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# Soluble Triggering Receptors Expressed on Myeloid Cell-1 and Proadrenomedullin for Diagnosis and Prognosis of Early Onset Neonatal Sepsis

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## Abstract

**Background:** Despite advances in medicine, neonates have high global rates of morbidity and mortality related to bacterial sepsis. Neonates are predisposed to infections during the perinatal period due to multiple exposures and a relatively compromised immune system and complex procedures.

**The aim of the study:** The aim of this study was to investigate the value of two proposed sepsis markers; serum pro adrenomedullin (Pro ADM) and serum soluble triggering receptor expressed on myeloid cell-1 (sTREM-1) for early diagnosis and prognosis of early onset neonatal sepsis.

**Methods:** This analytic case control study was conducted in Alzhraa University hospital, Egypt. Sixty five full term newborn infants with early onset sepsis and 25 newborn infants without sepsis were included in the study. For all cases Töllner and, Griffin scores, complete blood count, hematological score, blood culture, quantitative CRP, estimation of serum pro-adrenomedullin (Pro-ADM) and serum soluble triggering receptor expressed on myeloid cell-1 (sTREM-1) were done.

**Results:** Incidence of early onset sepsis was 17% from admitted cases during the study period. There was significant increase in Pro-ADM mean values in septic neonates than control group as well as sTREM-1, P was 0.001. The cut off value for Pro-ADM (ng/L) was > 20.5 ng/L with sensitivity 98.5% and specificity 100%, PPV 100 and NPP 93.8. The cut off value for sTREM-1 was > 55.5 ng/L with sensitivity 98.5%, specificity and PPV 100% and NPP 93.8. Blood culture was positive in 49.3% of cases.There was highly statistically significant increase in the level of serum pro-ADM, sTREM -1 and CRP in positive blood culture cases compared to negative blood culture cases. The percentage of mortality was 21.5% among sepsis group.Regarding prognostic values serum pro-ADM and sTREM -1 were significantly higher among dead cases than survival cases.

**Conclusions:** Negative blood culture cannot exclude sepsis. Pro-ADM and sTREM-1 can be used for early diagnosis of early onset neonatal sepsis and help in detecting the severity of sepsis. Töllner, Griffin scores may be used to pick up suspected cases of early onset neonatal sepsis especially in countries with limited resources.

***Keywords:*** *Newborn; Sepsis; Pro-ADM; sTREM-1*

## Abbreviations

EOS: Early Onset Sepsis; ENSTN: Egyptian Neonatal Safety Training Network; CRP: C-Reactive Protein; Pro-ADM: Pro-Adrenomedullin; ROC: Receiver Operating Characteristic; sTREM-1: Soluble Triggering Receptor Expressed on Myeloid Cell-1; SIRS: Systemic Inflammatory Response Syndrome

## Introduction

In spite of all the progresses in medicine, newborn infants still suffer globally from high rates of morbidity and mortality due to bacterial infection [1]. Neonates are predisposed to infections during the perinatal time due to various experiences to infectious agent and to their moderately compromised immune system. The burden of neonatal infection is varying by setting; differing estimates of disease burden have been reported from high-income countries compared with reports from low-income and middle-income countries [2]. Compliance with hand hygiene guidelines of CDC and WHO as the in standard 8 of Egyptian Neonatal Safety Training Network (ENSTN) may reduce the risk of infection [3].

There is a limitation for confirmed diagnosis of early neonatal sepsis which leads to improper use of antibiotics. Blood culture results take from 48 to 72 hours with delay to initiate treatment. Multiple diagnostic markers had been investigated for early diagnosis of septic neonates. Nevertheless, these markers do not have adequate sensitivity or specificity for diagnosis, also there is variable cut off points between different laboratories [4].

The triggering receptor expressed on myeloid cells-1 (TREM-1) is a member of the immunoglobulin superfamily, it is strongly expressed on activated phagocytes and released during infection [5].

Pro-adrenomedullin (Pro-ADM) is stable precursor molecule to human adrenomedullin which has immunomodulatory effect. Elevations of pro-ADM have been reported in systemic inflammatory response syndrome (SIRS), sepsis, and septic shock in adults [6].

Still insufficient data regarding the roles as of Pro-ADM and (sTREM-1) as early and prognostic markers for neonates with early onset sepsis due to inconsistent results and different cut off point [7].

### Research Questions

- Could serum Pro-adrenomedullin (Pro ADM) be used for early detection and prediction of prognosis of early onset neonatal sepsis?
- Could serum soluble triggering receptor expressed on myeloid cell-1 (sTREM-1) be used for early detection and prediction of prognosis of early onset neonatal sepsis?

## Aim of the Study

This study aims to investigate the value of two proposed sepsis markers; serum pro adrenomedullin (Pro ADM) and serum soluble triggering receptor expressed on myeloid cell-1 (sTREM-1) for early diagnosis and prognosis of early onset neonatal sepsis.

## Patients and Methods

This is analytical case control study that was conducted on (65) full term newborn infants who were admitted to NICU of, pediatric department, Al-Zahraa University hospital, Al-Azhar University, Cairo, Egypt with symptoms or signs of early onset sepsis (EOS) during first 72 hours after birth with or without maternal risk factors for neonatal sepsis. They were screened for sepsis by clinical and hematological sepsis scores.

Preterm infants postdate infants, cases with errors of metabolic and neonates with major congenital anomalies as well as cases of late onset sepsis were excluded from the study.

Age matched (25) full term newborn without clinical findings of sepsis (control group) were also included in the study.

Informed consent was obtained from the infants parents or legal guardian. The study was accepted by Faculty of Medicine for girls Institutional Board at 1/3/2015.

## Methods

All cases and control were subjected to full history taking, general and local clinical examinations. The manifestations of neonatal sepsis were evaluated using clinical sepsis scores including Griffin score [8] and Töllner score [9]. Blood samples were obtained for sepsis screen at the first day and 48 hours; complete blood count, blood culture, quantitative CRP, estimation of serum pro-adrenomedullin (Pro-ADM) and serum soluble triggering receptor expressed on myeloid cell-1 (sTREM-1) assay by ELISA kits.

Septic neonates were further classified into two subgroups: culture positive sepsis and culture negative sepsis according to the blood culture results and survival and non-survival cases.

## Statistical Analysis

Data were collected, revised, coded and entered to the statistical package for social science (IBM SPSS) version 20; (SPSS Inc., Chicago, IL, USA). Parametric data were compared using independent sample t-test, while non-parametric data we used Mann- Whitney- U test. The Chi-square test was used for comparing categorical variables between groups. Receiver operating characteristic (ROC) curve was used to define the cutoff point sensitivity, specificity area under the curve. P value < 0.05 was considered to be statistically significant.

## Results

| | Septic group (N = 65) | Control group (N = 25) | P value |
|---|---|---|---|
| Gestational age (week) (Mean ± SD) | (38.26 ± 0.70) | (37.66 ± 0.71) | 0.07* |
| Gender<br>Female %<br>Male % | <br>8 (53.33%)<br>46 (70.77%) | <br>19 (29.23%)<br>7 (46.67%) | 0.0055* |
| BW (kg) (Mean ± SD) | (3.07 ± 0.40) | (3.05 ± 0.46) | 0.873* |
| Length (cm) (Mean ± SD) | (48.67 ± 3.04) | (49.51 ± 2.95) | 0.343* |
| HC (cm) (Mean ± SD) | (33.80 ± 1.08) | (34.32 ± 1.05) | 0.105* |
| Mode of delivery<br>No.%<br>CS %<br>Vaginal % | <br><br>8 (53.33%)<br>18 (27.7%) | <br><br>47 (72.3%)<br>7 (46.67%) | 0.0055* |
| Apgar score at 1 min Median (IQR) | 5 (5 - 5) | 5 (4 - 5) | 0.179• |
| Apgar score at 5 min Median (IQR) | 9 (9 - 9) | 9 (9 - 10) | 0.586• |
| PROM >18 Hours | 10 (15.4%) | 1 (4 ) | 0.0004^ |
| DM | 15 (23.1%) | 2 (8 ) | 0.001^ |
| Tachypnea | 54 (81.3%) | 0 0 | |

***Table 1:*** *Comparison between newborn septic group and control group regarding demographic data.*

*BW: Body Weight; HC: Head Circumference.*

**: Independent t test.•: Mann-Whitney test, ^: chi square test P < 0.05: Significant*

| | Septic group (No = 65) | Control group (No = 25) | Mann-Whitney test |
|---|---|---|---|
| | Median<br>(IQ) | Median<br>IQ | P |
| Pro-ADM (ng/l) | 310<br>(686-168 ) 518 | 116<br>(148-87.5) 60.5 | 0.000 |
| sTREM-1 (ng/l) | 390<br>(580-280) 300 | 93<br>(109.5-66) 43,5 | 0.000 |
| CRP (mg/dl) | 10<br>(25-6) 19 | 3<br>(4-2) 2 | 0.000 |

***Table 2:*** *Comparison between septic newborn infants group and control group regarding to serum pro-adrenomedullin level serum soluble triggering receptor expressed on myeloid cell-1 and CRP.*

| | Positive blood culture<br>Median<br>IQ | Negative blood culture<br>Median<br>IQ | P |
|---|---|---|---|
| Pro-ADM (ng/l) | 187<br>(300 - 161.5) 138.5 | 432<br>(880 - 314.5) 565.5 | 0.000 |
| sTREM-1 (ng/l) | 345<br>(460 - 262.5) 197.5 | 458<br>(740.5 - 249) 491.5 | 0.001 |
| CRP (mg/dl) | 24.5<br>( 66.75 - 9) 57.75 | 8<br>(14 - 6) 8 | 0.000 |

***Table 3:*** *Comparison between results of blood culture and studied markers in newborn septic group. Mann-Whitney test P < 0.05: Significant*

| | Dead | Improved | P |
|---|---|---|---|
| Pro-ADM(ng/l)<br>Median<br>IQ | 900<br>997.5 - 675 = 322.5 | 195<br>400 - 164.5 = 235.5 | 0.000[a] |
| sTREM-1(ng/l)<br>Median<br>IQ | 862<br>988.5 - 702 = 286.5 | 343<br>422.5 - 260 = 162.5 | 0.000[a] |
| CRP(mg/dl)<br>Median<br>IQ | 26<br>86-9 = 77 | 9<br>17 - 6 = 11 | 0.000[a] |
| Griffin score Mean ± SD | 6.36 ± 1.28 | 4.47 ± 1.45 | 0.000* |
| Töllner score Mean ± SD | 10.50 ± 2.03 | 7.90 ± 2.05 | 0.000* |
| Hematological score Mean± SD | 4.79 ± 1.67 | 3.82 ± 1.11 | 0.059* |

***Table 4:*** *Comparison of the studied parameters in relation to the outcome of studied cases.*

**: Independent t test. •: Mann-Whitney test, P < 0.05: Significant*

| Test | AUC | Cut off value | Sensitivity | Specificity | PPV | NPP |
|---|---|---|---|---|---|---|
| Pro-ADM (ng/L) | 0.661 | > 20.5 | 98.5% | 100% | 100% | 93.8% |
| sTREM-1 (ng/L) | 0.678 | > 55.5 | 98.5% | 100% | 100% | 93.8% |
| CRP (mg/dl) | 1 | > 5.5 | 100% | 100% | 100% | 100% |

***Table 5:*** *Diagnostic accuracy of serum Pro-ADM, sTREM-1 and CRP.*

*This table showed that at a cutoff point 20.5 ng/L the level of Pro-ADM showed sensitivity 98.5 and specificity 100% with PPV 100% and NPV 93.8%, also showed that at a cutoff point 55.5 ng/L the level of sTREM-1 showed sensitivity 98.5 and specificity 100% with PPV 100% and NPV 93.8%. At a cutoff point 5.5 mg/dl the level of CRP showed sensitivity 100% and specificity 100% with PPV 100% and NPV 100%.*

| Test | Cut off value | Sensitivity | Specificity | PPV | NPP |
|---|---|---|---|---|---|
| Pro-ADM (ng/L) | 47 | 100% | 85.7% | 68% | 100% |
| sTREM-1 (ng/L) | 59.5 | 96.92% | 93.33% | 98.44% | 87.50% |
| CRP (mg/dl) | 7.5 | 75% | 33% | 83% | 24% |

***Table 6:*** *Diagnostic accuracy of serum Pro-ADM, sTREM-1 and CRP in first day.*

*The previous table showed that at a cutoff point 47 ng/L the level of Pro-ADM in the first day showed sensitivity 100% and specificity 85.7% with PPV 68% and NPV 100%, also showed that at a cutoff point 59.5 ng/L the level of sTREM-1 showed sensitivity 96.92% and specificity 93.33% with PPV 98.44% and NPV 87.50%. At a cutoff point 7.5 mg/dl the level of CRP in the first day showed sensitivity 75% and specificity 33% with PPV 83%and NPV 24%.*

| Test | AUC | Cut off value | Sensitivity | Specificity | PPV | NPP |
|---|---|---|---|---|---|---|
| Griffin Score | 1.0 | 1.5 | 100% | 100% | 100% | 100% |
| Töllner Score | 1.0 | 3.5 | 100% | 100% | 100% | 100% |
| Haematological score | 0.99 | 2.0 | 96.9% | 100% | 100% | 96.99% |

***Table 7:*** *Diagnostic accuracy of Griffin, Töllner and Haematological scores.*

*The previous table showed that at a cutoff point 1.5 Griffin score showed sensitivity 100% and specificity 100% with PPV 100% and NPV 100%, also showed that at a cutoff point 3.5 Töllner score showed sensitivity 100% and specificity 100% with PPV 100% and NPV 100%. At a cutoff point 2 hematological score showed sensitivity 96.9% and specificity 100% with PPV 100%and NPV 96.99%.*

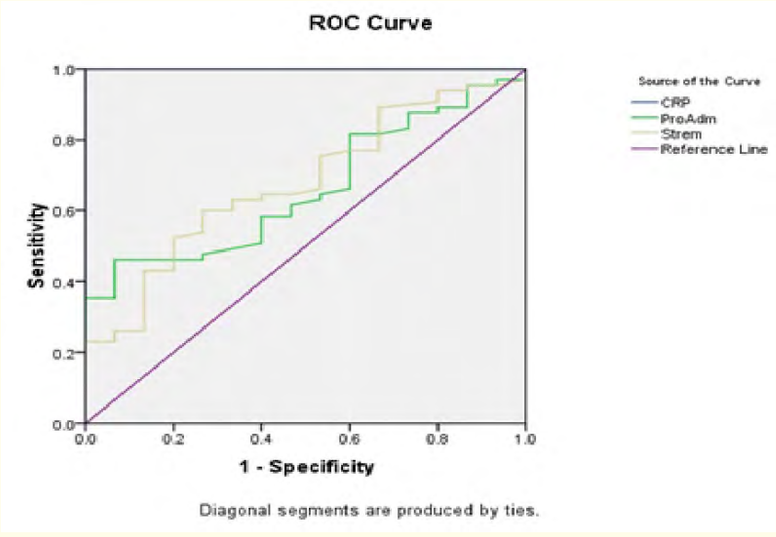


***Figure 1:*** *Receiver operating characteristic curve (ROC) curve of Pro-ADM, sTREM- 1 and CRP in the studied groups.*

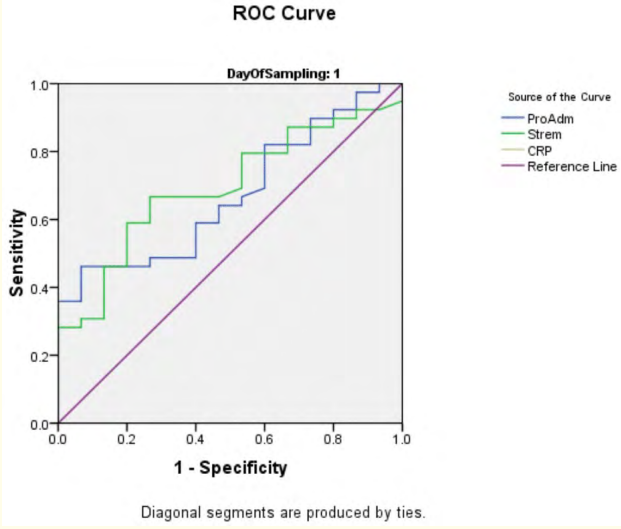


***Figure 2:*** *ROC curve of Pro-ADM, sTREM-1 and CRP in first day of sampling in septic group and control group.*

## Discussion

There is no single diagnostic test that can reliably diagnose sepsis in the newborn. The ultimate proof of sepsis depends primarily on isolating the infecting organism. However, the sole use of blood culture to diagnose neonatal infection has a number of limitations. It may take 24 - 72 hours to obtain culture results and the sensitivity of blood culture may be impaired by exposure to intrapartum antibiotic which are administrated to 15 - 40% of mothers in labour [10].

The aim of this study was to investigate the role of serum Pro-ADM and sTREM-1 in the diagnosis and prognosis of early onset neonatal sepsis. The studied groups were comparable as regards to gestational age, body weight, length and head circumference and Apgar score. 49.3% of sepsis group had positive blood culture. These results agreed with others [11,12]. Positive blood culture confirms the diagnosis of sepsis, but neonatal sepsis cannot be ruled out solely on the basis of a negative blood culture result [13].

Our results showed significant increase in the mean values of serum Proadrenomedullin in septic group. Also pro-ADM was significantly increased in newborn infants with positive blood culture than those with negative blood culture. These results agreed with other researchers [14-17]. Increased Pro-ADM level in sepsis could be due to different mechanisms; it is member of calcitonin receptor-like gene family, that upregulated by bacterial endotoxin and pro- inflammatory cytokines and widely expressed during sepsis. Also, lung is alternative site of Pro-ADM clearance, and infection related lung injury, may impair removal of Pro-ADM from pulmonary circulation [18]. Also there was non-statistical increase in pro-adrenomedullin with gram negative bacilli infection.

The initial results of Pro-ADM to detect early onset neonatal sepsis had the cut off value of 47 ng/L with 100% sensitivity, 85.7% specificity and 68% PPV and NPP 100%. Then at 48 hours the best cutoff point of Pro-ADM was 20.5 ng/L with sensitivity 98.5%, specificity 100%, PPV 100% and NPV 93.8%. Some authors reported more or less similar cutoff values, but others had different values, which may be due to different techniques of measurement of Pro-ADM [6,15,17,19].

Our findings support the role of sTREM-1 as a potential early reliable marker in neonatal sepsis, before obtaining culture results or in neonates who have clinical and laboratory evidence of sepsis even with negative blood cultures. There was significant increase in the level of sTREM-1 in septic group compared to control group. Also the mean value of sTREM-1 was significantly increased among cases with positive blood culture than those with negative blood culture. This results agreed with several researchers [11,20-23]. There was non-statistical increase in sTREM-1 with gram negative bacilli infection. TREM- 1 amplifies infection-induced inflammatory response signals primarily through the mediation of adapter protein DAP 12 on the cell surface. sTREM-1, as the soluble form of TREM- 1 released by activated phagocytes, may be a more "direct" marker of infection [24]. The best initial cutoff point of sTREM-1 to detect early onset neonatal sepsis was 59.5 ng/L with sensitivity 96.92%, specificity 93.3%, PPV 98.4% and NPP 87.5%.Then it was 55.5 ng/L with sensitivity of 98.5%, specificity 100%, PPV 100% and NPV 93.8%.

These results support the role of both markers in early diagnosis and prognosis of early onset neonatal sepsis.

The mean values of CRP level increased among septic group compared to control group and in positive blood culture cases. These results were agreed with Oncel., *et al* [15]. The initial best cutoff point of initial CRP to detect EOS was 7.5 mg/dl with sensitivity 75%, specificity 33%, PPV 83% and NPV 24%. Then it was 5.5 mg/dl with sensitivity 100%, specificity 100%, PPV100% and NPV 100%. These results were agreed with Benitz 2010 [25]. CRP levels are known to take at least 10 - 12 hours to rise after the onset of infection, and hence, it may be unhelpful in the initial diagnosis of early onset disease. Leal., *et al*. [26] considered CRP as a “specific” but “late” marker of neonatal infection. The best predictive ability of CRP for EONS lies when it is measured within 24 to 48 hours of birth or a rising CRP level is seen [27].

The risk factors in this study revealed predominance of male infants in 66.76% of sepsis cases. There is accumulating evidence in support of sex-based differences in innate and adaptive immune responses, consequently in the susceptibility to infectious diseases. X-linked genes, hormones and societal context are among the many factors that contribute to disparate immune responses in males and females. Androgen, have been shown to be suppressive on cell –mediated immune response. In contrast, female sex hormones exhibit protective effect which may contribute to the natural advantage of female under septic condition [28].

Our results showed that 72.3% of septic neonates were delivered by caesarian section. This leads to higher chance of developing newborn sepsis. Hansen., *et al*. [29] stated that vaginal delivery had protective effect, compared with elective CS for all gestational age group.

The maternal risk factors included significant increase in the percentage of maternal diabetes mellitus among septic group. Hyperglycemia was found to promote lipid peroxidation by a superoxide-dependent pathway resulting in the generation of free radicals. Excessively high levels of free radicals cause damage to cellular proteins, membrane lipids, and nucleic acids triggering of cell death pathways. The colostrum of diabetic mothers had lower IgA and IgG levels and the mononuclear cells from cord blood had lower functional activity [30].

There was significant increase in the percentage of premature rupture of membrane among septic group compared to control group. This result agreed with Christopher and Martina [31]. PROM > 18 hour lead to disruption of the barrier between the sterile amnion and the colonized environment with leakage of amniotic fluids and ascending of infections [32].

Tachypnea was the most common manifestation among septic group. Unexplained respiratory distress in full term infants should be considered sepsis until proved otherwise, in infants with mature lung respiratory distress is more likely to be due to sepsis or pneumonia [33]. EL Meneza., *et al*. [34] found that CD64 can be used for differentiation between infected and non-infected full term newborn infants presented with respiratory distress.

Clinical sepsis scores; Töllner, Griffin and hematological score were significantly increased among septic group compared to control group. Our results showed that at the first day, the best cutoff point for Griffin score to detect neonatal sepsis was 1 with sensitivity, specificity, PPV and NPV of 100%. The cutoff point of 2 for Töllner score had sensitivity, specificity, PPV and NPV 100%. A cutoff point of 1 for the hematological score showed sensitivity 97.44%, specificity100%, PPV100% and NPV93.7%. These findings mean that clinical scores can be used to pick up suspected cases of early onset neonatal sepsis.especially in developing countries.

Neonatal sepsis remains a major cause of death in developing countries [35]. Overall mortality from septicemia varies between 26 - 40%, for EOS it varies between 15 - 20% [36]. The percentage of mortality in our study was 21.5% among septic group. Mortality rate in neonatal sepsis could be due to socioeconomic, geographical and racial factors, use of invasive procedures as ventilators, virulence strains of microorganisms, impaired cardiac function [37] and use of non-sensitive antibiotics. Serum sTREM and Pro-ADM mean values were significantly increased among non-survived septic newborn infants, so sTREM and Pro-ADM can be used as prognostic markers to evaluate severity of illness. These results were agreed with several authors [17,19,23,38-40].

## Conclusions

Negative blood culture cannot exclude sepsis. Pro-ADM and sTREM-1 can be used for early diagnosis of early onset neonatal sepsis and help in detecting the severity of sepsis. Töllner, Griffin scores may be used to pick up suspected cases of early onset neonatal sepsis especially in countries with limited resources.

## Conflict of Interest

There is no any financial interest or any conflict of interest exists.

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