Presepsin as a New Marker for Early Detection Neonatal Sepsis in Al-Quwayiyah General Hospital
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ABSTRACT

Background: Early detection and start of antibiotic therapy neonatal sepsis (N.S) dramatically improves outcomes, so it is important to perform fast, reliable and specific early laboratory biomarkers.

Aim: This study aimed to detect the prevalence, the risk factors, hematology profile, microbial profile of neonatal sepsis patients and also investigate the value of PCT and CRP, in comparison to presepsin in establishing the early diagnosis of neonatal sepsis.

Methods: A cross sectional study was performed from March to September 2019 in Al Quwayiyah General hospital involving 120 neonates who were classified into 3 groups. The patients groups

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were: Proved N.S, suspected N.S and control healthy neonates, classified depending on Tollner score. Haematology profile and blood culture for each neonate were done. CRP, PCT and presepsin values were analyzed, compared, and their effectiveness as diagnostic markers was determined. Sensitivity, specificity, positive, and negative predictive values of the markers were calculated.

**Results:** The prevalence of neonatal sepsis was 20.8%. 75 neonates were males and 45 neonates were females. 74 neonates were preterm, while 46 were full term. Gestational age in weeks was 31.1±5.9w for neonates with proved sepsis, 32.4±6.7w for neonates with suspected sepsis and 36.4±4.4w for control group. The mean birth weight was 1740±105.3 g for neonates with proved sepsis, 2650±205.2 g for control group. 36 babies suffered from respiratory distress syndrome, 10 had jaundice, 8 had cough, 28 had fever and 8 complained of other symptoms. Blood cultures were positive for all patients of proved sepsis. The identified bacteria included Gram positive bacteria 22(55%) which were Coagulase negative staph. 13(32.5%) followed by *Staphylococcus aureus* 4(10%) while Gram negative bacteria 15(37.5%) which were *E. coli* 5(12.5%) followed by *Klebsiella pneumoniae* and also fungal infection (Candida species) detected in 3(7.5%) cases. There was significant difference between the mean and standard deviation of CRP, PCT and presepsin levels in proved and suspected N.S. groups when compared with healthy controls (P<0.05). CRP sensitivity and specificity (72%, 61% respectively) which were less useful in diagnosis of neonatal sepsis compared to presepsin which has the highest sensitivity and specificity (95%, 81% respectively) followed by procalcitonin with sensitivity and specificity (90%, 69% respectively).

**Conclusion:** The prevalence of neonatal sepsis among all admitted neonates in Al-Qwayiyah general hospital was 20.8%. Our results also detected higher sensitivity, specificity and positive and negative predictive values for presepsin more than and PCT CRP in the diagnosis of NS.

**Keywords:** C. reactive protein; presepsin; neonatal sepsis; procalcitonin.

### 1. INTRODUCTION

Neonatal sepsis (NS) is a common cause of neonatal morbidity and mortality. In neonate, rapid diagnosis and treatment of systemic bacterial infection is necessary as any delay in treatment of serious bacterial infections may lead to inappropriate effects [1]. The clinical signs of NS are unspecific and indistinguishable from non-infectious diseases, so the diagnosis of NS is quite complicated and may be misleading because critically ill neonates frequently experience systemic inflammatory response syndrome without infection [2].

It has been shown that early detection and appropriate clinical intervention are critical to improve the outcome of sepsis patients [3]. During the first hours of life, reliable infection markers are absent in NS. Therefore, neonatologists usually start early antibiotic treatment in newborn infants who have risk factors for infection, exposing many neonates to unnecessary treatments because of the limitation of the diagnostic tools in early diagnosis of sepsis, as the isolation of causative organisms from microbiological cultures takes up to 3 days and may be negative in newborns. Besides, it is impractical to obtain blood sample for serial blood culture from infants [4]. So, new laboratory methods for early diagnosis of the diseases, evaluation of prognosis and treatment efficiency are needed [5].

C-reactive protein (CRP) is a non specific marker for diagnosis of NS. High levels CRP are seen in infection, in autoimmune disease, in surgery, meconium aspiration and recent vaccination. Also, the CRP levels do not elevate significantly until almost 14-48 hr after the start of infection [6].

Procalcitonin is a calcitonin peptide precursor, and is part of the sepsis inflammatory cascade. Procalcitonin levels tend to rise in bacterial infections, whereas in viral infection they are depressed [7], procalcitonin are a calcitonine peptide precursor, and is a part of the sepsis inflammatory cascade. procalcitonin levels tend to rise in bacterial infections, whereas in viral infections they are depressed [8]. Procalcitonin is appeared in the serum within 4 hours of bacterial infections and has a half-life about 22–26 hours [9]. Sometimes, procalcitonin levels may be increased in patients who do not suffer from sepsis, with levels between 2–10 ng/mL detected in patients with autoimmune diseases [10], trauma [11], cardiac arrest [12], surgery [13], burns [14] and pancreatitis [15].
Presepsin has been emerged as a newer generation of the inflammatory markers with a sensitivity and specificity which is better than other markers. Presepsin increased earlier and faster in patients with sepsis, at 2 hours after sepsis model, peaked at 3 hours, and declined at 4–8 hours [16]. It is a CD14 polypeptide, CD14 present in two forms: Membrane-bound CD14 (mCD14) and soluble CD14 (sCD14). The mCD14 has a good affinity to Lipopolysaccarides (LPS), and is mainly expressed on the monocytes/macrophages cell surfaces. The sCD14 is detected in plasma, and is produced by mCD14 fall-off or cell secretion [17,18]. Two types of sCD14 could be detected in the plasma of healthy people at microgram level: 49KD and 55KD. sCD14 have an important role in mediating the immune responses to LPS of CD14-negative cells such as endothelial cells and epithelial cells. sCD14 is cleaved by cathepsin D and some proteases in plasma and the N-terminal fragments of 13kDa constitutes sCD14 subtype (sCD14-ST) which has been named as presepsin recently [19,20].

This study aimed to detect the prevalence, the characteristics of newborns, hematologic profile, microbial profile of neonatal sepsis patients and also investigate the value of PCT and CRP, in comparison to presepsin in establishing the early diagnosis of neonatal sepsis.

2. MATERIALS AND METHODS

2.1 Study Design

A cross sectional study was performed from March to September 2019 in nursery and neonatal intensive care unit (NICU) in Al Quwayiyah General hospital involving 120 neonates 90 with proved or suspected bacterial infection and 30 control (had no diagnosis of sepsis during hospital stay). The diagnosis of neonatal sepsis was done according to the presence of clinical, laboratory, or culture screen parameters:

a) Clinical signs consistent with infection based on the Tollner score [21] (respiratory distress, fever, cough, abnormal skin color, peripheral circulation impairment, hypotonia or seizures, abdominal distension).

b) Laboratory parameters (leukocyte count, left shift and thrombocytopenia).

c) Positive culture (blood, urine, and cerebrospinal fluid) or pneumonia (chest X-ray findings. Points are given for each parameter: 0, 1, 2, or 3; a higher number of points reflect a greater severity.

Three groups of neonates were investigated;

I. Proved sepsis group included 40 neonates based on clinical and laboratory findings (a Tollner score of ≥10).

II. Suspected sepsis group included 50 neonates based on clinical and laboratory findings (a Tollner score of 5-10).

III. Control group included 30 healthy neonates who had no clinical or laboratory data of infection and who were appeared to be healthy based on a Tollner score of ≤ 5.

Data was collected for each baby who included gender, gestational age, birth weight, age at time of presentation. The study was approved by the hospital ethics committee. Both verbal and written informed consent was given by the parents.

Exclusion criteria included history of antibiotics administration by the mother or the newborn, congenital malformations, TORCH complex related congenital infections, and refusal of parental consent.

2.2 Specimens Collection

- Blood samples were aseptically obtained from each neonate within the 24 hours of NICU admission as follows: 0.5 mL was inoculated immediately into blood culture bottles for blood culture.
- One to two ml venous blood were obtained by peripheral venous puncture and collected in plain tubes to separate serum, Blood samples were centrifuged within 30 min of collection, and the serum was stored at -20°C until analysis until used for assessment of CRP, Presepsin, and PCT.

2.3 Laboratory Methods

2.3.1 Blood culture

- Peripheral blood culture samples (pediatric bottle) were obtained from each patient as part of their routine evaluation in pediatric and nursery wards before initiation of antibiotic therapy in infants suspected with sepsis.
2. Blood samples collected were inoculated into one aerobic BacT/ALERT PF (BioMérieux) bottle which were incubated in the BacT/ALERT® 3D instrument (BioMérieux) at 35°C for 5 days or until microbial growth was detected.

3. Positive bottles were removed from the BACTEC blood culture system, and a Gram stain was done then sub-cultured on nutrient, MacConkey, blood and chocolate agar media and incubated at 35°C. The isolates were identified by Gram’s staining, colony characteristics and biochemical properties. Full identification of microorganisms was done with standard bacteriological and biochemical methods.

2.3.2 CRP

CRP was detected by the semi-quantitative latex agglutination test (AVITEX CRP kits; Catalog No. OD023; supplied by Omega Diagnostics, UK) the CRP kits measured ranges from 0.10 to 20.0 mg/l, cutoff value was 9 mg/ml.

2.3.3 Procalcitonin

Procalcitonin was measured using the PCT sandwich ELISA assay (BioVendor R&D, Germany) on evo1s machine (biomerieux, France). Absorbance is measured at 450 nm. For the analysis, cutoff value was 5.6 ng/ml.

2.3.4 Presepsin

Presepsin (sCD14 st) level was measured using human sCD 14 ELISA kit (Wuhan Fine Biotech Co., Ltd) on evo1s machine (biomerieux, France). This kit was based on sandwich enzyme-linked immune-sorbet assay technology. Read the O.D. absorbance at 450 nm cutoff value was 500 pg/mL.

2.4 Statistical Analysis

Data were entered into SPSS software version 22 (Chicago, IL, USA). Categorical variables were presented as frequencies and percentages. Chi square (X2) test and fisher exact test were used to find the association between the categorical variables. To detect the diagnostic importance of CRP, PCT and presepsin levels, the receiver operating characteristic (ROC) curve was analyzed and the sensitivities, specificities, and positive and negative predictive values were calculated. A P-value< 0.05 was considered as significant.

3. RESULTS

A total 120 neonates were included in our study 90 cases had either proved or suspected sepsis out of 432 admitted babies, which means that the prevalence of neonatal sepsis among all admitted neonates in Al-Guwayiyah general hospital was 20.8%. 75 neonates were males and 45 were females. 74 neonates were preterm, while 46 were full term. Gestational age in weeks was 31.1±5.9 w for neonates with proved sepsis, 32.4±6.7 w for neonates with suspected sepsis and 36.4±4.4w for control group. The mean birth weight was 1740±105.3 g for neonates with proved sepsis, 32.4±6.7 g for neonates with suspected sepsis and 2.650±205.2 g for control group. Moreover, Age at time of presentation was 16.3±18.4d for neonates with proved sepsis, 18.2±15.4d for neonates with suspected sepsis and 3.6±2.3d for control group.

Fig. 1 showed that out of 90 proved and suspected neonatal sepsis, 36(40%) babies had respiratory distress, 10(11.1%) had jaundice, 8(8.8%) had cough, 28(31.1%) had fever and 8(8.8%) complained of other symptoms.

| Table 1. Characteristics of newborns with neonatal sepsis |
|----------------------------------------------------------|
| Ch.Ch | Proved sepsis =40 | Suspected sepsis=50 | Control=30 |
|-------|------------------|-------------------|--------|
|       | NO | %       | NO | %   | NO | % |
| Gender |     |        |     |     |     |    |
| Male | 25 | 62.5%  | 34 | 68   | 16 | 53.3 |
| Female | 15 | 37.5%  | 16 | 32   | 14 | 46.7 |
| Gestational age |     |        |     |     |     |    |
| Preterm <37 weeks | 30 | 75%  | 39 | 78   | 5  | 16.7 |
| Term 37 weeks | 10 | 25%  | 11 | 22   | 25 | 83.3 |
| Gestational age in weeks | 31.1±5.9 | 32.4±6.7 | 36.4±4.4 |
| Birth weight in grams | 1740±105.3 | 1820±108.5 | 2.650±205.2 |
| Age at time of presentation | 16.3±18.4 | 18.2±15.4 | 3.6±2.3 |
Hematology profile and causative organisms of neonatal sepsis were shown in (Table 2). Platelet count/mm$^3$ was lower for neonates with proved sepsis 458914 ±110305, and for neonates with suspected sepsis 425891±141258 more than for control group 325148±810250. Leukocyte count/mm$^3$ also was higher for neonates with proved sepsis 18912±9541 and for neonates with suspected sepsis 10912±2451 more than for control group 6417±213. Blood cultures were positive for all patients of proved sepsis. The identified bacteria (Table 2) included Gram positive bacteria 22(55%) which were Coagulase negative staph. 13(32.5%) followed by Staphylococcus aureus 4(10%), then Streptococcus viridans & MRSA 2(5%) for each), while Gram negative bacteria 15(37.5%) which were E. coli 5(12.5%) followed by Klebsiella pneumoniae 4(10%) then Pseudomonas aeruginosa 3(7.5%). also fungal infection (Candida species) detected in 3(7.5%) cases.

Table 2. Shows hematologist profile and causative organisms of proved neonatal sepsis

|                      | Proved sepsis =40 | Suspected sepsis=50 | Control=30 |
|----------------------|-------------------|---------------------|-------------|
| **Platelet count/mm$^3$ Mean ± SD** | 458914 ±110305 | 425891±141258 | 325148±810250 |
| **Leukocyte count/mm$^3$ Mean ± SD** | 18912±9541 | 10912±2451 | 6417±213 |
| **Micro-organisms** | **NO** | **%** |
| Gram positive bacteria | 22 | 55% |
| Coagulase negative staph. | 13 | 32.5% |
| Staph. aureus | 4 | 10% |
| Strept. viridans | 2 | 5% |
| Group B strep. | 1 | 2.5% |
| MRSA | 2 | 5% |
| Gram negative bacteria | 15 | 37.5% |
| E. coli | 5 | 12.5% |
| Klebsiella pneumoniae | 4 | 10% |
| Enterobacter cloacae | 1 | 2.5% |
| Pseudomonas aeruginosa | 3 | 7.5% |
| Acinetobacter baumann | 2 | 5% |
| Fungal | 3 | 7.5% |
| Candida species | 3 | 7.5% |
The mean and standard deviation of CRP, PCT and presepsin levels in studied groups are shown in (Table 3). There was significant difference between the mean of CRP, PCT and presepsin levels in proved and suspected N.S. groups when compared with healthy controls (P< 0.05). Also, a significant difference was observed between proved and suspected N.S newborns (P< 0.0001).

Table 4 showed that CRP sensitivity and specificity (72%, 61% respectively) which were less useful in diagnosis of neonatal sepsis compared to presepsin which has the highest sensitivity and specificity (95%, 81% respectively) followed by procalcitonin with sensitivity and specificity (90%, 69% respectively). The positive and negative predictive rates were the lowest in CRP (28% and 80% respectively), whereas the positive and negative predictive rate showed high result in case of presepsin and PCT (presepsin positive predictive and negative predictive values were 84% and 95% respectively, while PCT positive predictive and negative predictive values were 55% and 95% respectively).

**Table 3. Comparison between serum levels of CRP, procalcitonin and presepsin among studied groups**

| Test       | Proved sepsis | Suspected sepsis | control | F test | P value |
|------------|---------------|------------------|---------|--------|---------|
| CRP (mg/ml)| 38.22±18.74   | 11.50±5.12       | 2.65±1.69 | 45.2   | <0.0001 |
| Procalcitonin (ng/ml) | 11.45±2.33   | 6.10±2.55       | 0.74±0.41 | 53.4   | <0.001  |
| Presepsin (pg/ml) | 1892.9±487.2 | 825.9±562.2     | 325.3±130.2 | 3.10   | <0.001  |

P-value< 0.05 was considered as significant

**Fig. 2. ROC curve**

ROC curves for biomarker, Area under the ROC curve for sepsis patients: CRP =0.43 (0.25 – 0.60), PCT = 0.72 (0.57 – 0.88) and PRE = 0.83 (0.70 – 0.97)

**Table 4. Sensitivity, specificity, PPV, NPV of CRP, procalcitonin and presepsin in detection of suspected neonatal sepsis**

|                  | CRP          | Procalcitonin | Presepsin |
|------------------|--------------|---------------|-----------|
| Sensitivity      | 72%          | 90%           | 95%       |
| Specificity      | 61%          | 69%           | 81%       |
| PPV              | 29%          | 55%           | 84%       |
| NPV              | 82%          | 95%           | 95%       |
| Cut off          | 9 mg/ml      | 5.6 ng/ml     | 500 pg/ml |

PPV: Positive predictive value NPV: Negative predictive value
4. DISCUSSION

The result of this study showed that the prevalence of neonatal sepsis among all admitted neonates in Al-Quwayiyah general hospital was 20.8% which was similar to the incidence of neonatal sepsis among neonates in king Khalid university hospital in 2016 which was 27% [22]. Also agreed with Eman M., et al. [23] who reported a high incidence of neonatal sepsis in three hospitals in Egypt, while this figure was higher than that were reported from Nepal (12.4%) [24] and India (7.6%) [25] as the study focused on admitted neonates in intensive care units in which most of the cases were critically ill and with high probability of sepsis than those admitted to other the general pediatric department as the case of our study.

This study focused on some factors that may precipitate the development of neonatal sepsis like prematurity, Gestational age in weeks, birth weight and age at time of presentation, there was an association being exist between these factors and the neonatal sepsis which agreed with a study in southeastern Mexico at 2012 [26], revealed that, prematurity, and low birth weight are significant contributing factors to the neonatal sepsis. This was similar also to the findings of previous studies on neonatal sepsis conducted internationally and regionally [27-29]. So special attention should be directed to babies with prematurity and low birth weight as they are more prone to develop neonatal sepsis, and appropriate empirical therapy should be started as early as possible.

Reporting the common signs and symptoms associated with neonatal sepsis can be beneficial in the early identification of the affected babies. Our results have showed that most patients with neonatal sepsis presented with respiratory distress 36(40%) babies, 10(11.1%) had jaundice, 8(8.8%) had cough, 28(31.1%) had fever and 8(8.8%) complained of other symptoms, also in a study conducted in Sanaa (Yemen) showed that the most common clinical pictures were Difficulty of breathing (42.2) [30]. Similar findings were reported in India; respiratory distress (44%) [31]. In contrast, Chiabi et al. have found that fever and irritability are more frequent than respiratory distress [32].

In our study platelet count/mm3 was lower (thrombocytopenia) for neonates with proved sepsis 45891±110305 and for neonates with suspected sepsis 425891±141258 more than for control group 325148±810250. Studies by Sartaj A. Bhat et al. were revealed that neonates developed thrombocytopenia in cases of neonatal sepsis [33]. Ahmed et al. also showed that mortality rate was also higher among children with thrombocytopenia [34]. Leukocyte count/mm3 also was higher (leukocytosis) for neonates with proved sepsis 18912±9541 and for neonates with suspected sepsis 10912±2451 more than for control group 6417±213. Similar findings by study by Philip et al. [35] showed that leukocytosis and neutrophilia were the two most predominant abnormal WBC results and these abnormalities were predicting neonatal sepsis. Multiple studies have examined total leucocytic count, immature to total neutrophil ratio and platelet count and shown that these routine investigations either have low sensitivity and specificity or varying delayed responses early in the course of infection [36].

The causative organisms of neonatal sepsis are varied from one region to another, and they are changing over time. In this study the blood cultures were positive for all patients of proved sepsis. The identified bacteria included Gram positive bacteria 22(55%) which were Coagulase negative Staph. 13(32.5%) followed by Staphylococcus aureus 4(10%), then Streptococcus viridans & MRSA 2 (5%) for each), while Gram negative bacteria 15(37.5%) which were E. coli 5(12.5%) followed by Klebsiella pneumoniae 4(10%) then Pseudomonas aeruginosa 3(7.5%) also fungal infection (Candida species) detected in 3(7.5%) cases. The reported microbiological etiologies in several studies also showed that CONS is the major causative pathogen [37-40], other studies from other developing countries have reported that gram-negative bacteria constituted the majority of the causative organisms of neonatal sepsis [41,42]. Alrafaiah et al. [43] showed similar results to our study that 35% of neonatal sepsis was caused by different types of gram-negative bacteria, with E. coli being the predominant one. E. coli is main pathogen causing early sepsis, and this is consistent also with the findings of Kilani and Basamad in a study from Riyadh published in 2000 [44]. Although CONS constitutes the highest percentage of neonatal sepsis in our hospital, it causes less severe disease and it is mostly related to inserted devices e.g. central lines. Alrafaiah et al. [43] showed also similar results of fungal infections that three cases of neonatal sepsis were caused by fungal infections, and all of them occurred exclusively in premature babies. This obviously
related to the immature immune system of those neonates.

In our study there was significant difference between the mean of CRP, PCT and presepsin levels in proved and suspected N.S. groups when compared with healthy controls (P< 0.05). Also some authors observed high concentrations of PCT during proved sepsis, [45,46] and comparable low concentrations in suspected sepsis. In a study by Guibourdenche et al. [47], very low PCT concentrations were measured during SIRS, but high concentrations when sepsis was diagnosed. Studies concerning with presepsin marker [48,49] found that the plasma concentration of presepsin was significantly higher in infected patients than in non-infected patients. Shozushima et al. [50] found that the concentration of presepsin was 1 992.9±1 509.2 pg/mL in proved sepsis group, 817.9±572.7 pg/mL in suspected sepsis group and 333.5±130.6 pg/mL in control group so the blood concentration of presepsin among the groups increased sequentially.

A rapid test with the best degree of sensitivity, reliability, and predictability is required for the early diagnosis and treatment of neonatal sepsis [51]. From ROC curve at cut off CRP 9 mg/l the sensitivity and specificity were (72%, 91% respectively) which were less useful in diagnosis of neonatal sepsis compared to presepsin at cut off 500 pg/ml which has the highest sensitivity and specificity (95%, 81% respectively) followed by procalcitonin which at 5.6 ng/ml cut off had sensitivity and specificity (90%, 69% respectively). The positive and negative predictive rates were the lowest in CRP (28% and 80% respectively), whereas the positive and negative predictive rate showed high result in case of presepsin and PCT (presepsin positive predictive and negative predictive values were 84% and 95% respectively, while PCT positive predictive and negative predictive values were 55% and 95% respectively). Hisamuddin E, et al. [52] showed also that CRP estimation does have a role in the diagnosis of neonatal sepsis but the test is not specific enough to be relied upon as the only indicator. Previous studies have reported the sensitivity and specificity of PCT as follows: 66.7%, 94.4% [53]; 75% and 59% [54]; 66.7% and 50%; [55]; 88.9% and 65.2% [56] respectively. These results suggested that PCT is a better clinical marker than CRP—although it is associated with a more expensive cost. Montaldo et al. [57] findings were recorded for presepsin sensitivity and specificity that were 93% and 100% respectively in the study of early-onset sepsis in newborns and showed better sensitivity and specificity of presepsin than PCT and CRP. Bellos et al. [58] reported that Head-to-head comparison with AUC values of C-reactive protein and procalcitonin revealed that presepsin was more sensitive in detecting neonatal sepsis.

5. CONCLUSION

This study showed that the prevalence of neonatal sepsis among all admitted neonates in Al-Quwayiyah general hospital was 20.8%. Our results also detected higher sensitivity, specificity and positive and negative predictive values for presepsin more than and PCT CRP in the diagnosis of NS. Although presepsin has an important role in diagnosing sepsis, we suggest that detection of presepsin be combined with other traditional markers, such as procalcitonin, C-reactive protein, and white blood cells until.

Large scale studies are done to confirm such findings in different Saudi Arabia health care settings.

CONSENT AND ETHICAL APPROVAL

The study was approved by the hospital ethics committee. Both verbal and written informed consent was given by the parents.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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