Journal Homepage: -www.journalijar.com
INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)
Article DOI:10.21474/IJAR01/1193
DOI URL: http://dx.doi.org/10.21474/IJAR01/1193
ISSN NO. 2320-5407

RESEARCH ARTICLE

SOLUBLE TRIGGERING RECEPTOR EXPRESSED ON MYELOID CELLS -1 (sTREM-1) AS A DIAGNOSTIC AND PROGNOSTIC MARKER FOR LATE-ONSET SEPSIS IN PRETERM NEONATES.

Noha Tharwat Abou El-khier[1*], Dalia Kamal Nassar[1], Sanaa Mohei El-Din Abd ElAal, Hesham EL-Sayed Abdel-Hady[2]

1. Medical Microbiology & Immunology Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt.
2. Neonatal Intensive Care Unit, Mansoura University Children`s Hospital, Mansoura, Egypt.

Manuscript Info

Manuscript History

Received: 18 June 2016
Final Accepted: 19 July 2016
Published: August 2016

Key words:-
Late onset sepsis, preterm, sTREM-1, prognosis.

Abstract

Background: -The most challenging aspect in late-onset neonatal sepsis (LOS) is the difficulty of its early and accurate diagnosis. sTREM-1 is a novel and promising marker of sepsis.
Objective: -Our aim was to investigate the role of serum levels of sTREM-1 in early diagnosis and prognosis of LOS.
Subjects &Methods: -Fifty nine preterm neonates admitted to NICU of Mansoura University Children's Hospital (MUCH), Egypt, were prospectively recruited in our study. Thirty infants with suspicion of LOS (sepsis group) and 29 gestational age and sex matched infants without sepsis served as a control group. All neonates were subjected to blood culture and routine sepsis screening. Levels of sTREM-1 were measured at enrollment and after 48-72 hours of antibiotic therapy in sepsis group.
Results: - Initial sTREM-1 levels of the sepsis group were statistically significantly higher than those of the control group (584.8 pg/mL, {IQR: 116.7-709.8}; versus 76 pg/mL, {IQR: 31.9-591}, *p* .003). sTREM-1 value of 77.5 pg/mL was established as a cut-off value, with 90% sensitivity and 51.7% specificity for diagnosis of LOS. As for prognosis, sTREM-1 cuttoff value of 91.5 pg/ml for prediction of survival had 96.3% sensitivity and 100% specificity. Serum levels of sTREM-1 showed gradual decrease during treatment.
Conclusion: - sTREM-1 can be used as a reliable biomarker for diagnosis, prognosis of LOS and for monitoring response to treatment in preterm infants

Introduction:-

Sepsis remains the most common cause of neonatal morbidity and mortality during the first month of life with the highest rates in preterm infants (Natale et al., 2014; El-Shiekh et al., 2016).

Corresponding Author: -NohaTharwatAbou El-khier
Address: -Medical Microbiology & Immunology Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt.

Neonatal sepsis is a systemic inflammatory response to infection that is characterized by presence of signs and symptoms of infection with or without concurrent bacteremia in the first month of life (Barman and Das, 2016; Behmadi et al., 2016). It is classified into early-onset sepsis (EOS) which occurs before 72 hours of life, and LOS after 72 hours (Martin et al., 2014).

The most challenging aspect in neonatal sepsis is the difficulty of its early and accurate diagnosis as it usually presents with subtle and non-specific signs that can be confused with other non-infective conditions with rapid deterioration of clinical condition (Ayazi et al., 2014; Hedegaard et al., 2015).

Although blood culture is regarded as the gold standard for confirmation of neonatal sepsis diagnosis (Delanghe and Speeckaert, 2015), it has many limitations such as unavailability of the results until 24-72 hours after starting the culture and its low sensitivity as 57% of septic infants may have false negative results (Haque, 2010). Many diagnostic tests such as white blood cell count (WBC), absolute neutrophilic count (ANC), and C- reactive protein (CRP) have been investigated for early diagnosis of septic neonates. However, they do not possess adequate sensitivity or specificity (Benitz et al., 2015; Coggins et al., 2016).

The triggering receptor expressed on the myeloid cells-1 (TREM-1) is a member of the immunoglobulin superfamily. It is a 30-kDa transmembrane glycoprotein expressed on polymorph nuclear (PMN) granulocytes and monocytes which amplifies the inflammatory response initiated by toll like receptors (TLRs) by triggering the release of pro inflammatory cytokines, activation of neutrophil degranulation and oxidative burst (Gomez-Pina et al., 2012; Sandquist and Wong, 2014). Soluble form of TREM-1 (sTREM-1) is a 27kDa protein produced through proteolytic cleavage of membrane–anchored TREM-1 by matrix metallo-proteinases (MMPs) (Gómez-Piña et al., 2007). It peaks 2 hours after infectious exposure where it can be measured in biological fluids providing an early marker for sepsis (Dupuy et al., 2013). Studies have reported increased levels of TREM-1 and sTREM-1 in the presence of infection while it is not up-regulated in patients with inflammatory conditions without infection so, it is useful for distinction between infectious and non-infectious diseases (Paolucci et al., 2012; Alqahtani et al., 2014).

Although several studies documented the role of serum level of sTREM-1 in diagnosis of neonatal sepsis (Su et al., 2012; Saldir et al., 2015), there is insufficient data regarding its prognostic value in neonatal sepsis. Hence, our study aimed at investigating the role of serum levels of sTREM-1 in early diagnosis and prognosis of LOS.

Subjects & methods:-

Study Design and Population:-

This prospective study was carried out on preterm neonates (<37 weeks of gestation) admitted to the NICU of MUCH from November 2014 to November 2015. Infants with chromosomal abnormalities or major congenital malformations were excluded. Informed consent was obtained from the infants` parents or legal guardian. The study was accepted by Mansoura Faculty of Medicine Institutional Review Board. A total of 59 preterm neonates were prospectively recruited in the study. Thirty of them had three or more clinical signs of LOS as recommended by Zaki and Elsayed(2009)constituting the sepsis group. Twenty-nine gestational age and sex matched newborns without clinical findings of sepsis served as the control group. Two blood samples were obtained from all enrolled neonates; one for blood culture and the other one for sTREM-1 assay by ELISA kits. Routine sepsis screening as CBC, TLC, ANC and CRP were recorded. The septic neonates were initially evaluated at clinical suspicion of sepsis and 48-72 hours after starting antibiotic therapy. All blood culture samples were sub cultured on blood, MacConkey and nutrient agar media (Oxoid) followed by microbiological identification by colonial morphology, Gram stained films and standard biochemical reactions (Koneman et al., 2006). Antimicrobial susceptibility testing was performed by the Kirby Bauer disc diffusion method according to CLSI, 2014 guidelines. Septic neonates were further classified into two subgroups: culture positive sepsis and culture negative sepsis according to the blood culture results.

STREM-1 Assay:-

Blood sample were allowed to coagulate for 10-20 min followed by centrifugation at 2000-3000 r.p.m for 20 min. The separated sera were kept at -20 °C until assayed by sTREM-1 ELISA kits (Sun Red Biotechnology,Shanghai, China) according to the manufacturer`s instructions.

Statistical Analysis:-

Data were analyzed by SPSS version 21 (SPSS Inc., Chicago, IL, USA). Qualitative data were described as numbers and percentages. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Parametric results were expressed as means ± standard deviations, while non-parametric data were expressed as median with inter-quartile range. The Chi-square test or Fisher 's exact test were used for comparing categorical variables between groups. Independent sample t-test was used for comparing parametric variables between groups. In the non-normally distributed variables, Mann- Whitney- U test was performed to compare between groups, while Wilcoxon signed ranks test was used to compare pretreatment and follow-up. Receiver operating characteristic (ROC) curves were plotted to determine the cutoff point and area under the ROC (AUC) curve was calculated. P value < 0.05 was considered to be statistically significant, *P* value <0.001 was highly significant.

Results:-

Fifty- nine preterm neonates were included in the study; 30 in the sepsis group and 29 in the control group. There were no statistically significant differences between the two groups in terms of demographic characteristics except for the postnatal age which was significantly higher in sepsis group (Table 1).

Table 1:-Demographic characteristics of sepsis and control groups.

	Sepsis group (No=30)	**Control group (No= 29)**	***P* value**
Gestational age, *weeks.*	31.7 ± 3.1	32 ± 3.1	0.7
Male, n (%)	13 (43.3%)	16 (55.2%)	0.3
Caesarian delivery, n (%)	19 (63.3%)	24 (82.8%)	0.09
Birth weight, *g.(IQR)*	1520 (1117.5-1925)	1470 (1090-2450)	0.8
Apgar score *1 min*	7.1 ± 2.3	7.3 ±2	0.7
Apgar score *5 min*	8.9 ± 1.2	9.2 ± 1.3	0.3
Postnatal age, days *(IQR)*	9.5 (6.75-14)	3 (1-6.5)	<0.001

In the sepsis group, 11 (36.7%) patients were diagnosed with culture-proven sepsis while 19 yielded no growth (63.3%). Among culture-proven sepsis, 3 patients (27.27%) had polymicrobial sepsis. In our study, 14 organisms were isolated from blood culture; 9 (64.29%) Gram-negative, 4 (28.57%) Gram-positive and 1 (7.14%) candida albicans (Table 2). The antibiotic susceptibility pattern of the isolated bacteria was determined (Table 3).

Table 2:- Blood Culture results of sepsis group.

Organisms isolated	**No (%)**
Klebsiella pneumoniae	4 (28.57)
Escherichia coli	2 (14.29)
Pseudomonas areuginosa	2 (14.29)
Serratiamarsecens	1 (7.14)
Methicillin-sensitive Staphylococcus aureus(MSSA)	3 (21.43)
Methicillin-resistant Staphylococcus aureus(MRSA)	1 (7.14)
Candida albicans	1 (7.14)

Table 3:- Antibiotic sensitivity pattern of the isolated organisms.

Antibiotic	**Gram negative organisms (n=9)**	**Gram positive organisms (n=4)**
Amoxicillin-clavulanic	11.1%	33.3%
Piperacillin-tazobactam	33.3 %	66.7%
Cefipime	22.2%	---
Amikacin	55.6%	---
Cefotaxime	11.1%	----
Ceftraixone	11.1%	-----
Imipenem	88.9%	50%
Gentamycin	33.3%	33.3%
Cefoxitin	---	66.7%
Cefuroxime	---	50%
Azithromycin	---	50%

Initial sTREM-1 levels of the sepsis group were statistically significantly higher than those of the control group (584.8 pg/mL, {IQR: 116.7-709.8}; versus 76 pg/mL, {IQR: 31.9-591}, p 0.003). Moreover, initial sTREM-1 levels were significantly higher than those measured after 48-72 hours of antibiotic therapy (584.8 pg/mL, {IQR: 116.7-709.8}; versus 123.5 pg/mL {IQR: 97-532.2}, p <0.001). Regarding the rest of laboratory parameters for sepsis diagnosis, WBC and platelet count were comparable between the sepsis and control groups with no significant statistical difference. Whereas hemoglobin was statistically significantly higher in control group, CRP and ANC were statistically significantly higher in sepsis group. (Table 4)

Table 4:-Value of laboratory parameters in sepsis and control groups.

Laboratory parameters	Sepsis group (NO=30)	Control group (NO=29)	*P* value
Initial sTREM-1, pg/ml *(IQR)*	584.8 (116.7-709.8)	76 (31.9-591)	0.003
Post therapy sTREM-1, pg/ml *(IQR)*	123.5 (97-532.2)	-----	<0.001
WBC,1000/mL*(IQR)*	16.2 (10.9-19.3)	13.7 (10.1-19.2)	0.2
Hemoglobin, g/dL	12.8 ±3.07	14.9 ±2.98	0.009
Platelets ,1000/mL *(IQR)*	258 (145.5-370.5)	226 (143-326.5)	0.6
ANC,1000/mL *(IQR)*	6.8 (4.5-11.3)	4.9 (3.5-7.2)	0.01
CRP, mg/L *(IQR)*	20.5 (0-74.7)	0 (0- 3)	<0.001

sTREM-1 value of 77.5 pg./ml was established by the ROC curve as a cutoff for diagnosis of LOS, it had 90% sensitivity, 51.7% specificity, 65.9% PPV, 83.3% NPV. As for CRP, at a cutoff 3 mg/L, it had 70% sensitivity, 75.9 % specificity, 75% PPV, 71% NPV for diagnosis of LOS. A combination of sTREM-1 and CRP had 100 % sensitivity, 44.8% specificity, 65.2% PPV and 100% NPV (Figure 1).

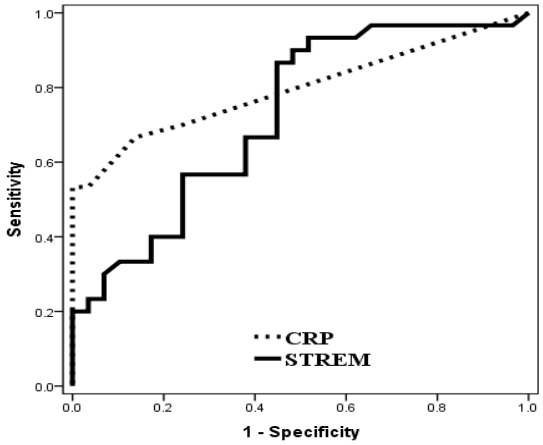

Fig 1:-ROC curves of sTREM-1 and CRP for diagnosis of LOS.

For prognosis of sepsis, sTREM-1 was statistically significantly elevated in survivors than non-survivors (p 0.006) being the highest discriminative marker for prognosis of sepsis. Regarding other laboratory parameters (WBC, hemoglobin, platelet and CRP), there was no statistical significant difference between survivors and non-survivors. However, ANC was statistically significantly elevated in non-survivors (Table 5).

Table 5:- Comparison of laboratory data between survivors and non-survivors.

Laboratory data	Survivors (No=27)	Non survivors (No=3)	*P* value
Initial sTREM-1, pg/ml (IQR)	591.2 (216-721.40)	56 (9.8-79)	0.006
WBC,1000/mL (IQR)	15 (10.8-18.5)	21.6 (18.7-24)	0.06
Hemoglobin, g./Dl	12.8 ± 3.2	12.5 ± 1.4	0.8
Platelets ,1000/mL (IQR)	269 (153-375)	220 (24-258)	0.2
CRP, mg/L (IQR)	12 (0-68)	80 (27-96)	0.1
ANC,1000/mL (IQR)	6.2 (4.5-10)	13.3 (11.2-15.9)	0.03

Roc curve of strem-1 for the prognosis of sepsis determined a cutoff value of 91.5 pg./ ml for predicting infants` survival with sensitivity, specificity, PPV, NPV of 96.3%,100%,100%,75% respectively (figure 2)

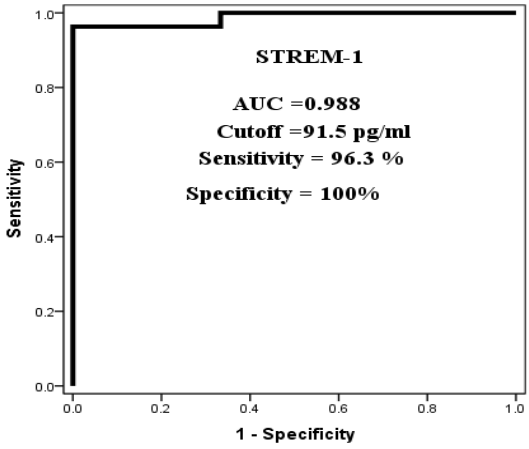

Fig 2:-ROC curve of sTREM-1 for prognosis of LOS.

Discussion:-

TREM-1 is a member of the immunoglobulin superfamily, which is expressed on human neutrophils and monocytes after the exposure to bacterial and fungal infections (Ford and McVicar, 2009). The role of sTREM-1 as a biomarker for infection has been studied throughout the last fifteen years with established efficacy in clinical settings (Pontrelli et al., 2016).

Regarding sTREM-1 levels at diagnosis, it was statistically significantly higher in sepsis than control group. Our results are consistent with those of Wang and Chen (2011); Su et al. (2012) and Saldir et al. (2015). In disagreement to these results, Bopp et al. (2009) and Schlapbach et al. (2013) found that sTREM-1 could not discriminate septic from non-septic group which is mainly due to different study population and different ELISA methods.

At cutoff 77.5 pg. /ml using ROC curve, sTREM-1 had 90% sensitivity, 51.7% specificity, 65.9% PPV, 83.3% NPV for diagnosis of LOS. This high sensitivity allows recognition of almost all septic neonates while ruling out LOS in clinically suspected neonates, while this moderate specificity would be acceptable in the setting of neonatal sepsis allowing for substantial reduction in antibiotic prescriptions. Moreover, PPV is acceptable meaning that only one out of three neonates will receive antibiotic therapy, but that is harmless than missing a truly infected neonate. The high NPV would help in ruling out LOS sepsis with confidence.

Variable cutoffs for sTREM-1 levels have been proposed in different studies starting from 24.4- 3500 pg/ml (Kofoed et al., 2007; Palmiere et al., 2013 and Bayram et al., 2015). This is mainly due to differences in the characteristics of patient groups, variable neonatal sepsis definitions, different sample size, lack of method standardization during measurement, timing and processing of sample, duration between sampling till performance of the test, threshold of measurement and different sensitivity of ELISA kits (Wu et al., 2012 and Dupuy et al., 2013).

CRP is an acute phase reactant that was studiedmeticulously for diagnosis of sepsis (Samraj et al., 2013).We found that CRP was statistically significantly higher in sepsis group. These findings are consistent with Chen et al. (2014); Celik et al. (2016) and Kumar et al. (2016). In contrast, Fleming et al. (2012) and Nierhaus et al. (2013)reported that CRP could not differentiate septic from non-septic neonates.

Different sensitivities ranging from 70% to 93% and specificities ranging from 41% to 98% have been reported for CRP (Chiesa et al., 2003; Kocabas et al., 2007). In our study, at a cutoff 3 mg/L, CRP had sensitivity (70%), specificity (75.9%), PPV (75%) and NPV (71%) for diagnosing LOS. These results go to a great extent with those of Celik et al. (2016)who reported 71.8% sensitivity, 76.3% specificity, 72.9% PPV and 72.5% NPV of CRP. Also, similar rates of sensitivity (76.9%, 72.6%) were reported by Hisamuddin et al. (2015) and Kumar et al. (2016)

respectively. The moderate sensitivity and specificity values reported in our study show that CRP alone is insufficient for diagnosis of neonatal sepsis.

Since there is no single marker with ideal sensitivity and specificity that was identified as the magic bullet for diagnosis of neonatal sepsis, a combination of markers is highly recommended specially one that can have high sensitivity which is more important that specificity in life threatening conditions with high morbidity and mortality as neonatal sepsis. The combination should also support the neonatologist decision to stop or continue empirical antibiotics without posing a threat to the infant (Bohnhorst et al., 2012; Walley, 2013).

So, we evaluated a combination of CRP and sTREM-1. This combination had 100% sensitivity, 44.8% specificity,65.2% PPV and 100% NPV. Accordingly, positive tests would identify all septic neonates helping to reduce the complication and mortality resulting from delay of treatment, while negative tests would rule out sepsis with absolute confidence. Also, PPV value of 65.2 % is acceptable given that only one out of three infants will be over treated with antibiotic which is considered to be harmless in respect to the fatal consequences of withholding therapy according to a false-negative result.

Regarding the prognostic value of sTREM-1, its levels were statistically significantly higher in survivor than non survivors at diagnosis stating that it is a perfect marker to stratify and recognize neonates for whom mortality or complication are expected, so that clinicians could monitor them closely. Similar results were documented by Wang and Chen (2011); Zhang et al. (2011) and Su et al. (2012), indicating that sTREM-1 is a valuable biomarker with better performance than CRP for the prognosis of sepsis. In contrast, other authors demonstrated no association of sTREM-1 levels to patient outcome (Phua et al., 2008; Bopp et al., 2009). Regarding the prognostic value of sTREM-1, a cutoff 91.5 pg/ ml for prediction of survival was determined by ROC curve, stating that levels of sTREM-1 above the cutoff value are protective with a sensitivity (96.3%), specificity (100%), PPV (100%) and NPV (75%).Consistent with our results, Gibot et al. (2005) and Giamarellos-Bourboulis et al. (2008)concluded that initial sTREM-1 levels were higher in survivors than non-survivors with good prognosis in patients who have sTREM-1 levels above 180 pg./ml. Also, similar results were reported in meningitis Salem and Elmoety (2015). On contrary, Porfyridis et al. (2010); Oku et al. (2013) and Li et al. (2014) reported that high initial levels were associated with bad outcome. This may be due to the difference of timing of sample and the difference in study groups. Variable cutoffs with varying sensitivity and specificity for sTREM-1 in prognosis of sepsis have been reported in previous studies ranging from 50-9000 pg/ml (Kofoed et al., 2008;Sun et al., 2011;Li et al., 2014)

In our study, we found that sTREM-1 levels showed highly significant statistical decrease 48-72 hrs after administration of antibiotics in relation to initial sTREM-1 levels indicating that sTREM-1 is a useful monitoring marker for follow-up of septic neonates to observe the effect of treatment which is consistent with the results of Sarafidis et al. (2010) and Saldir et al. (2015). The main limitation in our study was small sized sample number which can be validated by further large scale studies before application to general population.

Conclusion:-

In conclusion, sTREM-1 is considered a perfect marker for early and accurate diagnosis of LOS with an almost perfect sensitivity approaching 100%, which is reached when combined with CRP,This combination can identify allneonates who are at high risk of sepsis and in need of antibiotics, and those in which antibiotics can be withheld. This will ultimately lead to prevention the high mortality and the morbid complications associated with late diagnosis and administration of unnecessary therapy in neonatal sepsis. Furthermore, sTREM-1 is a reliable biomarker for prognosis of LOS, and its serial levels can determine the efficiency of treatment, helping the clinicians to decide whether to stop or continue antibiotics.

References:-

1. Alqahtani, M. F., Marsillio, L. E., &Rozenfeld, R. A. (2014). A review of biomarkers and physiomarkers in pediatric sepsis. ClinPediatrEmerg Med, 15(2): 177-184.
2. Ayazi, P., Mahyar, A., Daneshi, M. M., Jahanihashemi, H., Esmailzadehha, N., &Mosaferirad, N. (2014). Comparison of serum IL-1beta and C reactive protein levels in early diagnosis and management of neonatal sepsis. Infez Med, 22(4): 296-301.
3. Barman, M., & Das, B. (2016). A Study of Validity of Haematological Parameters in the Diagnosis of Neonatal Sepsis. Indian J Appl Res, 6(3): 532-535.

4. Bayram, H., TÜNger, Ö., ÇİVİ, M., YÜCeyar, M. H., Ulman, C., DİNÇ Horasan, G., et al. (2015). Diagnostic and prognostic value of procalcitonin and sTREM-1 levels in sepsis. Turk J Med Sci, 45: 578-586.
5. Behmadi, H., Borji, A., Taghavi-Rad, A., Soghandi, L., &Behmadi, R. (2016). Prevalence and Antibiotic Resistance of Neonatal Sepsis Pathogens in Neyshabour, Iran. Arch Pediatr Infect Dis, 4(2): e33818
6. Benitz, W. E., Wynn, J. L., &Polin, R. A. (2015). Reappraisal of guidelines for management of neonates with suspected early-onset sepsis. J Pediatr, 166(4): 1070-1074.
7. Bohnhorst, B., Lange, M., Bartels, D. B., Bejo, L., Hoy, L., & Peter, C. (2012). Procalcitonin and valuable clinical symptoms in the early detection of neonatal late-onset bacterial infection. ActaPaediatr, 101(1): 19-25.
8. Bopp, C., Hofer, S., Bouchon, A., Zimmermann, J. B., Martin, E., &Weigand, M. A. (2009). Soluble TREM-1 is not suitable for distinguishing between systemic inflammatory response syndrome and sepsis survivors and nonsurvivors in the early stage of acute inflammation. Eur J Anaesthesiol, 26(6): 504-507.
9. Celik, H. T., Portakal, O., Yigit, S., Hascelik, G., Korkmaz, A., &Yurdakok, M. (2016). Efficacy of new leukocyte parameters versus serum C-reactive protein, procalcitonin, and interleukin-6 in the diagnosis of neonatal sepsis. PediatrInt, 58(2): 119-125.
10. Chen, M., Wang, B., Xu, Y., Deng, Z., Xue, H., Wang, L., et al. (2014). Diagnostic value of serum leptin and a promising novel diagnostic model for sepsis. ExpTher Med, 7(4): 881-886.
11. Chiesa, C., Pellegrini, G., Panero, A., Osborn, J. F., Signore, F., Assumma, M., et al. (2003). C-reactive protein, interleukin-6, and procalcitonin in the immediate postnatal period: influence of illness severity, risk status, antenatal and perinatal complications, and infection. ClinChem, 49(1): 60-68.
12. Coggins, S. A., Weitkamp, J. H., Grunwald, L., Stark, A. R., Reese, J., Walsh, W., et al. (2016). Heart rate characteristic index monitoring for bloodstream infection in an NICU: a 3-year experience. Arch Dis Child Fetal Neonatal Ed. 101(4): F329-332.
13. Delanghe, J. R., &Speeckaert, M. M. (2015). Translational research and biomarkers in neonatal sepsis. ClinChimActa, 451: 46-64.
14. Dupuy, A.M., Philippart, F., Péan, Y., Lasocki, S., Charles, P.-E., Chalumeau, M., et al. (2013). Role of biomarkers in the management of antibiotic therapy: an expert panel review: I–currently available biomarkers for clinical use in acute infections. Ann Intensive Care, 3(1): 22.
15. El-Shiekh, H., Gaafar, M., Yosri, M., Hassan, D. M., & Said, H. (2016). Study of Bacteria Causing Septicemia in Neonatal Intensive Care Unit. Egypt J Med Microbiol, 25(1): 37-44.
16. Fleming, P. F., Forster, D., Savage, T., Sudholz, H., Jacobs, S. E., & Daley, A. J. (2012). Evaluating suspected sepsis in term neonates. J Neonatal Nurs, 18(3): 98-104.
17. Ford, J. W., &McVicar, D. W. (2009). TREM and TREM-like receptors in inflammation and disease. CurrOpinImmunol, 21(1): 38-46.
18. Giamarellos-Bourboulis, E. J., Mouktaroudi, M., Tsaganos, T., Koutoukas, P., Spyridaki, E., Pelekanou, A., et al. (2008). Evidence for the participation of soluble triggering receptor expressed on myeloid cells-1 in the systemic inflammatory response syndrome after multiple trauma. J Trauma, 65(6): 1385-1390.
19. Gibot, S., Cravoisy, A., Kolopp-Sarda, M. N., Béné, M. C., Faure, G., Bollaert, P.E., et al. (2005). Time-course of sTREM (soluble triggering receptor expressed on myeloid cells)-1, procalcitonin, and C-reactive protein plasma concentrations during sepsis. Crit Care Med, 33(4): 792-796.
20. Gómez-Piña, V., Soares-Schanoski, A., Rodríguez-Rojas, A., del Fresno, C., García, F., Vallejo-Cremades, M. T., et al. (2007). Metalloproteinases shed TREM-1 ectodomain from lipopolysaccharide-stimulated human monocytes. J Immunol, 179(6): 4065-4073.
21. Gómez-Piña, V., Martinez, E., Fernandez-Ruiz, I., del Fresno, C., Soares-Schanoski, A., Jurado, T., et al. (2012). Role of MMPs in orchestrating inflammatory response in human monocytes via a TREM-1-PI3K-NF-κB pathway. J LeukocBiol, 91(6): 933-945
22. Haque, K. N. (2010). Neonatal Sepsis in the Very Low Birth Weight Preterm Infants: Part 2: Review of Definition, Diagnosis and Management. J Med Sci, 3(1): 11-27.
23. Hedegaard, S. S., Wisborg, K., &Hvas, A. M. (2015). Diagnostic utility of biomarkers for neonatal sepsis-a systematic review. Infect Dis, 47(3): 117-124.
24. Hisamuddin, E., Hisam, A., Wahid, S., & Raza, G. (2015). Validity of C-reactive protein (CRP) for diagnosis of neonatal sepsis. Pak J Med Sci, 31(3): 527-531.
25. Kocabas, E., Sarikçioglu, A., Aksaray, N., &Seydaoglu, G. (2007). Role of procalcitonin, C-reactive protein, interleukin-6, interleukin-8 and tumor necrosis factor-[alpha] in the diagnosis of neonatal sepsis. Turk J Pediatr, 49(1): 7-20.
26. Kofoed, K., Andersen, O., Kronborg, G., Tvede, M., Petersen, J., Eugen-Olsen, J., et al. (2007). Use of plasma C-reactive protein, procalcitonin, neutrophils, macrophage migration inhibitory factor, soluble urokinase-type

plasminogen activator receptor, and soluble triggering receptor expressed on myeloid cells-1 in combination to diagnose infections: a prospective study. Crit Care, 11(2): R38.
27. Kofoed, K., Eugen-Olsen, J., Petersen, J., Larsen, K., & Andersen, O. (2008). Predicting mortality in patients with systemic inflammatory response syndrome: an evaluation of two prognostic models, two soluble receptors, and a macrophage migration inhibitory factor. Eur J ClinMicrobiol Infect Dis, 27(5): 375-383.
28. Koneman, E.W., Allen, S.D., Janda, W.M., Schreckenberger, R.C., Winn, W.C., Procop, G.W., et al. (2006). Charts. In Koneman, E.W., Allen, S.D., Janda, W.M., Schreckenberger, R.C., Winn, W.C., Procop, G.W., et al. (Eds.), Koneman's color atlas and textbook of diagnostic microbiology (6th ed.). Philadelphia: Lippincot, pp. 1443-81.
29. Kumar, N., Singh, M. K., Dayal, R., Gupta, S., & Garg, R. (2016). Diagnostic role of IL-6 in Neonatal sepsis. Annals of Applied Bio-Sciences, 3(1): A67-71.
30. Li, Z., Wang, H., Liu, J., Chen, B., & Li, G. (2014). Serum Soluble Triggering Receptor Expressed on Myeloid Cells-1 and Procalcitonin Can Reflect Sepsis Severity and Predict Prognosis: A Prospective Cohort Study. Mediators Inflamm, 2014: 1-7.
31. Martin, R. J., Fanaroff, A. A., & Walsh, M. C. (2015). In Martin, R. J., Fanaroff, A. A., & Walsh, M. C (Eds). Fanaroff and Martin's Neonatal-perinatal medicine: diseases of the fetus and infant (10th ed). Philadelphia: Saunders, pp. 1-833
32. Natale, F., Bizzarri, B., Cardi, V., & De Curtis, M. (2014). Early and late onset sepsis in late preterm infants. Ital J Pediatr, 40(2): A 23.
33. Nierhaus, A., Klatte, S., Linssen, J., Eismann, N. M., Wichmann, D., Hedke, J., et al. (2013). Revisiting the white blood cell count: immature granulocytes count as a diagnostic marker to discriminate between SIRS and sepsis - a prospective, observational study. BMC Immunol, 14(1): 1-8.
34. Oku, R., Oda, S., Nakada, T.-a., Sadahiro, T., Nakamura, M., Hirayama, Y., et al. (2013). Differential pattern of cell-surface and soluble TREM-1 between sepsis and SIRS. Cytokine, 61(1): 112-117.
35. Palmiere, C., Bardy, D., Mangin, P., &Augsburger, M. (2013). Value of sTREM-1, procalcitonin and CRP as laboratory parameters for postmortem diagnosis of sepsis. J Infect, 67(6): 545-555.
36. Paolucci, M., Landini, M. P., &Sambri, V. (2012). How can the microbiologist help in diagnosing neonatal sepsis? Int J Pediatr, 2012: 120139.
37. Phua, J., Koay, E., Zhang, D., & Lee, K. (2008). How well do serum sTREM-1 measurements prognosticate in septic shock? Anaesth Intensive Care, 36(5): 654- 658.
38. Pontrelli, G., De Crescenzo, F., Buzzetti, R., Calo Carducci, F., Jenkner, A., Amodio, D., et al. (2016). Diagnostic value of soluble triggering receptor expressed on myeloid cells in paediatric sepsis: a systematic review. Ital J Pediatr, 42: 44.
39. Porfyridis, I., Plachouras, D., Karagianni, V., Kotanidou, A., Papiris, S. A., Giamarellou, H., et al. (2010). Diagnostic value of triggering receptor expressed on myeloid cells-1 and C-reactive protein for patients with lung infiltrates: an observational study. BMC Infect Dis, 10(1): 286.
40. Saldir, M., Tunc, T., Cekmez, F., Cetinkaya, M., Kalayci, T., Fidanci, K., et al. (2015). Endocan and Soluble Triggering Receptor Expressed on Myeloid Cells-1 as Novel Markers for Neonatal Sepsis. PediatrNeonatol, 56(6): 415-421.
41. Salem, G., &Elmoety, H. (2015). Usefulness of Various Biomarkers for the Differentiation of Bacterial from Viral Meningitis. Int J Trop Dis Health, 9(2): 1-8.
42. Samraj, R. S., Zingarelli, B., & Wong, H. R. (2013). Role of biomarkers in sepsis care. Shock, 40(5): 358-365.
43. Sandquist, M., & Wong, H. R. (2014). Biomarkers of sepsis and their potential value in diagnosis, prognosis and treatment. Expert Rev ClinImmunol, 10(10): 1349-1356.
44. Sarafidis, K., Soubasi-Griva, V., Piretzi, K., Thomaidou, A., Agakidou, E., Taparkou, A., et al. (2010). Diagnostic utility of elevated serum soluble triggering receptor expressed on myeloid cells (sTREM)-1 in infected neonates. Intensive Care Med, 36(5): 864-868.
45. Schlapbach, L. J., Graf, R., Woerner, A., Fontana, M., Zimmermann-Baer, U., Glauser, D., et al. (2013). Pancreatic stone protein as a novel marker for neonatal sepsis. Intensive Care Med, 39(4): 754-763.
46. Su, L., Han, B., Liu, C., Liang, L., Jiang, Z., Deng, J., et al. (2012). Value of soluble TREM-1, procalcitonin, and C-reactive protein serum levels as biomarkers for detecting bacteremia among sepsis patients with new fever in intensive care units: a prospective cohort study. BMC Infect Dis, 12(1): 157.
47. Sun, J., Song, S. D., & Zhao, H. J. (2011). [Expression of soluble triggering receptor expressed on myeloid cells-1 in septic patients and its relation with prognosis]. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue, 23(5): 305-308. Chinese.
48. Walley, K. R. (2013). Biomarkers in Sepsis. Curr Infect Dis Rep, 15(5): 413-420.

49. Wang, H.x., & Chen, B. (2011). Diagnostic role of soluble triggering receptor expressed on myeloid cell-1 in patients with sepsis. World J Emerg Med, 2(3): 190-194.
50. Wu, Y., Wang, F., Fan, X., Bao, R., Bo, L., Li, J., et al. (2012). Accuracy of plasma sTREM-1 for sepsis diagnosis in systemic inflammatory patients: a systematic review and meta-analysis. Crit Care, 16(6): R229.
51. Zaki, M. E. S., & El Sayed, H. (2009). Evaluation of Microbiologic and Hematologic Parameters and E-Selectin as Early Predictors for Outcome of Neonatal Sepsis. Arch Pathol Lab Med., 133(8): 1291-1296.
52. Zhang, J., She, D., Feng, D., Jia, Y., &Xie, L. (2011). Dynamic changes of serum soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) reflect sepsis severity and can predict prognosis: a prospective study. BMC Infect Dis., 11(1): 53.