ISSN: 2091-2331 (Print) 2091-234X (Online)

Journal of Nobel Medical College

Volume 12, Number 02, Issue 23, July-December 2023, 103-108

Original Article

Serum Procalcitonin as a Biomarker for Diagnosing Neonatal Sepsis in a Tertiary Care Hospital of Eastern Nepal

Arun Giri*, Sunil Kumar Yadav, Vijay Kumar Sah, Amaresh Kumar Kushwaha

Department of Pediatrics, Nobel Medical Collage Teaching Hospital, Biratnagar, Nepal

Article Received: 15th October, 2023; Accepted: 28th November, 2023; Published: 31st December, 2023

DOI: https://doi.org/10.3126/jonmc.v12i2.61483

Abstract

Background

Sepsis is the main cause of morbidity and mortality in neonates. Early diagnosis and appropriate treatment can reduce the mortality rate. Blood culture is the gold standard for diagnosis of bacterial sepsis, but it requires 3-5 days for results. Since the disease may progress rapidly in neonates, a faster diagnostic test is needed. This study aimed to investigate and evaluate the role of serum procalcitonin as a marker for diagnosis of neonatal sepsis, aiming to enhance early detection and improve clinical outcomes.

Materials and Methods

This was a hospital-based cross-sectional observational study carried out in 350 neonates admitted with suspicion of neonatal sepsis in Neonatal Intensive Care Unit (NICU) of Nobel Medical College Teaching Hospital (NMCTH), Biratnagar, Nepal during 1 year between October 2021 to September 2022.

Results

The study included 350 cases, with a median age of 4days (1day to 4 days). Males made up the majority of cases (69.71%), as did Hindus (70.29%). Similarly, 78.86% of the cases had serum procalcitonin levels more than or equivalent to 0.5 ng/ml. Possible sepsis (43.43%) accounted for the majority of cases. The cases age, gender, and religion were shown to have a statistically significant relationship with serum procalcitonin.

Conclusion

Therefore, we draw the conclusion that serum procalcitonin may not be the only diagnostic marker to diagnose neonatal sepsis in term/near term newborns, but it may be helpful when paired with other test indicators.

Keywords: *Biomarker, Neonatal sepsis, Serum procalcitonin*

***Corresponding Author:**
Dr Arun Giri
Associate Professor
Email: drarungiri1977@gmail.com
ORCID: https://orcid.org/0000-0002-7471-3164

Citation
Giri A, Yadav SK, Sah VK, Kushwaha AK, Serum Procalcitonin as a Biomarker for Diagnosing Neonatal Sepsis in a Tertiary Care Hospital of Eastern Nepal, JoNMC. 12:2 (2023) 103-108. DOI: https://doi.org/10.3126/jonmc.v12i2.61483

Introduction

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life [1]. It can be also defined as “life-threatening organ dysfunction, caused by a deregulated host response to infection". Sepsis has traditionally been considered as a result of uncontrolled inflammatory response, a "cytokine storm" that results in shock or organ dysfunction [2].

As per Nepal Demographic and Health Survey (NDHS) 2022, neonatal mortality was 21 deaths per 1,000 live births [3]. As we know blood culture is considered as gold standard for diagnosis, high chances of false negativity and delay in culture results often lead to inappropriate use of antibiotics [4]. Biomarkers are useful for early diagnosis of sepsis, to predict outcomes, and to guide choice of antibiotic therapy [5]. Amongst the newer ones, serum procalcitonin (PCT) has been extensively studied and shows promising results. The main aim of this study is to investigate and evaluate the role of serum procalcitonin as a diagnostic marker in neonatal sepsis, determine the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of serum procalcitonin level in diagnosing neonatal sepsis and to find out the incidence of Neonatal Sepsis [6].

Materials and Methods

This was a hospital based cross sectional observational study carried out in 350 neonates (Term as well as preterm) admitted with suspicion of neonatal sepsis in Neonatal Intensive Care Unit (NICU) of Nobel Medical College Teaching Hospital (NMCTH), Biratnagar-05, Morang, Nepal during a 1 year period between October 2021 to September 2022 after obtaining approval for the study from the Institutional Review Committee of Nobel Medical College Teaching Hospital .All term and preterm newborns ≤28 days with risk factors for neonatal sepsis (maternal and neonatal risk factors) and those who developed clinical features of sepsis were included in the study. The maternal risk factors considered were: prolonged premature rupture of membrane >18 hours, offensive odor of amniotic fluid, single unclean or >3 sterile vaginal examination(s) during labor and the clinical syndrome of maternal intrauterine infections. Clinical features in neonates considered for suspected neonatal sepsis were: hypothermia or hyperthermia, irritability, lethargy, respiratory distress, apnea, gasping respiration, hypo/hyperglycemia and bradycardia/ tachycardia. However newborns who were started on antibiotics before admission to NICU and newborns with major congenital anomalies, hypoxic ischemic encephalopathy were excluded from the study. Sample size was350 which was calculated by using formula Sample size (N) = $(Z^2 \text{ p X q})/l^2$ Where, Z is standard normal variant, which is equal to 1.96 for 95% confidence, P=prevalence of neonatal sepsis taken as 37.1% as per a prospective cohort study done by Budhathoki S et.al [7] “Epidemiology of neonatal infections in hospitals of Nepal” and q = 1- p or 100-p and l= absolute error of precision (10%) After collecting the data, they were verified and coded accordingly and entered in Microsoft excel 2007 and converted into statistical package for social science (SPSS v.20) for statistical analysis. Descriptive statistical tools like frequency and percentage (%) were calculated and also the graphical representation was made. For inferential analysis, the Chi-square test was applied to find out the significant difference between dependent and independent variables at a 95% confident interval. Statistical analysis like Sensitivity, Specificity and Predictive values were calculated for diagnostic tests wherever possible and p-value <0.05 was considered significant.

Results

The median age of neonates enrolled in this study was 4 days (1day to 4days) whereas median gestational age of the neonate was 38 weeks and 2 days (38weeks to 39weeks 6 days). The youngest neonate was 2 hours old and eldest was 21days old. Similarly, the gestational age of the neonates in our study ranged between 31 weeks to 42 weeks. While the mean birth weight of the neonates in our study was 2.84 kg, however the birth weight ranged from 1.90kg to 4.20 kg.

Table 1: Demographic profile of Neonates (n=350)

Selected Variables	Category	Frequency (n)	Percentage (%)
Gender	Male	244	69.71
	Female	106	30.29
Gestationalage	<37 weeks	44	12.57
	=37 weeks	306	87.43
Ageof neonate	=7 days	246	70.29
	>7 days	104	29.71
Birth weight	<2.5kg	30	8.57
	=2.5kg	320	91.43
Religion	Hindu	246	70.29
	Others	104	29.71

Table1depicts the majority of neonates (69.71%) were male. Similarly, the majority of neonates (87.43 %) were of gestational age ≥ 37 weeks. Likewise, most of the neonates (70.29%) were of age ≤ 7 days. In the same way (91.43%) were of birth weight ≥ 2.5 kg and (70.29%) followed Hindu religion.

Table 2: Distribution of Chief Complaints of the Neonates

Chief Complaints	Present		Absent	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
Fever	136	38.86	214	61.14
Breathing Problems	290	82.86	60	17.14
Decreased Feeding	132	37.71	218	62.29
Reducedmovements	20	5.71	330	94.29
Seizures	40	11.43	310	88.58
Slowor Fast Heart Rate	12	3.43	338	96.57

The commonest symptoms among the neonates studied was breathing problems (82.86%) followed by fever (38.86%) and decreased feeding (37.71%). Other symptoms like Seizures, reduced movements and slow or fast heart rate accounted for 11.43%, 5.71% and 3.43% respectively as depicted in Table 2

Table 3: Distribution of Investigation Profile of the Neonates

	SerumProcalcitonin	
Cut off	Frequency	Percentage
<0.5ng/ml	74	21.14
=0.5 ng/ml	276	78.86
Blood C/S		
Negative	292	83.43
Positive	58	16.57
CRP		
<10mg/L	70	20.00
=10mg/L	280	80.00
TLC		
>5000/mm^3	342	97.71
=5000/mm^3	8	2.29
ANC		
Normal	130	37.14
Abnormal	220	62.86
I/T Ratio		
=0.2	218	62.29
>0.2	132	37.71
Micro ESR		
=(Ageindays+3)	324	92.57
>(Ageindays+3)	26	7.43
>15mm	0	0

The table 3 showed that during laboratory investigation for septic marker value of PCT above normal (≥0.5 ng/ml) was 78.86% and ≤ 5000/mm3) was 2.29%, abnormal ANC findings was 62.86%, I/T ratio >0.2 was 37.71% and abnormal micro ESR was 7.43%.

Table 4: Distribution of types of Neonatal Sepsis

Neonatal Sepsis	Probable Sepsis		Culture Proven Sepsis		Possible Sepsis	
	N	%	N	%	N	%
Present	140	40.00	58	16.57	152	43.43
Absent	210	60.00	292	83.43	198	56.57

Table 4 reveals that (43.43 %) of neonates was possible sepsis followed by (40 %) was probable sepsis and 16.57% was culture proven sepsis.

Table 5: Association between Procalcitonin, CRP and Neonatal Sepsis

Neonatal Sepsis	Sensitivity(%)		Specificity(%)		PPV(%)		NPV(%)		P-value	
	PCT	CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT	CRP
Culture Proven Sepsis	89.66	89.66	23.29	21.92	18.84	18.57	91.89	91.43	2.40	2.02
Probable Sepsis	77.14	84.29	20.00	22.86	39.13	42.14	56.76	68.57	0.20	1.33
Possible Sepsis	76.32	72.37	19.19	14.14	42.03	39.29	51.35	40	0.52	4.8

Discussion

This is a study done among 350 neonates admitted to NICU of Nobel Medical College, Biratnagar to assess the role of serum procalcitonin as a marker for diagnosis of Neonatal Sepsis. In the study majority (69.71%) of male child were included and the birth weight was ≥ 2.5(91.43%) kg. Most of the children (87.43%) were term. Similarly, majority of neonates (70.29%) were ≤ 7 days of age followed by Hindu religion (70.29%). In our study majority of neonates CT(≥0.5ng/ml) were78.86%,CRP (≥ 10 mg/l) were 80%. Blood culture was positive in 16.57% in which sensitivity, specificity, PPV and NPV of PCT were 89.66%, 23.29%, 18.84% and 91.89% and CRP were 89.66%, 21.92%, 18.57%, and 91.43% respectively. The incidence of neonatal sepsis was found to be 36.84%.

In this study occurrence of sepsis soon after birth to 7days of life is referred as early onset neonatal sepsis and after a week is considered as late onset neonatal sepsis which is supported by study done by Mezgebu T.et.al [8], whereas study done by Vergnano S, Roble A.K. et.al., Shah R [9,10,11]refute our findings. As per our current study the mean age of neonates was 5.8 days (±5 SD) which is identical to the other study conducted by Akalu T. et. al. [12] and Jatsho J. et al, Getabelew A. et. al and Nur A et. al [13,14,15]. The gestational age of the neonates in this study

ranged from 31 weeks to 42 weeks and this finding is also supported by Akalu T. et. al and Nur A. et. Al [12, 15]. In the current study more than half of the neonates were male which is similar to the findings of Park I.H. et. al., Roble AK. et. al. and Covino M. et al [10,16], whereas study conducted by Bekele K. et. al and NUR A et. al. does not support this findings as equal percentage of both the gender got admitted with neonatal sepsis during study period [17,15].

In our study majority of birth weight of the neonates were more than and equal to 2.5kg which is similar to the findings of Bekele K.et.al, NurA.et.al and RobleA.K.et.al [17,15,10]. In this study majority of neonates developed early onset neonatal sepsis and the same findings were observed by Bekele K. et. al and Getabelew A. et. al [17,14]. Majority of the neonates belonged to Hindu religion and this result might be due to location of hospital which is around Hindu hub region. Hinduism is the majority religion in Nepal, constituting more than 81 per cent of the country's population [18]. In current study majority of neonates had developed breathing problem followed by fever, decreased sucking, and seizures and only few of the case had developed reduced movement and bradycardia or tachycardia as a clinical manifestation. Earlier studies also reflect similar findings. Bekele K. et. al and Getabelew A. et. al [17,14] but study done by Yadav S. et. al [19] had feeding intolerance and abdominal distension as the commonest symptoms of presentation.

In this study majority of the neonates had serum procalcitonin≥0.5 ng/ml. The main problem with PCT is that there is physiological increase during the first 48 hour of life which returns to normal on the 4th day. Further studies have shown that premature birth is associated with rise in PCT without any bacterial infection [4]. In our study 16. 57% neonates had blood culture positive and this finding was similar to study done by Hasan F et.al [20]. The blood culture positivity ranged from 16 to 65% in various studies done in low and middle-income countries [20]. In this study most of the cases80% had C-reactive protein≥10mg/L. There was increase in CRP concentration in non-infected clinical conditions such as meconium aspiration, prolonged rupture of membranes. In this study majority of the case 97.70% had TLC more than 5000/mm^3. In this study most of the cases 62.86% had ANC within abnormal limit and the majority of the cases 62.29% had I/T ratio less than or equal to 0.2 and 92.57% of cases had normal value of micro ESR and this was similar to the findings done by Kaur S et.al [21]. In the current study majority of the case 46.43%belong to possible sepsis followed by probable sepsis 40% and culture proven sepsis 16.57% which is supported by study conducted by Pravin Charles M. et. al [22] (12%) culture proven sepsis and 62.6% possible sepsis. Similarly in another study conducted by Manandhar and Basnet in 75 babies, confirmed sepsis was observed in 17.3%, probable sepsis in 53.4%, and possible sepsis in 29.3% [23].

In this study, PCT sensitivity was 77.14%, specificity was 20%, PPV 39.13%, and NPV was 57.76% in probable sepsis. Similarly in case of Possible Sepsis sensitivity was 76.32%, specificity was 19.19%, PPV was 42.03%, and NPV was 51.35%. While in case of Culture Proven Sepsis sensitivity was 89.66%, specificity was 23.29%, PPV 18.84%, NPV 91.43% which is supported by the findings illustrated by Gupta PK et.al [24], Thota U et.al. in which sensitivity 89.6%, and negative predictive value (NPV) was 93.6% [25] and Morad EA et.al. showed sensitivity 97.6%, specificity 89%, PPV97.6%, NPV 88.9% in culture proven sepsis [26]. Similarly, the Adib M. et al. and Bharti AK. et. al result differs from this study, where the cut-off value of PCT was 1.1 ng/ml and > 2 ng/ml respectively [27, 28]. In our study in probable sepsis CRP sensitivity was 84.29%, specificity was 22.86%,PPV 42.14% NPV was 68.57%similarly in case of Possible Sepsis sensitivity was 72.37% specificity was 14.14%PPV was 39.29% , NPV was 40% . While in case of Culture Proven Sepsis sensitivity was 89.66% specificity was 21.92% PPV 18.84% NPV 91.43% which is supported by Dollner H et.al, in which sensitivity70% to 93%; specificity 41% to 98%; positive predictive accuracy 6% to 83%; and negative predictive accuracy 97% to 99% [29].

Similar findings were also noted by Ahmed Z et.al. where sensitivity was 85.7% in culture proven sepsis and 80.5% in probable sepsis [30]. The findings by Kaur S et. al. sensitivity, specificity, PPV, and NPV of CRP were 87.5%, 43.2%, 35.9%, and 90.5%, respectively at cut- off value of CRP > 0.6 mg/dl [21] .There were important limitations as our study was a single-center study. Hence there might be some selection bias related to sepsis, so the result should be generalized with caution. Our study was a prospective study with a relatively small sample size. So, the true association of serum procalcitonin and neonatal sepsis may not be precise as compared to other studies conducted on a large scale. In procalcitonin-based trials, treatment group blinding is impossible, so the possibility of treatment bias cannot be ruled out.

Conclusion

Serum procalcitonin did not show a distinct advantage over the existing sepsis markers. Therefore, we draw the conclusion that serum PCT may not be the only diagnostic marker to diagnose neonatal sepsis in term/near term newborns, but it may be helpful when paired with other test indicators.

Acknowledgement

The authors would like to acknowledge the residents, interns and nursing staffs of NICU and pediatric ward for their help during the data collection

Conflict of interest: None

References

[1] Agrawal R, Deorari A, Paul V, Sankar M, Sachdewa A, AIIMS Protocols inNeonatology, Second Edition. Vol. 1. New Delhi: Medical book Publishers; 2019.303p.

[2] Hotchkiss RS, Karl IE, The pathophysiology and treatment of sepsis, New England Journal of Medicine 348:2 (2003)138-50. DOI:10.1056/NEJMra021333.

[3] Ministry of Health and Population, Nepal; New ERA; and ICF. 2022, Nepal Demographic and Health Survey 2022: Key Indicators Report. Kathmandu, Nepal: Ministry of Health and Population, Nepal.https://mohp.gov.np/n

[4] Altunhan H, Annagür A, Örs R, Mehmeto?lu I, Procalcitonin measurement at 24hours of age may be helpful in the prompt diagnosis of early-onset neonatal sepsis. International Journal of Infectious Diseases. 15:12 (2011) e854-58. DOI: 10.1016/j.ijid.2011.09.007

[5] Cho SY, Choi JH, Biomarkers of sepsis. Infect Chemother.46:1 (2014) 1-12. DOI: 10.3947/ic.2014.46.1.1.

[6] Naher B, Mannan M, Noor K, Shahidullah M, Role of serum procalcitonin and C- Reactive Protein in the diagnosis of neonatal sepsis, Bangladesh Medical Research Council Bulletin. 37:2 (2011) 40-6. DOI:10.3329/bmrcb.v37i2.8432. PMID: 21877603.

[7] Budhathoki S, Sunny A, Paudel P, Thapa J, Basnet L, Karki S et al, Epidemiology of neonatal infections in hospitals of Nepal: evidence from a large-scale study, Archives of Public Health. 78:1 (2020)78:39. DOI: https://doi.org/10.1186/s13690-020-00424-z

[8] Taye Mezgebu, Getachew Ossabo, Asnakech Zekiwos, Mohammed H, Zerihun Demisse, Neonatal sepsis and its associated factors among neonates admitted to the neonatal intensive care unit in Wachemo University Comprehensive Specialized Hospital, Southern Ethiopia, 2022, Frontiers in Pediatrics. 11: 1184205 (2023) 01-08 .DOI: https://doi.org/10.3389/fped.2023.1184205

[9] Vergnano S, Neonatal sepsis: an international perspective, Archives of Disease in Childhood-Fetal and Neonatal Edition. 90:3 (2005) F220-f224. DOI: 10.1136/adc.2002.022863

[10] Roble AK, Ayehubizu LM, Olad HM, Neonatal Sepsis and Associated Factors Among Neonates Admitted to Neonatal Intensive Care Unit in General Hospitals, Eastern Ethiopia 2020, Clinical Medicine Insights: Pediatrics. 16:117955652210983 (2022) 01-08. DOI: 10.1177/11795565221098346.

[11] Sah R, Bhattarai S, Basnet S,Pokhrel BM,Shah NP,Sah S,et al, A Prospective Study on Neonatal Sepsis in a Tertiary Hospital, Nepal, Journal of Pure and Applied Microbiology. 15:4 (2021) 2409-19.DOI: 10.22207/JPAM.15.4.66.

[12] Akalu TY, Aynalem YA, Shiferaw WS, Desta M, Amha H, Getaneh D, et al. Prevalence and determinants of early onset neonatal sepsis at two selected public referral hospitals in the Northwest Ethiopia: a cross-sectional study. BMC Pediatrics. 10:1 (2023) 01-09. DOI: https://doi.org/10.1186/s12887-022-03824-y.

[13] Jatsho J, Nishizawa Y, Pelzom D, Sharma R, Clinical and Bacteriological Profile of Neonatal Sepsis: A Prospective Hospital-Based Study, International Journal of Pediatrics. 2020:1835945 (2020) 01-09. DOI: 10.1155/2020/1835945.

[14] Getabelew A, Aman M, Fantaye E, Yeheyis T, Prevalence of Neonatal Sepsis and Associated Factors among Neonates in Neonatal Intensive Care Unit at Selected Governmental Hospitals in Shashemene Town, Oromia Regional State, Ethiopia, 2017, International Journal of Pediatrics. 2018:7801272 (2018) 01-07 DOI: 10.1155/2018/7801272.

[15] Nur A, Osman M, Assessment of neonatal sepsis and associated factors among neonates admitted neonatal intensive care unit in selected public hospitals in Somali Region, Ethiopia, The European Research Journal. 7:6 (2021) 617-27.DOI: 10.18621/eurj.596108

[16] Covino M, Manno A, De Matteis G, Taddei E, Carbone L, Piccioni A, et al, Prognostic Role of Serum Procalcitonin Measurement in Adult Patients Admitted to the Emergency Department with Fever, Antibiotics. 10:7 (2021) 788. DOI: 10.3390/antibiotics10070788.

[17] Bekele K, Bekele F, Edosa D, Mekonnen M, Benayew M, Magnitude and associated factors of neonatal sepsis among neonates admitted to neonatal intensive care unit of Northern oromia hospitals, Ethiopia: A multicenter cross-sectional study, Annals of Medicine and Surgery. 78:103782 (2022) 01-06 DOI: 10.1016/j.amsu.2022.103782.

[18] The Times of India, Nepal is "theoretically" and "practically" a Hindu nation, saysPuri Shankaracharya. https://timesofindia. indiatimes.com/staticsitemap/toi/2023-February-2.xml[cited 2023 Aug 20]

[19] Yadav S, Sharif M, Saxena A, Kolhe S, Dhole D. Role of Procalcitonin and C-Reactive Protein in the Early Diagnosis of Neonatal Sepsis. Indian Journal of Neonatal Medicine and Research 9:2 (2021) PO01-PO05. DOI: 10.7860/IJNMR/2021/48641.2295

[20] Hasan F, Khan SA, Maharoof MK, Muhammed N, Role of procalcitonin in early diagnosis of neonatal sepsis, International Journal of Contemporary Pediatrics. 4:2 (2017) 383-9. DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20170477.

[21] Kaur S, Singh K, Early-Onset Neonatal Sepsis: Role of C-Reactive Protein, Micro-ESR, and Gastric Aspirate for Polymorphs as Screening Markers, International journal of pediatrics. 2021:1544553 (2021) 01-06. DOI: 10.1155/2021/1544553.

[22] Pravin Charles M, Kalaivani R, Venkatesh S, Kali A, Seetha K, Evaluation of procalcitonin as a diagnostic marker in neonatal sepsis, Indian Journal of Pathology and Microbiology. 61:1 (2018)81-4. DOI: 10.4103/IJPM.IJPM_820_16.

[23] Manandhar S. R., Basnet R, Micro-erythrocyte sedi-

mentation rate in neonatal sepsis of a tertiary hospital: a descriptive cross-sectional study, JNMA; Journal of the Nepal Medical Association. 58:226 (2020) 377-82. DOI: https://doi.org/10.31729/jnma.4984
[24] Gupta P,Narang A, P447 Role of serum procalcitonin as marker of neonatal sepsis. Archives of Disease in Childhood. 104:Suppl 3(2019) A331-1. DOI:10.1136/archdischild-2019-epa.783.
[25] Usharani Thota, N, Srinivasa Suresh, Nanu Som, Role of Procalcitonin in Diagnosis of Neonatal Sepsis, Indian Journal of Applied Research. 6:6 (2016) 144-46. DOI: 10.36106/ijar.
[26] Morad E, Rabie R, Almalky M, Gebriel M, Evaluation of Procalcitonin, C-Reactive Protein, and Interleukin-6 as Early Markers for Diagnosis of Neonatal Sepsis, International Journal of Microbiology 2020:8889086 (2020) 01-09 DOI: 10.1155/2020/8889086.
[27] Adib M, Bakhshiani Z, Navaei F, SahebFosoul F, Fouladi S, Kazemzadeh H, Procalcitonin: a reliable marker for the diagnosis of neonatal sepsis. Iran J Basic Med Sci. 15:2 (2012)777-82. PMID: 23493845.
[28] Bharti AK, Verma MK, Gupta A, Mishra DK, Role of procalcitonin in diagnosis of neonatal sepsis and procalcitonin guided duration of antibiotic therapy. International Journal of Contemporary Pediatrics. 7:8 (2020) 1692-1700. DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20203088.
[29] Dollner H, Vatten L, Austgulen R, Early diagnostic markers for neonatal sepsis: Comparing C-reactive protein, interleukin-6, soluble tumor necrosis factor receptor and soluble adhesion molecules, Journal of Clinic Epidemiology. 54:12 (2001) 1251-7. DOI: 10.1016/s0895-4356(01)00400-0.
[30] Ahmed Z, Ghafoor T, Waqar T, Ali S, Aziz S, Mahmud S, Diagnostic value of C- reactive protein and haematological parameters in neonatal sepsis, Journal of the College of Physicians and Surgeons--Pakistan: JCPSP 15:3 (2005) 152-6. PMID: 15808093.