Study of Correlation of CRP with Blood Culture in Neonatal Sepsis in Neonatal Ward of Kurji Holy Family Hospital, Patna, Bihar

I.   Introduction

Neonatal sepsis is the single most important cause for neonatal deaths in developing countries specially in preterm and Very low birth babies.If diagnosed early and treated it is possible to save most of the neonates but neonatal sepsis remains a diagnostic and therapeutic challenge for neonatal care giver.Sepsis is defined as SIRS(systemic inflammatory response syndrome) resulting from a suspected or proven infectious etiology.The clinical spectrum of sepsis begins when a systemic(eg.bacteremia,viremia,fungemia,rickettsial disease) or localized(eg.meningitis,pneumonia,pyelonephritis,peritonitis,nectrotizing fasciitis) infection progresses from sepsis to severe sepsis(i.e.presence of sepsis combined with organ dysfunction).Further clinical deterioration leads to septic shock(severe sepsis plus persistence of hypoperfusion or hypotension despite adequate fluid resuscitation or a requirement of vasoactive agents),MODS and possibly death[1].Successful management depends on early intervention but due to non-specific clinical presentations it may be difficult to diagnose.Blood culture still remains the gold standard for the diagnosis of sepsis but many times the culture may be negative even in a symptomatic neonate and takes longer time for result hence we need investigation which is fast and reliable.When blood culture is negative we have to depend on other parameters for diagnosis of neonatal sepsis.These tests should be economical,fast and reliable.One of this is C-reactive protein which is supposed to be very specific for neonatal sepsis.C-reactive protein is an excellent marker for established neonatal bacterial infections.[2]

II.   Review Of Literature

1.**Jaswal RS et al.(2003)[3]:** In their study conducted in the department of Pediatrics,Indira Gandhi Medical College,Shimla from June 2000 to May 2001,CRP levels were used to evaluate the duration of antibiotic therapy in 50 neonates with suspected sepsis.In 44% of cases therapy was stopped on 3rd day,as CRP was normal.In 8% cases antibiotics could be stopped within 5-7 days as CRP returned to normal and in 48% therapy was extended beyond 7th day as CRP values were high or rising persistently.Negetive predictive value of serial CRP was 100% in deciding upto 7 days.The correlation between CRP and positive blood culture was significant(p<0.005).
2.**Hisamuddin et al.(2015)[4]:**in their cross sectional study conducted at Neonatology unit in KRL general hospital (emergency/OPD) of 7 months duration from February 2012 to August 2012 used purposive sampling technique.147,sample size was calculated by using WHO sample size calculator taking sensitivity 75%, specificity 95%, expected prevalence 50%, desired precision 10% and confidence level 95%.Mean age of the neonates was 5.72 days + 3.86. Male patients were 81(55.1%) while 66(44.9%) were female. Neonatal sepsis was observed in 43(29.25%) and were confirmed through blood culture while 104(70.75%) were not confirmed on blood culture as neonatal sepsis.The

sensitivity and specificity of CRP in diagnosis of acute neonatal sepsis was 76.92% and 53.49% respectively while it had a positive predictive value of 80% and negative predictive value of48.94%.Overall the diagnostic accuracy of CRP in diagnosis of neonatal sepsis was 70.07%.

3.**Monga Niza et al.(2018)**[5]:did their study in Department of Microbiology,SMS Medical College, Jaipur, Rajasthan, India where out of the 100 neonates studied,47 were blood culture positive while 70 were CRP positive.The sensitivity, specificity, positive and negative predictive values and diagnostic accuracy of CRP were 85.11%, 43.40%, 57.14%,76.67% and 63% respectively.

4.**Bunduki et al.(2020)**[6]:in their study in Butembo,the Democratic Republic of the Congo,in sub- Saharan Africa found out of the 228 neonates screened for sepsis,69 (30.3%) had a positive blood culture.Of the 228 neonates with suspected sepsis,94 (41.2%) had a positive CRP. Among the 69 cases with positive blood culture,CRP identified 66 cases.The sensitivity, specificity,positive and negative predictive value of CRP were 95.7%,82.4%,70.2% and 97.8% respctively.

AIMS AND OBJECTIVES
 1. To estimate CRP in clinically suspected Neonatal sepsis.
 2. Positivity of Blood culture in clinically suspected sepsis.
 3. To correlate CRP with Blood culture.

INCLUSION CRITERIA-
Neonates admitted to neonatal ward of Kurji
Holy Family Hospital with clinical suspicion of sepsis.

EXCLUSION CRITERIA-
1. Neonates with perinatal asphyxia .
2. Neonates with any major congenital anomalies.
3. Syndromic babies.
4. Neonates with confirmed Inborn errors of metabolism(IEM).
5. Babies age more than 28 days and
6. Neonates with meconium aspiration syndrome(MAS).

III.   Methodology-
        A prospective observational hospital based study was done from December 2020 to May 2022.205 neonates with suspected neonatal sepsis admitted to neonatal ward of KHFH,Patna during the study period of December 2020 to May 2022 were the subject for this study.During admission all the babies were evaluated with detailed history of their mother and perinatal events including maternal factors that predisposing to sepsis.Bacteriological profiles in all 205 neonates were studied by Blood culture and other cultures like urine culture will be done depending on requirement and their comparison were done with CRP.Correlation of CRP with Blood culture and other necessary culture was done.In the study other septic workup parameters were also be taken into account and they were analysed and compared with each other and with CRP.All the neonates subjected to detailed septic screening workup as follows-
    *CBC,
    * Peripheral Blood Smear,
*Absolute Neutrophil Count(ANC)
*Immature/Band cells to Total neutrophil (I:T) ratio,
*Micro-ESR,
*CRP:CRP levels will be estimated by quantitative method of Immunoturbidimetry in VITROS   5600 analyser.
*Blood Culture-
1ml of blood collected aseptically was inoculated into blood culture bottle (Colorcult Pediatric Culture Vial) containing 30 ml of BRAIN-HEART INFUSION(BHI) BROTH. All cultures were collected from fresh venipuncture.After overnight incubation blood culture bottles were examined for indicators of growth like turbidity, gas production, hemolysis or discrete colonies

on the surface of sedimented RBCs.If any of these present, subculture was done on Blood agar and MacConkey agar.The colonies grown were identified by conventional methods according to the standard laboratory protocol including colony morphology,gram staining and biochemical reaction.All blood cultures were observed for at least 72 hours before they were reported as sterile.

IV.   Results and observations

The study was conducted in Department of Pediatrics, Kurji Holy Family Hospital from December 2020-May 2022. Total 205 neonates admitted to NICU and neonatal wards of Kurji Holy Family Hospital with clinical suspicion of sepsis were included in the study. Bacteriological profiles were studied by blood culture and other cultures like urine,csf depending on requirement and their comparison were done with CRP and results are as follows.

Association of blood culture with sepsis.

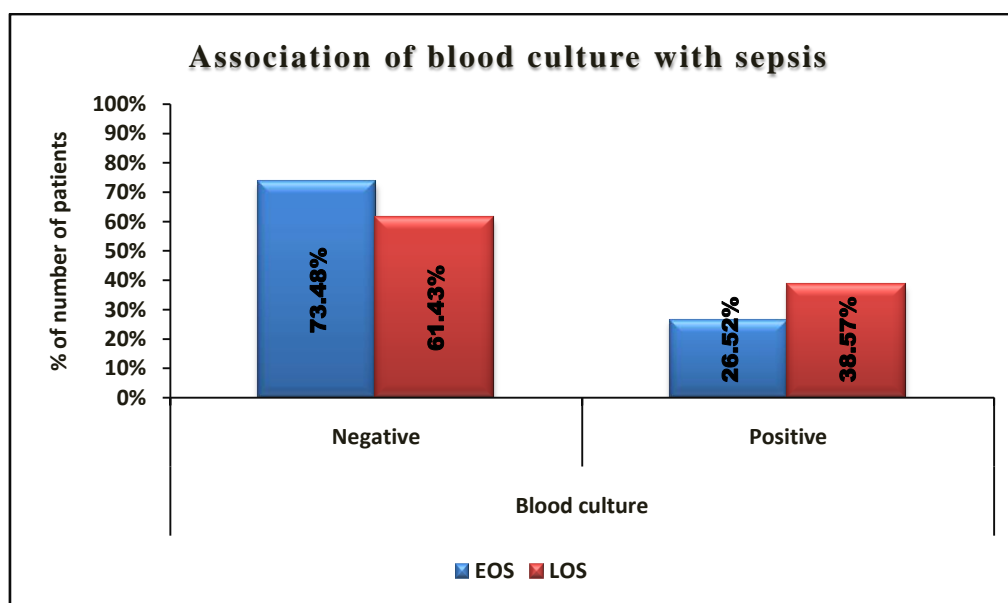| Blood culture	EOS(n=132)	LOS(n=70)	Total	P value
Negative	97 (73.48%)	43 (61.43%)	140 (69.31%)	
Positive	35 (26.52%)	27 (38.57%)	62 (30.69%)	0.077[†]
Total	132 (100%)	70 (100%)	202 (100%)	

[†] **Chi square test**

Figure 1:-Association of blood culture with sepsis.

Blood culture was positive in 26.52% and 38.57% in EOS and LOS respectively. (p value=0.077).It is shown in table 1, figure1.

Sensitivity, specificity, positive predictive value and megative predictive value of Leucopenia(<5000/cmm), Neutropenia(<1800/cmm), I/T ratio(>0.2) and CRP positive for predicting blood culture positive.

Variables	Leucopenia(<5000/cmm)	Neutropenia(<1800/cmm)	I/T ratio(>0.2)	CRP positive
Sensitivity (95% CI)	9.68%(3.63% to 19.88%)	9.68%(3.63% to 19.88%)	93.55%(84.30% to 98.21%)	93.55%(84.30% to 98.21%)
Specificity (95% CI)	58.74%(50.21% to 66.90%)	33.57%(25.89% to 41.94%)	11.19%(6.53% to 17.53%)	**4.2%**(1.56% to 8.91%)
AUC (95% CI)	0.34(0.28 to 0.41)	0.22(0.16 to 0.28)	0.52(0.45 to 0.59)	0.49(0.42 to 0.56)
Positive Predictive Value (95% CI)	9.23%(3.46% to 19.02%)	5.94%(2.21% to 12.48%)	31.35%(24.74% to 38.57%)	29.74%(23.42% to 36.69%)
Negative Predictive Value (95% CI)	60%(51.39% to 68.18%)	46.15%(36.33% to 56.20%)	80%(56.34% to 94.27%)	60%(26.24% to 87.84%)

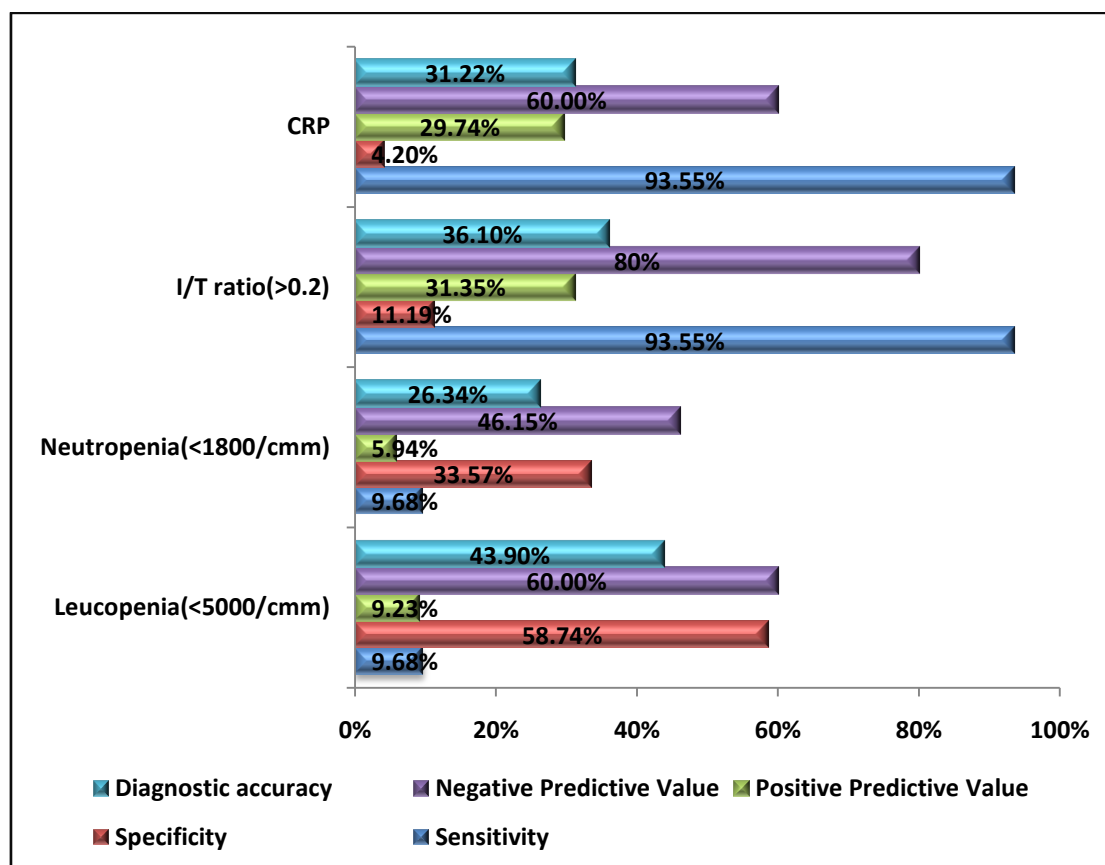| Diagnostic accuracy	43.90%	26.34%	36.10%	31.22%

Figure 2:-Sensitivity, specificity, positive predictive value and negative predictive value of Leucopenia(<5000/cmm), Neutropenia(<1800/cmm), I/T ratio(>0.2) and CRP positive for predicting blood culture positive.

I/T ratio(>0.2) and CRP positive had sensitivity of 93.55% each followed by leucopenia(<5000/cmm) (9.68%) and neutropenia(<1800/cmm) (9.68%). On the other hand, leucopenia(<5000/cmm) had specificity of 58.74% followed by neutropenia(<1800/cmm) (33.57%), I/T ratio(>0.2) (11.19%) and CRP positive (4.20%). Highest positive predictive value was found in I/T ratio(>0.2) (31.35%) and highest negative predictive value was found in I/T ratio(>0.2) (80.00%). It is shown in table 2, figure 2.

Association of blood culture with EOS and LOS.

| Blood culture	EOS	LOS	Total	P value
Gram positive isolates				
Coagulase-negative staphylococci	3 (18.75%)	2 (20%)	5 (19.23%)	0.892[*]
Enterococcus	3 (18.75%)	1 (10%)	4 (15.38%)	
MRSA	7 (43.75%)	4 (40%)	11 (42.31%)	
MSSA	3 (18.75%)	3 (30%)	6 (23.08%)	
Gram negative isolates				
Acinetobacter baumannii	5 (26.32%)	2 (25%)	7 (25.93%)	0.269[*]
E.coli	4 (21.05%)	4 (50%)	8 (29.63%)	
Klebsiella	10 (52.63%)	2 (25%)	12 (44.44%)	
Fungal infection				
Candiadiasis	0(0%)	9 (100%)	9 (100%)	NA

[*] **Fisher's exact test**
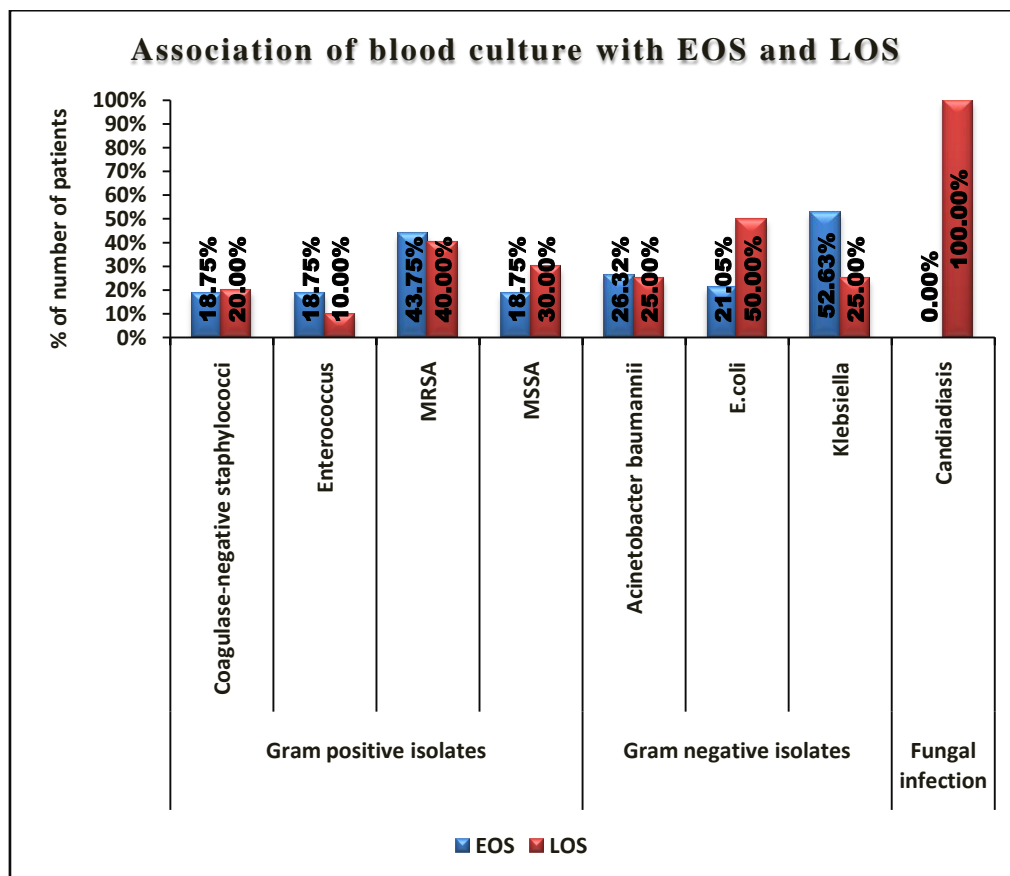
Figure 3:-Association of blood culture with EOS and LOS.

Distribution of gram positive isolates was comparable between EOS and LOS. (Coagulase-negative staphylococci:- 18.75% vs 20% respectively, Enterococcus:- 18.75% vs 10% respectively, MRSA:- 43.75% vs 40% respectively, MSSA:- 18.75% vs 30% respectively) (p value=0.892).Distribution of gram negative isolates was comparable between EOS and LOS. (Acinetobacter baumannii:- 26.32% vs 25% respectively, E.coli:- 21.05% vs 50% respectively, Klebsiella:- 52.63% vs 25% respectively) (p value=0.269).All the neonates with fungal infection had candiadiasis{fungal infection} in LOS group and none of neonates with EOS had fungal infection.It is shown in table 3, figure 3.

LIMITATIONS
The limitations of my study was:-

1.Small sample size and to correlate CRP and blood culture in neonatal sepsis large number of samples may be tested.

2.Observational in nature.

3.Correlation of micro-esr with blood culture could not be done due to laboratory difficulties.

4.Many factors such as antibiotic use with age,gestational age,maternal history of infecting were not recorded.Such factors would be helpful to examine such asociation in depth.

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