Diagnostic yield of at admission estimation of serum IL-6 and high-sensitivity CRP for Early-onset Neonatal Sepsis

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Abstract: Objectives: To evaluate the ability of at admission estimation of serum high-sensitivity C-reactive protein (hs-CRP) and interleukin (IL)-6 for discrimination between neonates had early-onset sepsis (EOS) and those free of infection and to act as early predictor for result of blood culture (BC). **Patients & Methods**: The study included 87 neonates admitted to neonatal ICU (NICU) underwent evaluation using the Score for Neonatal Acute Physiology Perinatal Extension II (SNAPPE II) with higher scores indicated more severe infection. Neonates were categorized into: Infected neonates had clinical manifestations of sepsis and positive BC, Clinically infected neonates had clinical manifestations of sepsis and negative BC and EOS-free neonates had negative BC and no clinical manifestations. Two venous blood samples were obtained: The first at time of NICU admission for ELISA estimation of hsCRP and IL-6 serum levels and the second sample was obtained either at time of development of clinical signs of sepsis or at of 72 hours in non-infected groups was used for BC and for complete blood count. **Results:** Blood culture was positive in 43 neonates (Infected), 19 neonates were clinically infected and 25 neonates were EOS-free. Mean SNAPPE II score and serum hs-CRP levels were significantly lower in EOS-free neonates compared to infected neonates with non-significant difference between clinically infected neonates. Mean total WBC count and serum IL-6 levels were significantly lower in EOS-free compared to infected and in clinically infected compared to infected neonates. Regression analysis for studied parameters as predictors for sure neonatal EOS confirmed by positive BC defined high total WBC count and high serum IL-6 as the most significant predictors and as predictors for EOS among those had negative BC defined high total WBC count, high serum IL-6, elevated serum hsCRP and birth weight in decreasing order of significance. **Conclusion:** Combined at admission estimation of serum hsCRP and IL-6 levels in conjunction with at 72-hr WBC count could differentiate between infected and non-infected neonates and provide early prediction for positive BC so allowing early initiation of therapy for infected neonates.

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Kew words: Early-onset neonatal infection, interleukin-6, high-sensitivity CRP, Total leucocytic count.

1. Introduction

Infants in the neonatal intensive care unit (NICU) are at risk for sepsis; in a large study, the National Institute of Child Health and Human Development Neonatal Research Network found a 2.5-fold increase in mortality and >30% increase in hospital stay in 21% of infants admitted to ICU and concluded that strategies to reduce the incidence and severity of neonatal sepsis are "needed urgently." One such strategy might be continuous noninvasive physiologic monitoring of NICU patients optimized to detect early signs of illness **(Stoll *et al.*, 2011; Shane & Stoll, 2013)**.

One of the best strategies is early identification of neonates vulnerable to sepsis; however, this target is complicated by variability in clinical presentation. Moreover, despite the incidence of early onset sepsis (EOS) resulting from invasive group B streptococcal infections has been notably reduced by the widespread delivery of intrapartum antibiotic prophylaxis; the rates of EOS attributable to non-group B streptococcal etiologies have remained constant, and ampicillin-resistant *Escherichia coli* has become more prevalent **(Al-Taiar *et al.*, 2011; Leibovitz *et al.*, 2012)**.

Blood culture, the "gold standard" for detection of systemic infection, can take up to 2 days to reliably provide a "negative" result. Furthermore, blood cultures are dependent on the presence of bacteremia and growth can be suppressed if blood cultures are drawn after initiation of antibiotic therapy. Due to this delay and uncertainty, a care provider must often fall back on clinical symptoms and less predictive laboratory measures, in an attempt to document the presence of infection **(Hashavya *et al.*, 2011; Zakariya *et al.*, 2012)**.

Cytokines initiate, control and influence a number of biological processes like inflammation,

sepsis and wound healing. With regard to their functions, all cytokines behave pleiotropic and redundant. In the case of auto/paracrinal regulation they are characterized by minimal effective concentrations, fast stimulation ability as well as short activity and presence time. However, it must be considered that plenty of diseases may influence the systemic levels of pro-inflammatory cytokines **(Boué, 2007)**.

Pro- and anti-inflammatory cytokines such as IL-6, IL-8 or IL-10 play a dominant role as local or systemic regulators in the acute inflammatory response. Previous studies have established that the host response to inflammation is mediated largely by the release of pro-inflammatory cytokines such as IL-1, tumor necrosis factor-α and IL-6. Blocking IL-1 binding to its type I receptor or inhibiting IL-6 with monoclonal antibodies leads to a marked attenuation of inflammatory response **(Markuszewski *et al.*, 2009, Cernada *et al.*, 2010)**.

C-reactive protein (CRP) is a conventional inflammatory marker as a kind of acute phase protein. Concentrations of CRP increase at around 24 hours after onset of infection, peak between 36 and 50 hours and remain elevated throughout infection. CRP necessarily has a limitation for the early identification of infection within 24 hours of onset; therefore, serial measures are required 24 hours later for accurate detection of infection **(Batlivala *et al.*, 2009, Mair *et al.*, 2010, Nabulsi *et al.*, 2012)**.

Thus, the current study tried to evaluate the ability of at admission estimation of serum hs-CRP and IL-6 for discrimination between neonates had EOS and those free of infection and to act as early predictor for result of blood culture so as to allow early initiation of treatment.

2. Patients and Methods

The current prospective study was conducted at Neonatal Intensive Care Unit (NICU) Pediatrics Department and Clinical Pathology Department, Aladan and Alfarawanya Hospitals in Kuwait. All neonates enrolled in the study underwent evaluation using the Score for Neonatal Acute Physiology Perinatal Extension II (SNAPPE II), (Table 1) with higher scores indicated more severe infection **(Richardson *et al.*, 2001)**.

Sepsis was defined by a positive blood culture and at least one clinical sign or symptom from each of at least three of the following six categories: (1) cyanosis, pallor, heart rate >180 beats per minute or <80 beats per minute, arterial blood pressure (BP) below 2SD of the mean BP for age and weight or poor peripheral perfusion; (2) metabolic acidosis with a pH < 7.25 or poor peripheral perfusion; (3) respiratory distress or respiratory rate >60 per minute, subcostal and/or intercostals retractions, grunting or respiratory pause lasting >10 seconds; (4) abdominal distension, feeding intolerance and/or vomiting; (5) temperature instability or central temperature >37.5^{o}C lasting at least 4 hours; and (6) lethargy, hypotonia or convulsions **(Tollner, 1982; Garner *et al.*, 1988)**.

Neonates were categorized according to the presence of sepsis into the following groups: Infected neonates had clinical manifestations of sepsis and positive blood culture, Clinically infected neonates who had clinical manifestations of sepsis and negative blood culture and EOS-free neonates who showed no clinical manifestations and had negative blood culture at 72 hours **(Baltimore, 2003)**.

Investigations:

Sampling: Two venous blood samples were obtained:

1. The first blood samples (5 ml) were obtained at time of admission to NICU, put in clean dry tube and allowed to clot and then serum was separated in clean dry Eppendorff tube to be stored at -80°C till assayed for ELISA estimation of serum high-sensitivity C-reactive protein (hsCRP) level (biosystem, Barcelona, Spain) **(Koenig *et al.*, 2004)** and Interleukin-6 (IL-6) was measured in serum using a commercially available ELISA kit (Quantikine, USA), for the quantitative determination of human IL-6 **(Engvall & Perlmann, 1972)**.
2. Another venous blood sample was obtained either at time of development of clinical signs of sepsis or at of 72 hours in non-infected groups; the obtained blood sample was divided into two parts:
   a. The first part was used for blood culture to assure diagnosis of infected cases. Cultures for bacterial growth were carried out by inoculating blood samples onto thioglycolate broth, chocolate agar 5%, and blood agar plates. The chocolate agar plates were incubated aerobically and the blood agar plates were incubated anaerobically, for 72 hours.
   b. The second part (20 µl) was used for complete blood count.

3. Results

The study included 87 neonates; 49 males and 38 females with mean age of 6.1±1.7; range: 4-9 days. Mean gestational age of enrolled neonates was 35.8±2.1; range: 33-39 weeks and mean birth weight was 3151.7±214.8; range: 2750-3500 gm. Mean

Apgar score 7.3±1.3; range: 5-9 and mean head circumference was 35±0.6; range: 34-36.5 (Table 2).

Clinical evaluation defined 62 patients (71.3%) with evident clinical infection, while the remaining 25 patients (28.7%) had no clinical manifestations. Blood culture was positive in 43 patients (49.5%) of those had clinical manifestation and those was grouped as Infected group. The remaining 44 patients (50.5%) had negative blood culture and so 19 patients (21.8%) had clinical manifestations and negative blood culture and were grouped as clinically infected neonates. The remaining 25 patients (28.7%) had no clinical manifestations of infection and had negative blood culture and were grouped as EOS-free neonates. Mean SNAPPE II score was significantly (p<0.05) lower in EOS-free neonates compared to infected neonates, but it was non-significantly (p>0.05) lower compared to clinically infected neonates with non-significantly (p>0.05) score in clinically infected neonates compared to infected group, (Fig. 1). As regards other enrollment data, there was non-significant (p>0.05) difference between study groups; despite being in favor of EOS-free group, (Table 2).

Mean total WBC count was significantly (p<0.05) higher in infected neonates compared to clinically infected and EOS-free neonates with significantly higher count in clinically infected compared to EOS-free neonates. Additionally, mean neutrophil percentage was significantly (p<0.05) lower in EOS-free neonates compared to other groups with non-significantly (p>0.05) lower percentage in clinically infected compared to infected neonates. On contrary, the percentage of lymphocytes showed non-significant (p>0.05) difference between studied groups despite being lower in EOS-free neonates, (Table 3, Fig. 2).

Mean estimated hsCRP level was significantly (p<0.05) lower in EOS-free neonates compared to infected and clinically infected neonates with non-significantly (p>0.05) lower levels in clinically infected compared to infected neonates, (Table 3, Fig. 3). On the other hand, mean estimated serum IL-6 levels were significantly (p<0.05) higher in infected neonates compared to clinically infected and EOS-free neonates with significantly (p<0.05) higher levels in clinically infected compared to EOS-free neonates, (Table 3, Fig. 4).

The occurrence of EOS showed a positive significant correlation with high SNAPPE II clinical scoring, high total WBC count, high neutrophil percentage and elevated serum hsCRP and IL-6 levels. However, the correlation was negative but non-significant with age, gestational age, birth weight Apgar score and head circumference, (Table 4).

ROC curve analysis for predictability of evaluated parameters for sure diagnosis of EOS as confirmed by positive blood culture showed that elevated serum IL-6, high total WBC count, elevated serum hsCRP, and high neutrophil percentage are the significant predictors for positive blood culture in that frequency of decreasing significance, (Table 5).

Regression analysis for verification of studied parameters as predictors for sure neonatal EOS confirmed by positive blood culture defined high total WBC count as the most significant predictor followed by high serum IL-6, while the other parameters could not distinguish between neonates who will have positive and negative blood culture, (Table 6). Regression analysis for verification of studied parameters as predictors for neonatal EOS among those had negative blood culture defined high total WBC count as the most significant predictor in four models of analysis followed by high serum IL-6 in three models, elevated serum hsCRP in two models and birth weight in one model, while the other parameters could not distinguish between neonates had clinical infection and neonates who EOS-free, (Table 7).

Table (1): Score for neonatal acute physiology perinatal extension II (SNAPPE II), (Richardson et al., 2001)

Variable	Measure	Score
Lowest men arterial pressure (mmHg)	>29	0
	20-29	9
	<20	19
Lowest temperature (^{o}C)	>35.6	0
	35-35.6	8
	<35	15
PO2/FiO2 ratio	>2.49	0
	1.0-2.49	5
	0.3-0.9	16
	<0.3	28
Lowest pH	>7.19	0
	7.10-7.19	7
	<7.10	16
Seizure	None	0
	Yes	5
Urine output (ml/kg/hr)	>0.9	0
	0.1-0.9	5
	<0.1	18
Birth weight (gm)	>999	0
	750-999	10
	<750	17
Small for gestational age	>3rd percentile	0
	<3rd percentile	12
Apgar score at 5 minutes	>7	0
	<7	18

Table (2): Patients enrollment data

	Infected	Clinically infected	EOS-free	Total
Number (%)	43 (49.5%)	19 (21.8%)	25 (29.7%)	87 (100%)
Age (days)	5.8±1.8 (4-9)	6±1.6 (4-9)	6.3±1.8 (4-9)	6.1±1.7 (4-9)
GA (weeks)	35.4±2 (33-39)	36±1.9 (33-39)	36.3±2.1 (33-39)	35.8±2.1 (33-39)
Birth weight (gm)	3124.7±194.1 (2770-3500)	3162.1±217.5 (2770-3500)	3163.7±241.9 (2750-3500)	3151.7±21.8 (2750-3500)
Apgar score	7±1.1 (6-9)	7.1±1.5 (5-9)	7.5±1.1 (5-9)	7.3±1.3 (5-9)
HC (cm)	34.9±0.6 (34-36)	35±0.7 (34-36)	35±0.6 (34-36.5)	35±0.6 (34-36.5)
SNAPPE II	43.3±19.9 (10-85)	33.1±15.3 (18-72)	25.8±7.1 (10-34)*	36.1±17.8 (10-85)

Data are presented as mean±SD & numbers; ranges & percentages are in parenthesis; GA: gestational age; HC: head circumference; SNAPPE II: Score for Neonatal Acute Physiology Perinatal Extension II

Table (3): Patients' laboratory findings

		Infected	Clinically infected	EOS-free
Blood culture		Positive	Negative	Negative
WBC data	Total count (10^3/dl)	17.36±1.92 (14.78-21.46)	15.2±2.1* (11.45-17.82)	7.33±0.69*† (5.87-8.94)
	Lymphocyte (%)	28.9±3.71 (21.7-34.5)	27.9±2.7 (23.1-31.8)	29.4±2.95 (23.4-34.2)
	Neutrophil (%)	62.3±3.4 (52-65)	60.1±4.2 (52-65)	54.45±3.59*† (49.7-62.6)
Serum data	hsCRP (mg/l)	2.86±0.47 (2.1-3.9)	2.668±0.3 (2.3-3.4)	0.889±0.226*† (0.563-1.283)
	IL-6 (mg/ml)	90.3±25.8 (39-154)	69.5±15.7 (34-92)*	32±7 (19-45)*†

Data are presented as mean±SD & numbers; ranges & percentages are in parenthesis; WBC: White blood cell count; hsCRP: high-sensitivity C-reactive protein; IL-6: interleukin-6

Table (4): Correlation coefficient "r" between constitutional, clinical and laboratory data and the occurrence of EOS

		"r"	*p*
Age (days)		0.109	>0.05
GA (weeks)		-0.237	>0.05
Birth weight (gm)		-0.315	>0.05
Apgar		-0.198	>0.05
HC (cm)		-0.134	>0.05
SNAPPE II score		0.406	<0.001
WBC data	Total count (10^3/dl)	0.714	<0.001
	Lymphocyte (%)	0.128	>0.05
	Neutrophil (%)	0.551	<0.001
Serum data	hsCRP (mg/l)	0.636	<0.001
	IL-6 (mg/ml)	0.664	<0.001

"r": correlation coefficient; GA: gestational age; HC: head circumference; SNAPPE II: Score for Neonatal Acute Physiology Perinatal Extension II; WBC: White blood cell count; hsCRP: high-sensitivity C-reactive protein; IL-6: interleukin-6.

Table (5): ROC curve analysis for the predictability of constitutional, clinical and laboratory data and diagnosis of EOS confirmed by positive blood culture

		AUC	Std error	Sig.	95% CI	
					Lower	Upper
Age (days)		0.555	0.062	>0.05	0.433	0.677
GA (weeks)		0.394	0.063	>0.05	0.271	0.517
Birth weight (gm)		0.515	0.063	>0.05	0.391	0.638
Apgar		0.577	0.062	>0.05	0.454	0.699
HC (cm)		0.462	0.063	>0.05	0.339	0.585
SNAPPE II score		0.703	0.056	=0.001	0.593	0.813
WBC data	Total count (10^3/dl)	0.882	0.036	<0.001	0.811	0.953
	Lymphocyte (%)	0.532	0.063	>0.05	0.403	0.656
	Neutrophil (%)	0.813	0.047	<0.001	0.721	0.906
Serum data	hsCRP (mg/l)	0.833	0.044	<0.001	0.748	0.919
	IL-6 (mg/ml)	0.898	0.031	<0.001	0.837	0.960

AUC: area under curve; Std error: standard error; Sig.: significance versus the null hypothesis that AUC=0.5; CI: confidence interval; GA: gestational age; HC: head circumference; SNAPPE II: Score for Neonatal Acute Physiology Perinatal Extension II; WBC: White blood cell count; hsCRP: high-sensitivity C-reactive protein; IL-6: interleukin-6.

Table (6): Regression analysis of constitutional, clinical and laboratory data as predictors for diagnosis of EOS confirmed by positive blood culture

		β	t	Sig.
Model 1	Total count (10^3/dl)	0.470	0.882	<0.001
	Serum IL-6 (mg/ml)	0.350	0.532	=0.001
Model 2	Total count (10^3/dl)	0.713	3.508	<0.001

β: Standardized coefficient; Sig.: significance; GA: gestational age; HC: head circumference; SNAPPE II: Score for Neonatal Acute Physiology Perinatal Extension II; WBC: White blood cell count; hsCRP: high-sensitivity C-reactive protein; IL-6: interleukin-6.

Table (7): Regression analysis of constitutional, clinical and laboratory data as predictors for exclusion of EOS in neonates had negative blood culture

		β	t	Sig.
Model 1	Total count (10^3/dl)	0.478	7.793	<0.001
	Serum IL-6 (mg/ml)	0.418	6.543	<0.001
	Serum hsCRP	0.138	3.497	=0.001
	Birth weight	0.092	2.992	=0.004
Model 2	Total count (10^3/dl)	0.500	7.825	<0.001
	Serum IL-6 (mg/ml)	0.402	6.022	<0.001
	Serum hsCRP	0.130	3.161	=0.002
Model 3	Total count (10^3/dl)	0.520	7.779	<0.001
	Serum IL-6 (mg/ml)	0.466	6.963	<0.001
Model 4	Total count (10^3/dl)	0.923	21.928	<0.001

β: Standardized coefficient; Sig.: significance; GA: gestational age; HC: head circumference; SNAPPE II: Score for Neonatal Acute Physiology Perinatal Extension II; WBC: White blood cell count; hsCRP: high-sensitivity C-reactive protein; IL-6: interleukin-6.

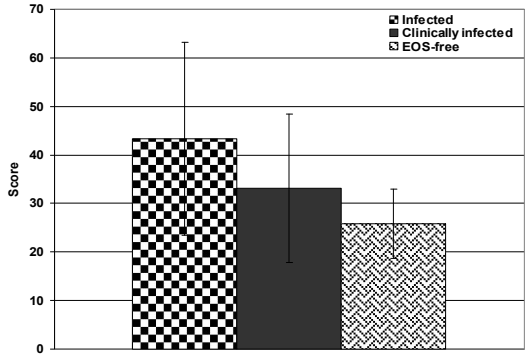

Fig. (1): Mean (±SD) at admission SNAPPE II score of enrolled neonates in the studied groups

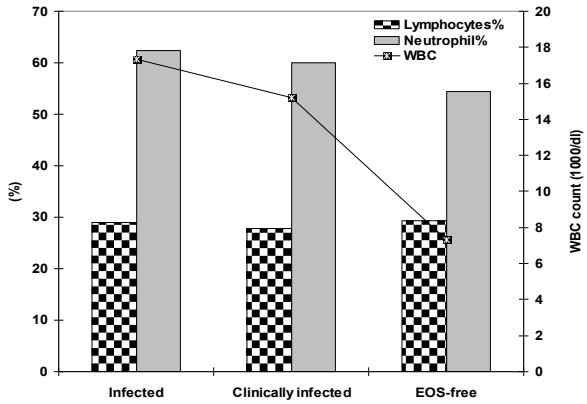

Fig. (2): Mean number of WBC and percentage of neutrophils and lymphocytes determined in studied groups

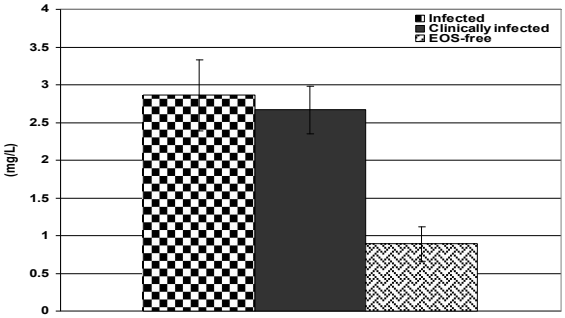

Fig. (3): Mean (±SD) at admission serum hsCRP levels estimated in studied groups

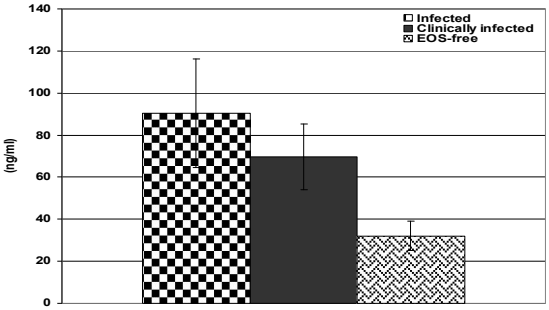

Fig. (4): Mean (±SD) at admission serum IL-6 levels estimated in studied groups

4. Discussion

Clinical categorization of enrolled neonates had relied on the Score for Neonatal Acute Physiology Perinatal Extension II (SNAPPE II), which is validated by **Dammann *et al.* (2009 & 2010)** who documented that the physiologic instability in the first 12 postnatal hours could be identified by illness severity scores which conveys information about the risk of morbidities and mortalities among infants especially those at the lowest gestational ages and high SNAPPE II scores might be indicators of immaturity and vulnerability to morbidities. Also, **Carvalho *et al.* (2011)**

documented that SNAPPE-II shows accuracy in the prediction of adverse outcome for neonates especially the highly selective group of very low BW infants compromised by severe placental insufficiency.

For assurance of diagnosis, blood samples were obtained at completion of 72 hours of NICU stay. Neonates developed positive blood culture showed significantly higher WBC count with higher neutrophil and lymphocyte percentages compared to clinically infected and EOS-free neonates with significantly higher WBC counts in clinically infected neonates compared to EOS-free neonates. These data indicated the ability of WBC counting for differentiation between the three categories of neonates. In support of these data, Regression analysis defined high WBC count as the most significant parameter for discrimination between those had positive and negative blood culture and between those clinically infected from free neonates among neonates had negative culture. However, the limitation of this ability is the determination at 72 hours after NICU admission so there is time lag between admission and diagnosis.

In line with the utility of blood cell count for differentiation, **Murphy & Weinner (2012)** and **Celik *et al.*(2012)** found the combination of 2 serial normal immature to total neutrophil (I:T) ratios and a negative blood culture at 24 hours in the evaluation of EOS shortly after birth is indicative of a non-infected neonate. **Hornik *et al.* (2012a)** also, found white blood cell count; absolute neutrophil count and high immature-to-total neutrophil ratio were associated with increasing odds of infection with high specificity and negative predictive values. In support of specificity of WBC counting for diagnosis of EOS, **Hornik *et al.* (2012b)** reported that no complete blood cell count index possessed adequate sensitivity to reliably rule out late-onset neonatal sepsis.

At admission serum hsCRP levels were significantly higher in infected and clinically infected neonates compared to EOS-free neonates with non-significantly higher levels in infected compared to clinically infected neonates. In line with these results, **Ohlin *et al.* (2010)** found apnea; hypotension and CRP were independently predictive of positive blood culture. **West *et al.* (2012)** tried to determine the usefulness of CRP for evaluation of neonatal sepsis versus blood culture as gold standard and reported that qualitative estimation of CRP which is cheap and rapid has moderate sensitivity, specificity and negative predictive value of neonatal sepsis.

The reported variability of predictability of at admission serum CRP levels could be attributed to the effect of gestational age and intrauterine development, as manifested by birth weight, on immune system maturation. In support of this assumption, Regression analysis defined birth weight as a significant predictor for infection in line with elevated WBC count, serum hsCRP and IL-6. In hand with this attribution, **Hofer *et al.* (2011)** found that CRP values were significantly lower in preterm compared to term newborns, and its application in the diagnosis of sepsis in preterm newborns was not as reliable as in term newborns and meconium aspiration syndrome, surfactant application, and high birth weight were associated significantly with increased CRP values

On contrary, at admission serum IL-6 levels were significantly higher in infected neonates compared to both clinically infected and EOS-free neonates with significantly higher levels in clinically infected compared to EOS-free neonates. These data indicated that the discriminative predictability of elevated serum IL-6 levels between neonates had proven infection and those with suspicious infection superceded that of CRP, despite the ability of both markers to differentiate neonates free of infection from infected neonates. In line with these data, **Sarafidis *et al.* (2010)** found infected neonates had significantly higher soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) and IL-6 than non-infected neonates and statistical analyses documented acceptable diagnostic performance of sTREM-1 and IL-6, but diagnostic accuracy of IL-6 was better than sTREM-1 which did not improve the prognostic yield if used in combination with IL-6. Also, **Dilli *et al.* (2010)** found estimation of CD64 expression on surface of neutrophil in combination with IL-6 and CRP could be used for early diagnosis of neonatal sepsis. **Cernada *et al.* (2012)** compared diagnostic accuracy of cord blood of IL-6 and CRP as predictors of EOS in newborns with prenatal risk factors for infection and found cord blood IL-6 showed superior likelihood ratios than CRP; therefore, it is a better predictor to initiate treatment in neonates with prenatal infectious risk factors immediately after birth.

Thus, combined at admission estimation of hs-CRP and IL-6 with at 72-hrs WBC count determination is an appropriate policy for early prediction and later on confirmation of EOS. In support of the multiplex marker estimation, **Rego *et al.* (2010)** found the combination of IL-6 at 0-hr and CRP at 24-h estimation is helpful for excluding early onset infection in preterm infants with respiratory distress. **Celik *et al.* (2013)** found estimations of IL-6 and CRP in combination with neutrophil volume, conductivity and scatter parameters could be a useful screening tool for neonatal sepsis.

It could be concluded that at admission estimation of serum hsCRP and IL-6 in conjunction with total leucocytic count could differentiate

between infected and non-infected neonates and provide early prediction for positive blood culture so allow initiation of therapy for infected neonates.

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