratory tests are required for an accurate diagnosis (6).

Nowadays, the diagnostic standard of sepsis is culturing of blood as well as body fluids and tissues (7). However, this test is commonly time-consuming with low sensitivity and specificity (8). The minimum time which is needed for the initial results of blood test is 24 hours and might cause problems for the neonate because of delay in the treatment (9). Given the limitations related to these laboratory tests, it is required to apply other methods with more accurate results and higher specificities (10). Previous studies have indicated that measuring biochemical markers such as C Reactive Protein (CRP), Procalcitonin, IL1b, IL8, IL6 and Ferritin can all be applied for a quick diagnosis of this disease (10-14).

CRP is an acute-phase protein of non-specific reaction that is commonly formed by liver through non-inflammatory processes (15). CRP test is inexpensive, quick, and accessible, and it is now considered as one of the para-clinical markers either alone or in combination with other para-clinical factors for initiating the treatment processes of neonatal sepsis (15, 16). Procalcitonin (PCT) is another marker being assessed by researchers for the quick diagnosis of neonatal sepsis (17, 18). Procalcitonin is a prohormone of calcitonin that is naturally produced by the C cells of the thyroid gland (19). Numerous studies have reported that in bacterial infection and sepsis, the PCT existing in patients' serum is measurable and it is closely related to the intensity of sepsis (19, 20). Thus, PCT is known as one of the markers of bacteremia and sepsis as similar as cytokines, interleukins, and C-reactive proteins (21, 22). Ferritin is another marker that is being greatly discussed for its application in the quick diagnosis of neonatal sepsis (23). Previous studies indicated that the Ferritin level of neonates suffering from sepsis is higher than that of healthy neonates (24, 25).

The sensitivity, specificity, and cut-off points of these markers have been varied in different studies (26-30). Given the significance of this disease, the role of time in its prognosis and treatment, the limited information available on Ferritin marker especially in neonates suspected with sepsis, and the accessible, inexpensive, and quick application of biomarkers applied in this study, the present study was conducted to investigate the relationship between the above mentioned diagnostic factors and sepsis and their application as a marker of early diagnosis and treatment.

Materials & Methods

The statistical population of this descriptive cross-sectional study included all term neonates hospitalized in the neonatal ward and NICU of Ali ibn Abi Talib Hospital of Rafsanjan/ Iran in 2015-2016. Through applying measurement methods, as well as sample size determination formula (Power=90 and α=0·05), the sample size was defined to be 60 neonates. The investigated samples were randomly selected among the term neonates suspected to sepsis symptoms. Blood samples were

collected at the time of admission and after the completion of antibiotic treatment. The inclusion criteria were 1-to-28-day-old term neonate, having one or more maternal risk factors of neonatal sepsis (history of maternal urinary tract or genital infection during pregnancy, maternal fever during the delivery, Chorioamnionitis, Premature Rupture of Membranes for more than 18 hours, meconium stained amniotic fluid, and preterm delivery), the presence of one or more clinical symptoms of sepsis such as fetal tachycardia, intolerance to breastfeeding, respiratory distress, apnea, hypotonia, reduced reflexes, seizure, hypothermia, hyperthermia, biliary vomiting, and localized infections, stable and controlled vital signs of the neonate and parental satisfaction for conducting interviews, examinations, and tests.

The exclusion criteria were neonatal death, leaving the hospital before receiving the test results, and having a disease rather than sepsis during the hospitalization (22).

Measurement of Ferritin

The serum levels of Ferritin of neonates were measured through ELISA test and using ELISA Kit. The test method of this kit is immune enzymometry. This test has been designed by using exclusive monoclonal antibody in a sandwich method; an anti-Ferritin monoclonal antibody is applied for stabilization on the solid phase and an anti-Ferritin antibody is used for conjugation with the enzyme (HRP). By adding the serum sample, Ferritin reacts with the above mentioned antibodies and sandwiched between the antibody connected to the solid phase and the antibody conjugated with the enzyme. After the incubation time (45 minutes) at room temperature, irrigating the wells by the irrigating solution, adding substrate and dye solution, and incubating for 15 minutes, the blue color appears. By adding the stop solution, the blue color turns into yellow. The color intensity is measured at 450 nanometer wavelength. The color intensity is closely related to Ferritin density in the sample.

Measurement of CRP

CRP measurement was conducted three times; at the beginning of admission (first hour) and 24 and 48 hours after the admission with a latex agglutination method. For conducting of such a test, initially, specific anti-CRP antibodies are prepared by injecting CRP to laboratory animals and then they are linked to latex polystyrene particles. Thus, when the patient's serum containing CRP is mixed with the above mentioned particles, agglutination is created. This test is rather sensitive. By conducting this method (according to the manufacturing institute), CRP can be measured in one milliliter of serum (31). Sometimes, CRP level of the serum is high, and as a result, due to a regional phenomenon, it is possible that a positive serum is mistakenly reported as a negative serum. Therefore, in negative cases, it is better to repeat the test with the dilation of 1:5 or higher before reporting the test results (32). It is worth mentioning that in this study, conducting CRP for the second and third rounds was done for those neonates whose CRP was reported to be negative in the first round. Moreover, for neonates whose CRP was positive at the first round, the test was conducted to assess the antibiotic treatment response.

Measurement of Procalcitonin

For measuring Procalcitonin level, the sample was centrifuged and serum was detached and was frozen at-40º C before conducting the analysis. Two hours after sample collection, the Procalcitonin level was measured using immunoluminometric assay with the Lumi Kit of Brahamas test (Brahamas Diagnostic Berlin Germany).

Blood culture was conducted in neonates, and the diagnostic results of the markers were compared with this gold

standard. Sampling was carried out by the researchers and in the laboratory of the Faculty of Medicine, Rafsanjan University of Medical Sciences. In addition, all neonates received the same treatment.

Statistical analysis

The results of examinations and tests were registered on neonates' special forms and they were then recorded on a computer. Variables included sex, age, temperature, birth weight, maternal age, abdominal distension, abdominal distension, reduced sucking reflex, Moro reflex, Routing reflex, poor feeding, tracheal discharge, vomiting, intercostal retraction, granting, blood pressure, heart rate, respiratory rate and Ferritin, Procalcitonin and CRP levels. Data were then entered into the SPSS version 20 and analyzed by using chi-squared test, Paired t-test, and drawing a ROC curve for determining the best cut-off point and measuring the sensitivity and specificity. The ethical committee of Rafsanjan University of Medical Sciences approved the protocol of the study (IR.RUMS.REC.1394.124).

Results

In the present study, from 60 hospitalized neonates suspected with sepsis, 42 neonates (70%) were male, and 18 neonates (30%) were female. In terms of the age range, 34 neonates (56.7%) had less than 7 days old and 26 neonates (43.3%) had 7-28 days old. From these neonates, 58 neonates (96.7%) had natural birth weights (2500-4000 grams) and 2 neonates (3.3%) weighed more than 4000 grams. The maternal age of the investigated neonates is classified in three categories; two mothers (3.3%) had less than 18 years old, 54 ones (90%) had 18-35 years old and 4 ones (6.7%) had more than 35 years old.

The clinical symptoms of the neonates participating in the present study were investigated as well. Among the investigated clinical symptoms, poor feeding and reduced sucking reflexes had the highest frequencies (Table 1).

Table 1. The frequency distribution of clinical symptoms in the investigated neonates

Clinical symptoms	Frequency (%)
Abdominal distension	
present	4 (6.7)
absent	56 (93.3)
Reduced sucking reflex	
present	31 (51.7)
absent	29 (48.3)
Moro reflex	
present	22 (36.7)
absent	38 (63.3)
Routing reflex	
present	24 (40)
absent	36 (60)
Poor feeding	
present	52 (86.7)
absent	8 (13.3)
Tracheal discharge	
present	.
absent	60 (100)
Vomiting	
present	21 (35)
absent	39 (65)
Intercostal retraction	
present	16 (26.7)
absent	44 (73.3)
Granting	
present	17 (28.3)
absent	43 (71.7)

In terms of vital signs, most of the neonates (48.3%) had the temperature of less than 36 degrees. All of the neonates had normal blood pressures and 83.3% of the neonates had the heart rate of 100-180 and 60% of the neonates had normal respiratory status (Table 2).

Table 2. The frequency distribution of vital signs in the investigated neonates

Vital Signs		Frequency (%)
Temperature	Less than 36	29 (48/3)
	36-37.8	10 (16/7)
	More than 37.8	21 (35)
Blood pressure	Hypotension	0
	Normal	60 (100%)
	Hypertension	0
Heart rate	Less than 100	2 (3/3)
	100-180	50 (83/3)
	More than 180	8 (13/3)
Respiratory status	Bradypnea	36 (60)
	Tachypnea	24 (40)

Data analysis related to pre- and post-treatment was conducted using paired t- test (after making sure about the accuracy of the defaults). According to the obtained results, the mean of all three markers significantly reduced in response to the treatment (Table 3).

Table 3. The values of the markers investigated both before and after the treatment

Marker	status	Mean±SD	P value (Paired t test)
Ferritin	Pre-treatment	453.50±40.22	0.001
	Post-treatment	254.52±255.85	
Procalcitonin	Pre-treatment	33.68±23.71	0.001
	Post-treatment	23.18±17.47	
CRP	Pre-treatment	28.35±27.01	0.001
	Post-treatment	8.26±7.97	

The results of blood culture were compared with the golden standard. In whole, 14 cases had positive blood culture and 46 cases had negative blood culture. Data analysis was conducted to investigate sensitivity and specificity. Moreover, the cut-off points of the markers were obtained by using Receiver Operating Characteristic (ROC) curve. The sensitivity, specificity, and best cut-off point of Ferritin were respectively 64.3%, 43.5% and 257.8 with the area under the curve of 55% (p value: 0.507). For Procalcitonin, the sensitivity, specificity, and best cut-off point were respectively 78.6%, 50% and 23 with the area under the curve of 64% (p value: 0.114). The sensitivity, specificity, and best cut-off point of CRP were respectively 85.7%, 65.2% and 21.5 with the area under the curve of 83% (p value: 0.000). The results have been shown in figure 1.

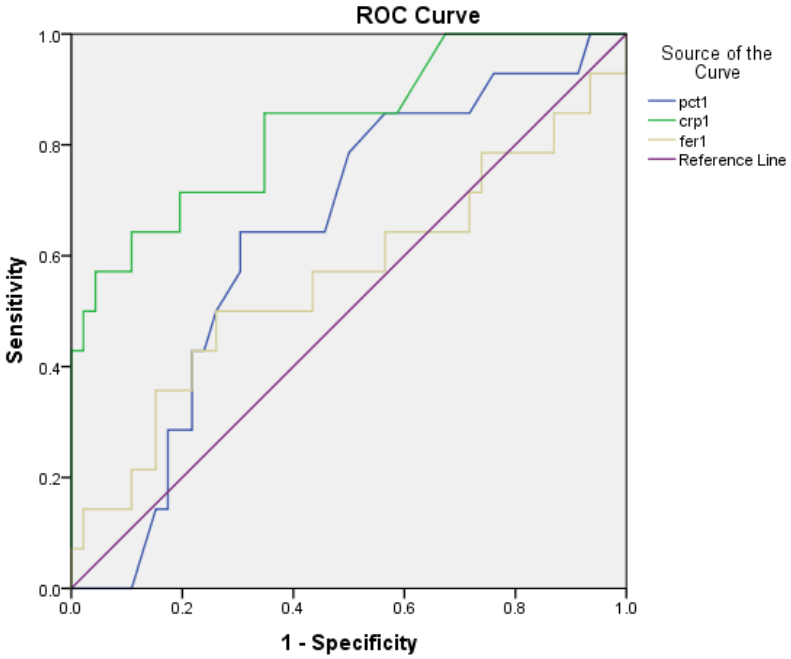

Figure 1. The sensitivity and specificity of the investigated markers

Discussion

Sepsis is one of the most important causes of mortality in neonates. Its prevalence in the developing countries is approximately ten times higher than that in the developed countries (33, 34). Despite their diagnostic limitations, clinical observations are the best way available for the early diagnosis of bacterial infection in neonates (35).

In terms of laboratory findings, separating microorganism from the blood, cerebrospinal fluid, urine, and other important organs of the body is the most important tool to confirm sepsis diagnosis. However, these tests are sometimes false negative and they are time-consuming as well. Thus, other non-specific tests such as complete counting of peripheral blood cells, counting premature white blood cells, platelets, and other tests including specific microbial antigen through CIE, Limulus assay, latex agglutination, micro-sedimentation, CRO, and Procalcitonin can be applied (36-38).

The pre- and post-treatment analysis of the data related to the investigated markers indicated significant change of the markers after the treatment. The findings of the present study are greatly similar to those of the studies conducted on the comparison of Procalcitonin and CRP. This indicates that both of the aforementioned markers are subject to significant changes in neonatal sepsis (39). In the study conducted by Abedini et al., on the changes of Procalcitonin, CRP, and number of peripheral white blood cells (both before and three days after the treatment) with the diagnosis of SIRS, a proper consistency between Procalcitonin and CRP has been reported while no significant consistency between serum Procalcitonin with CRP and the number of blood leukocytes on the third day of the treatment has been reported (37). In another study conducted by Casado-Flores to compare Procalcitonin with serum CRP and peripheral blood neutrophils, it was reported that the value of serum Procalcitonin has priority over CRP and

is a useful and valuable marker in determining the intensity of bacterial infections (39).

In the present study, both Procalcitonin and CRP were applied for diagnosing neonatal sepsis and significant results were found. However, it seems that the number of positive cases in the relationship of CRP with positive blood culture is higher than that of Procalcitonin. Furthermore, in a study conducted by Jalali et al., the findings indicated that Procalcitonin can be used as a valuable marker in diagnosing neonatal sepsis. The sensitivity and specificity of PCT were respectively 75% and 42.6% in all neonates, 100% and 22.5% in 48-hour-old and younger neonates, and 71.4% and 71.4% in neonates older than 48 hours (40).

Results of a study performed by Aqeela Ayub et al., indicated that blood parameters can be applied as acceptable markers in diagnosing neonatal sepsis; the sensitivity, specificity, and accuracy of CRP were respectively reported to be 75%, 83.9%, and 80%. Moreover, the sensitivity, specificity, and accuracy of blood Ferritin level were 88.6%, 69%, and 78, respectively (41). In Garcia et al. study, the sensitivity and specificity of serum Ferritin in diagnosing neonatal sepsis were reported to be 100% and 58%, respectively (22). In a study performed by Halstead ES et al, it has been discussed that applying blood Ferritin index in neonates is likely to be greatly helpful in diagnosing neonatal sepsis (23). The findings of the study conducted by Demet Demirkol et al., as well as the findings of the study conducted by Kanda et al., indicated higher level of blood Ferritin in neonates suffering from sepsis (24, 25). One of the main reason behind the low sensitivity and specificity of these markers in the present study (in comparison to those of the aforementioned studies) is that the present study aimed at investigating neonates suspected with sepsis and the inclusion criteria were different.

In the present study, the clinical symptoms of poor feeding and reduced sucking reflexes were the most frequent ones. In terms of vital signs status, most of the neonates had a temperature of less than 36ºC, normal blood pressure, natural heart rate, and 60% of the neonates had normal respiratory status. The findings of the studies have reported symptoms such as hyperthermia, respiratory distress, anorexia, and vomiting as the most prevalent symptoms of suffering from sepsis (34, 42, 43). Based on the gestational age and the intensity of infection, the clinical symptoms of sepsis in neonates are different. Fever is one of the rare symptoms and hypothermia is one of the most prevalent symptoms in these neonates.

The general symptoms are hypothermia and poor feeding and non-specific symptoms are anuria and acidosis (26). The findings of the present study are consistent with those of the previous studies.

It is worth mentioning that the present study, like any other study, has some limitations affecting the generalizability and accuracy of its findings. The limitations of the present study include the cross-sectional design, as well as the limited number of samples. On the other hand, the present study attempted to investigate the serum levels of the mentioned markers and determining their sensitivity and specificity in neonates suspected with sepsis and given the limited number of studies conducted in this field, this can be regarded as one of its strong points.

Conclusion

Since sepsis is regarded as one of the dangerous situations threatening life, the diagnostic tests are required that have high

sensitivity. Given the sensitivity of markers, one cannot merely use these markers for diagnosing the sepsis. Thus, given the ease of application as well as the short time spent for them, they can be applied as a part of the diagnostic methods in combination with other methods. Also, these methods can save time and are cost- effective. Given what stated above, it is recommended to conduct further studies with higher sample sizes to acquire more definite results.

Ethical code: IR.RUMS.REC.1394.124

Conflict of interest

None of authors declared conflict of interest.

Acknowledgement

This project was financially supported by Rafsanjan University of Medical Sciences. The Authors would like to thank the Clinical Research Development Unit of Ali-Ibne Abi-Talib Hospital in Rafsanjan University of Medical Sciences for its support and collaboration. Authors also warmly thank both mothers of control and neonates for their cooperation.

References

1. Wynn JL. Defining neonatal sepsis. Curr Opin Pediatr 2016; 28(2):135-40.
2. Obiero CW, Seale AC, Berkley JA. Empiric treatment of neonatal sepsis in developing countries. Pediatr Infect Dis J 2015; 34(6):659-61.
3. Kale A, jaybhaye D, Bonde V. Neonatal Sepsis: An Update. Iranian Journal of Neonatology 2014; 4(4): 39-51.
4. Zea-Vera A, Turin CG, Ochoa TJ. Unifying criteria for late neonatal sepsis: proposal for an algorithm of diagnostic surveillance. Rev Peru Med Exp Salud Pública 2014; 31(2):358-63. [In Spanish]..
5. Camacho-Gonzalez A, Spearman PW, Stoll BJ. Neonatal infectious diseases: evaluation of neonatal sepsis. Pediatr Clin North Am 2013; 60:367-89.
6. Oeser C, Lutsar I, Metsvaht T, Turner MA, Heath PT, Sharland M. Clinical trials in neonatal sepsis. J Antimicrob Chemother 2013; 68(12):2733-45.
7. Bedford Russell AR, Kumar R. Early onset neonatal sepsis: diagnostic dilemmas and practical management. Arch Dis Child Fetal Neonatal Ed 2015; 100(4):F350-4.
8. Saleh MA, Kasem YT, Amin HH. Evaluation of neonatal sepsis and assessment of its severity by red cell distribution width indicator. The Egyptian Journal of Community Medicine 2017; 35(3):21-32.
9. Tröger B, Göpel W, Faust K, Müller T, Jorch G, Felderhoff-Müser U, et al. Risk for late-onset blood-culture proven sepsis in very-low-birth weight infants born small for gestational age: a large multicenter study from the German Neonatal Network. Pediatr Infect Dis J 2014; 33(3):238-43.
10. Gokmen Z, Ozkiraz S, Kulaksizoglu S, Kilicdag H, Ozel D, et al. Resistin-a novel feature in the diagnosis of sepsis in premature neonates. Am J Perinatol 2013; 30(6):513-7.
11. Kibe S, Adams K, Barlow G. Diagnostic and prognostic biomarkers of sepsis in critical care. J Antimicrob Chemother 2011; 66(suppl-2):ii33-40.
12. Gibot S, Béné MC, Noel R, Massin F, Guy J, Cravoisy A, et al. Combination biomarkers to diagnose sepsis in the critically ill patient. Am J Respir Crit Care Med 2012; 186(1):65-71.

13. Wu J, Hu L, Zhang G, Wu F, He T. Accuracy of presepsin in sepsis diagnosis: a systematic review and meta-analysis. PLoS One 2015; 10(7):e0133057.
14. Hedegaard SS, Wisborg K, Hvas AM. Diagnostic utility of biomarkers for neonatal sepsis–a systematic review. Infect Dis (Lond) 2015; 47(3):117-24.
15. Patra S. Procalcitonin in neonatal sepsis. Int J Sci Res. 2018; 6(3).
16. Kalil AC, Van Schooneveld TC. Is procalcitonin-guided therapy associated with beneficial outcomes in critically ill patients with sepsis? Critic Care Med 2018; 46(5):811-2.
17. Schlattmann P, Brunkhorst FM. Procalcitonin as a diagnostic marker for sepsis. Lancet Infect Dis 2014; 14(3):189.
18. Chivate CG, Belwalkar GJ, Limaye RP, Patil RV. Procalcitonin as a marker for the diagnosis of sepsis. Int J Res Med Sci 2016; 4(4):1216-8.
19. Prucha M, Bellingan G, Zazula R. Sepsis biomarkers. Clin Chimica Acta 2015; 440:97-103.
20. Cho SY, Choi JH. Biomarkers of sepsis. Infect Chemother 2014; 46(1):1-2.
21. Branco RG, Garcia PC. Ferritin and C-reactive protein as markers of systemic inflammation in sepsis. Pediatr Critic Care Med 2017; 18(2):194-6.
22. Garcia PC, Longhi F, Branco RG, Piva JP, Lacks D, Tasker RC. Ferritin levels in children with severe sepsis and septic shock. Acta Paediatr 2007; 96(12):1829-31.
23. Halstead ES, Rajasekaran S, Fitzgerald JC, Weiss SL. Hyperferritinemic sepsis: an opportunity for earlier diagnosis and intervention? Front Pediatr 2016; 4:77.
24. Kanda J, Mizumoto C, Ichinohe T, Kawabata H, Saito T, Yamashita K, et al. Pretransplant serum ferritin and C-reactive protein as predictive factors for early bacterial infection after allogeneic hematopoietic cell transplantation. Bone Marrow Transplant 2011; 46(2):208-16.
25. Demirkol D, Yildizdas D, Bayrakci B, Karapinar B, Kendirli T, Koroglu TF, et al. Hyperferritinemia in the critically ill child with secondary hemophagocytic lymphohistiocytosis/sepsis/multiple organ dysfunction syndrome/macrophage activation syndrome: what is the treatment? Critic Care 2012; 16(2):R52.
26. Arif SK, Suyata MP, Gaus S, Ahmad MR. Procalcitonin and C-reactive protein as a predictor of organ dysfunction and outcome of sepsis and septic shock patients in intensive care unit. Glob J Health Sci 2017; 9(12):169.
27. Abdollahi E, Farshi S, Hajian Motlaq N, Abdollahi S. Patient satisfaction in the emergency department of Savodjbolaq hospitals. Alborz University Medical Journal 2015; 4(3):176-83. [In Persian].
28. Celik HT, Portakal O, Yigit S, Hascelik G, Korkmaz A, Yurdakok M. Efficacy of new leukocyte parameters versus serum C-reactive protein, procalcitonin, and interleukin-6 in the diagnosis of neonatal sepsis. Pediatr Int 2016; 58(2):119-25.
29. Aydemir C, Aydemir H, Kokturk F, Kulah C, Mungan AG. The cut-off levels of procalcitonin and C-reactive protein and the kinetics of mean platelet volume in preterm neonates with sepsis. BMC Pediatr 2018; 18(1):253.
30. Farhadi K, Ghaemipour F, Nikravan M, Alavi Majd H. The study of the quality of triage of the patients admitted to intensive care unit. Iranian Journal of Cardiovascular Nursing 2013; 2(1):12-6. [In Persian].
31. Charles E, Nolan I, Hickey A, Greenough A, Kassim Z. C-reactive protein in otherwise well

babies with risk factors for sepsis. Infant journal 2017; 13(4):154-5.

32. Van Herk W, El Helou S, Janota J, Hagmann C, Klingenberg C, Staub E, et al. Variation in current management of term and late-preterm neonates at risk for early-onset sepsis: an international survey and review of guidelines. Pediatr Infect Dis J 2016; 35(5):494-500.

33. Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-onset neonatal sepsis. Clin Microbiol Rev 2014; 27(1):21-47.

34. Ng PC, Ma TP, Lam HS. The use of laboratory biomarkers for surveillance, diagnosis and prediction of clinical outcomes in neonatal sepsis and necrotising enterocolitis. Archives of Disease in Childhood-Fetal and Neonatal Edition 2015; 100(5):F448-52.

35. Benitz WE, Wynn JL, Polin RA. Reappraisal of guidelines for management of neonates with suspected early-onset sepsis. J Pediatr 2015; 166(4):1070-4.

36. Pontrelli G, De Crescenzo F, Buzzetti R, Jenkner A, Balduzzi S, Carducci FC, et al. Accuracy of serum procalcitonin for the diagnosis of sepsis in neonates and children with systemic inflammatory syndrome: a meta-analysis. BMC Infect Dis 2017; 17(1):302.

37. Abedini M, Delpisheh A, Nikkhu B, Vahabi A, Afkhamzadeh A. Procalcitonin and white blood cellcount (WBC),erythrocyte sedimentation rate(ESR) and serumC-reactive protein(CRP)alterations in children with systemic inflammatory response syndrome before and after treatment. African Journal of Biotechnology 2012; 11(49):10989-93.

38. Benitz WE. Adjunct laboratory tests in the diagnosis of early-onset neonatal sepsis. Clin Perinatol 2010; 37(2):421-38.

39. Casado-Flores J, Blanco-Quirós A, Asensio J, Arranz E, Garrote JA, Nieto M. Serum procalcitonin in children with suspected sepsis: a comparison with C-reactive protein and neutrophil count. Pediatr Crit Care Med 2003; 4(2):190-5.

40. Jalali SZ, Heidarzadeh A, Khatti Dizabadi B. Diagnostic value of procalcitonin for sepsis diagnosis in ill neonate hospitalized in neonatal ward and NICU. Journal of Guilan University of Medical Sciences 2014; 22(88):12-7. [In Persian].

41. Ayub A, Chishti AL, Hassen KA. The validity of hematologic markers for diagnosis of neonatal sepsis. Annals of King Edward Medical University 2015; 21(4):240-6.

42. Jin M, Khan AI. Procalcitonin: uses in the clinical laboratory for the diagnosis of sepsis. Lab Med 2015; 41(3):173-7.

43. Wynn JL, Guthrie SO, Wong HR, Lahni P, Ungaro R, Lopez MC, et al. Postnatal age is a critical determinant of the neonatal host response to sepsis. Mol Med 2015; 21:496-504.