ORIGINAL ARTICLE

Comparison between D-Dimer and Highly Sensitive C-Raective Protein in Diagnosis of Neonatal Sepsis in Preterm Infants

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Abstract

Background: ***Sepsis is a predominant etiology of morbidity and mortality in neonates admitted to neonatal intensive care units (NICUs) worldwide.***

Aim: ***To measure D-dimer and highly sensitive C-reactive protein levels in premature infants with early and late-onset sepsis and compare them to diagnose neonatal sepsis.***

Patients and methods: ***This case-control investigation was carried out on ninety preterm infants with a gestational age of up to 36 weeks at the Neonatal Intensive Care Unit (NICU) at Alzahraa University Hospital over a duration of one year from February 2023 to February 2024.***

Results: ***D-dimer level was higher in EOSG with a median of 2.8 mg/l, ranging from 2.3 to 3.6, and LOSG with a median of 3.1 mg/l, ranging from 2.2 to 3.6, than in the control group with a median of 0.7 mg/l, ranging from 0.6 to 0.9, with no significant difference between EOSG and LOSG. While HS-CRP was higher in EOSG, with a median of 3.8 mg/l, ranging from 5.4 to 2.6 than in LOSG, with a median of 3.1 mg/l, ranging from 4.6 to 1.6, it was also higher in EOSG than in the control group with a median of 0.28 mg/l, ranging from 0.22 to 0.46.***

Conclusion: ***In this study, HS-CRP was more specific and sensitive for diagnosing neonatal sepsis in preterm infants than D-dimer, although D-dimer elevated with the severity of cases with a poor prognosis; therefore, it might be used for prognosis.***

Keywords: D-Dimer; C-Reactive Protein; Sepsis; Preterm; DIC

1. Introduction

Sepsis is a predominant etiology of morbidity and mortality in neonates who are admitted to neonatal intensive care units worldwide. The significance of early discovery and proper treatment of these vulnerable cases is crucial in enhancing the results.[1]

Babies born prematurely are born before the 37th week of gestation (258 days). Extremely preterm babies are born prior to 28 weeks of gestation, early-preterm babies are born prior to 34 weeks of gestation, and late-preterm babies are born between 34 0/7 and 36 6/7 weeks of gestation.[2]

The lysis of fibrin in sepsis initiates a coagulation cascade, which results in the simultaneous production of the D-dimer. The activation of the coagulation system is reflected by the D-dimer test.[3]

The highly sensitive C-reactive protein (HS-CRP) is a critical marker in the identification of neonatal sepsis due to its ability to identify inflammation at a reduced level. The highly sensitive C-reactive protein assay has a lower cutoff threshold than traditional CRP assays, with one mg/l value that indicates high sensitivity for neonatal sepsis. [4]

The objective of this investigation was to compare the levels of D-dimer and highly sensitive C-reactive protein in the identification of neonatal sepsis in premature babies, as well as to calculate the levels of D-dimer in early & late onset sepsis in premature babies.

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2. Patients and methods

This case-control investigation has been carried out on ninety preterm infants with a gestational age of up to 36 weeks at the Neonatal Intensive Care Unit (NICU) at Alzahraa University Hospital over a duration of one year from February 2023 to February 2024. They were divided into three groups: Early onset sepsis group (EOSG), 30 preterm infants who had sepsis within the 1st 72 hours following birth; late-onset sepsis group (LOSG), 30 preterm infants who had sepsis ≥ 72 hours following birth; and Control group: 30 healthy, age- and sex-matched preterm infants.

Inclusion criteria: Preterm infants with high maternal risk factors for EOS 5: prolonged rupture of membranes (ROM) (more than eighteen hours), maternal urinary tract infection, intraamniotic infection (chorioamnionitis), and intrapartum fever (>38°C) and sepsis was confirmed by blood culture. Preterm infants with high-risk factors of LOS 5: young maternal age, lack of maternally derived protective antibody, colonization of the infant from maternal and community sources, and invasive procedures: intravascular catheterization, respiratory (endotracheal intubation), metabolic support (total parenteral nutrition), and mechanical ventilation and continuous positive airway pressure, they developed sepsis ≥ 72 hours of life, and sepsis was confirmed by blood culture.

Exclusion Criteria for septic and control groups: Small for gestational age, clinically diagnosed congenital anomalies, clinical suspicion of inborn errors of metabolism, clinical suspicion of hereditary coagulopathy, and preterm infants with hypoxic-ischemic encephalopathy.

Methods

Septic and control groups were subjected to the following:

History taking, complete clinical evaluation, laboratory investigation: Complete blood count on Sysmex Kx-21N, differential leukocytic count, arterial blood gases for septic groups (ABG), blood culture and sensitivity test for septic groups, prothrombin time (PT), and activated partial thromboplastin time (APTT).

D-dimer test: The human D-dimer ELISA kit was used to determine protein concentration. Venous blood samples were collected and centrifuged to avoid air bubbles. Plasma was used for PT, APTT, and D-dimer. A particle-enhanced immunoturbidimetric assay was used, coating latex particles with monoclonal antibodies to the D-Dimer epitope. The absorbance change depends on sample concentration. Highly Sensitive C-Reactive Protein (HS CRP): The sample was collected from venous blood and centrifuged at 2000-3000 m. The serum was stored at -20 °C. Plates were coated with human HS-CRP, antibodies were added, biotinylated antibodies were added, and streptavidin-HRP was added. Incubation was conducted, and color was developed proportionally to the amount of highly sensitive C-reactive protein in humans. The reaction was terminated with an acidic stop solution, and absorbance was measured at 450 nanometers. Interpretation of HS-CRP Levels: Less than 0.3 milligrams per deciliter: Normal, 0.3 to 1.0 milligram per deciliter: Normal or minor increase, 1.0 to 10.0 milligrams per deciliter: Moderate increase, more than 10.0 milligrams per deciliter: Marked increase and more than 50.0 milligrams per deciliter: Severe increase[6] and follow up of septic cases until they were discharged or died.

Statistical Analysis

The data has been gathered, revised, coded, and entered into the Statistical Package for Social Science (IBM SPSS) version 23. When parametric, the quantitative data has been presented as the mean, standard deviations, and ranges. When non-parametric, the median and inter-quartile range (IQR) have been used.[7]

Ethical Considerations

The investigation has been accomplished following the permission of the ethical committee of the pediatric department and the ethical committee of the Faculty of Medicine for Girls at Al-Azhar University. According to the regulations of the committee, IRP will be given at the time of publication of the research from the thesis.

3. Results

Table 1. Dremographic data and characteristics of the examined preterm infants

		CONTROL GROUP	EOSG	LOSG	TEST-VALUE	P-VALUE	SIG.
		No.=30	No.=30	No.=30			
	Range	0.21 – 10	2 – 4	5 – 21			
GA(W)	Mean±SD	35.6 ± 0.77	32.77 ± 2.75	33.4 ± 2.06	16.044•	0.000**	HS
	Range	33 – 36	28 – 36	29 – 36			
SEX	Female	8 (26.7%)	14 (46.7%)	9 (30%)	3.051*	0.218	NS
	Male	22 (73.3%)	16 (53.3%)	21 (70%)			
POSTNATAL AGE (DAYS)	Median(IQR)	2 (1-3)	3 (3-3)	9 (7-12)	58.375‡	0.000**	HS
MOOD OF DELIVERY	C.S	27 (90.0%)	25 (83.3%)	24 (80%)	1.184*	0.553	NS
	V.D	3 (10%)	5 (16.7%)	6 (20%)			

POST HOC ANALYSIS

PARAMETERS	Control vs Early	Control vs Late	Early vs Late
GA(W)	0.000**	0.000**	0.231
POSTNATAL AGE (DAYS)	0.604	0.000**	0.000**

EOSG: Early Onset Sepsis Group, LOSG: Late Onset Sepsis Group, GA: Gestational age, BW: Body weight, BL: Body length, HC: Head circumference *: Chi-square test; •: One Way ANOVA test; ‡: Kruskal-Wallis test P-value > 0.05: non-significant (NS); P-value < 0.05: significant (S); P-value < 0.01: highly significant (HS), *:

significant, **: highly significant.

An insignificant distinction in gestational age has been observed among EOSG and LOSG with a p-value of more than 0.05, but a significant decrease in gestational age in EOSG and LOSG compared to the control group and a statistically significant increase in postnatal age in LOSG with a p-value of less than 0.05.

Table 2. Comparison among the two septic groups regarding clinical presentation

		EOSG No.=30	LOSG No.=30	TEST-VALUE	P-VALUE	SIG.
PALLOR		19 (63.3%)	22 (73.3%)	0.693	0.405	NS
JAUNDICE		2 (6.7%)	2 (6.7%)	0.000	1.000	NS
CYANOSIS		26 (86.7%)	22 (73.3%)	1.667	0.197	NS
LETHARGY		20 (66.7%)	20 (66.7%)	0.000	1.000	NS
SUCKLING REFLEX		27 (90%)	30 (100%)	3.158	0.076	NS
TACHYPNEA		30 (100%)	30 (100%)	-	-	-
RETRACTION		30 (100%)	30 (100%)	-	-	-
GRUNTING		24 (80%)	19 (63.3%)	2.052	0.152	NS
SILVERMAN SCORE	Median(IQR)	6 (5-7)	5 (5-6)	2.775	0.006**	HS
	Range	4 – 7	4 – 7			
DOWNS SCORE	Median(IQR)	6 (5-7)	5 (5-6)	2.774	0.005*	S
	Range	4 – 7	4 – 7			
APNEA		22 (73.3%)	19 (63.3%)	0.693	0.405	NS
TACHYCARDIA		2 (6.7%)	3 (10%)	0.218	0.640	NS
BRADYCARDIA		5 (16.7%)	4 (13.3%)	1.080	0.400	NS
MOTTLING		23 (76.7%)	21 (70%)	0.341	0.559	NS
HYPOTENSION		4 (13.3%)	4 (13.3%)	0.000	1.000	NS
SCLEREMA		4 (13.3%)	0 (0%)	4.286	0.038*	S
POOR PERFUSION		27 (90%)	23 (76.7%)	1.920	0.166	NS
OLIGURIA		18 (60%)	23 (76.7%)	1.926	0.165	NS
FEEDING INTOLERANCE		29 (96.7%)	30 (100%)	1.017	0.313	NS
ABDOMINAL DISTENTION		10 (33.3%)	5 (16.6%)	0.222	1.36	NS
HEPATOMEGALY		4 (13.3%)	3 (9.9%)	1.040	0.760	NS
CONVULSIONS		11 (36.7%)	19 (63.3%)	4.267	0.039*	S

There was a significant increase in Silverman score, Downs score, and sclerema in EOSG than LOSG, with a p-value less than 0.05. While convulsions are significantly greater in LOSG than EOSG, the p-value is less than 0.05.

Table 3. Comparison among the examined groups regarding D-dimer & HS-CRP levels

		CONTROL GROUP No.=30	EOSG No.=30	LOSG No.=30	TEST-VALUE	P-VALUE	SIG.
D-DIMER (MG/L)	Median(IQR)	0.7 (0.6-0.92)	2.8 (2.3-3.6)	3.19 (2.22-3.67)	56.674‡	0.000**	HS
	Range	0.3 – 1.9	0.89 – 4	1.69 – 4.5			
HS-CRP(MG/L)	Median(IQR)	0.28 (0.25-0.33)	3.8 (3.06-4.34)	3.15 (2.57-4.01)	62.441‡	0.000**	HS
	Range	0.22 – 0.46	2.61 – 5.41	1.67 – 4.61			

POST HOC ANALYSIS

PARAMETERS	Control vs Early	Control vs Late	Early vs Late
D-DIMER	0.000**	0.000**	0.351
HS-CRP	0.000**	0.000**	0.008*

An insignificant distinction has been observed among EOSG and LOSG in the level of D-dimer p-value more than 0.05, but a significant elevation in D-dimer has been observed in the EOSG and LOSG than in the control group p-value less than 0.05. While the level of highly sensitive C-reactive protein was significantly greater in EOSG than LOSG and also significantly greater in EOSG and LOSG than the control group, the p-value was less than 0.05.

Table 4. Association of D-dimer & HS-CRP with other examined parameters among early onset sepsis group

EOSG	D-DIMER r	D-DIMER P-value	HS-CRP r	HS-CRP P-value
D-DIMER (MG/L)	--	--	0.153	0.420
HS-CRP (MG/L)	0.153	0.420	--	--
AGE (DAYS)	-0.344	0.062	0.055	0.773
GESTATIONAL AGE (W)	-0.439*	0.015*	0.090	0.637
BW (KG)	-0.382*	0.037*	0.036	0.849
SILVERMAN SCORE	0.533**	0.002**	0.078	0.684
DOWNES SCORE	0.592**	0.001**	0.164	0.385
TLC (×1000/ML)	-0.017	0.930	-0.122	0.520
LYMPH (×1000/ML)	-0.072	0.706	-0.029	0.878
NEUTROPHILS (×1000/ML)	0.041	0.831	-0.121	0.525
I/T RATIO	-0.021	0.912	-0.030	0.874
RBCS (×10M/MM3)	-0.027	0.886	-0.056	0.770
HGB (G/DL)	0.025	0.897	0.095	0.616
PLT (×1000/L)	-0.359*	0.034*	0.283	0.129
PT(SEC)	-0.149	0.431	0.147	0.439
APTT (SEC)	-0.079	0.678	0.051	0.789
HSC	0.122	0.522	0.003	0.988
TOLLNER SCORE	0.510**	0.004**	-0.098	0.607
HOSPITAL STAY (DAYS)	0.460**	0.001**	-0.005	0.978

EOSG: Early onset sepsis group, TLC: Total leukocytes count, PT: Prothrombin time, APTT: Activated partial thromboplastin time, HSS: Hematological sepsis score. Spearman correlation coefficient *: Significant; **: Highly significant

A significant negative association has been observed among D-dimer and gestational age, BW, BL, and PLT with a p-value less than 0.05. A significant positive association has been observed among D-dimer and Silverman Score, Downes Score, Tollner Score, and Hospital Stay, with a p-value less than 0.05. An insignificant positive association has been observed between the highly sensitive C-reactive protein level and the other examined parameters, with a p-value of more than 0.05.

Table 5. Association of D-dimer & HS-CRP with other examined parameters among late onset sepsis group

LOSG	D-DIMER r	D-DIMER P-value	HS-CRP r	HS-CRP P-value
D-DIMER (MG/L)	--	--	-0.237	0.208
HS-CRP (MG/L)	-0.237	0.208	--	--
AGE (DAYS)	-0.016	0.933	0.065	0.734
GESTATIONAL AGE (W)	0.004	0.983	0.063	0.743
BW (KG)	-0.122	0.520	0.075	0.695
SILVERMAN SCORE	0.163	0.390	0.024	0.901
DOWNES SCORE	0.112	0.556	-0.195	0.301
TLC (×1000/ML)	-0.135	0.477	0.127	0.504
LYMPH (×1000/ML)	-0.136	0.473	0.104	0.584
NEUTROPHILS (×1000/ML)	-0.001	0.994	0.067	0.726
I/T RATIO	-0.008	0.965	0.245	0.193
PLT (×1000/L)	-0.464**	0.010**	0.189	0.318
PT (SEC)	0.363*	0.049*	-0.173	0.361

APTT (SEC)	0.410*	0.025*	-0.129	0.497
HSC	0.204	0.280	0.076	0.691
TOLLNER SCORE	0.327	0.078	-0.051	0.788
HOSPITAL STAY (DAYS)	0.345*	0.044*	0.135	0.478

A significant negative association has been observed among D-dimer level and PLT level, and also a significant positive association has been observed among D-dimer level and PT and APTT levels and hospital stay length of the LOSG P-value less than 0.05, but an insignificant positive or negative association has been observed between HS-CRP and examined parameters in the LOSG P-value more than 0.05.

Table 6. Receiver operating characteristic curve (ROC) for D-dimer & HS-CRP levels for diagnosis of early onset sepsis group

	CUT OFF POINT	AUC	SENSITIVITY	SPECIFICITY	PPV	NPV
D DIMER	>1.42	0.977	90.0	96.7	96.4	90.6
HS CRP	>0.46	1.000	100.0	100.0	100.0	100.0

This ROC curve shows that the cut-off point for D-dimer level for diagnosis of EOS is > 1.42 with 90.0% sensitivity, 96.7% specificity, and 0.977 AUC, while the cut-off point for HS-CRP for diagnosis of EOS is > 0.46 with 100.0% sensitivity, 100.0% specificity, and 1.000 AUC .

Table 7. Receiver operating characteristic curve (ROC) for D-dimer & HS-CRP levels for diagnosis of late onset sepsis group

	CUT OFF POINT	AUC	SENSITIVITY	SPECIFICITY	PPV	NPV
D DIMER	>1.62	0.996	100.0	96.7	96.8	100.0
HS CRP	>0.46	1.000	100.0	100.0	100.0	100.0

The cut-off point for D-dimer level for diagnosis of LOS is > 1.62 with 100.0% sensitivity, 96.7% specificity, and 0.996 AUC, while the cut-off point for HS-CRP level for diagnosis of LOS is > 0.46 with 100.0% sensitivity, 100.0% specificity, and 1.000 AUC.

4. Discussion

Regarding the demographic data of examined preterm infants, an insignificant distinction has been observed among EOSG and LOSG in gestational age (weeks) and a significant reduction in gestational age (weeks) in EOSG and LOSG compared to the control group (p-value less than 0.001). The observed occurrence of infection in babies may be inversely correlated with both birth weight and gestational age.

This outcome was agreed with the research of Andi et al.[8] who found significant distinctions in means of gestational age among infected and non-infected newborn infants.

In the current investigation, a statistically significant elevation in the postnatal age has been observed in LOSG than EOSG and the control group (p-value less than 0.001), but an insignificant distinction has been observed among EOSG and the control group regarding postnatal age. This could be explained by the difference in the onset of sepsis between early and late neonatal sepsis. These outcomes were agreed with by ELMeneza et al.[9] who observed an insignificant distinction between the EOS newborn group and the control group with regard to postnatal age.

This study showed insignificant distinction with regard to sex and mood of delivery between the EOSG, LOSG, and control groups. These results agreed with El Meneza et al.[10] who observed insignificant distinctions among cases and controls with regard to sex and mood of delivery.

In the current study regarding clinical examination, an insignificant distinction has been observed among EOSG and LOSG with regard to the percentage of preterm infants with apnea, tachypnea, retraction, grunting, cyanosis, lethargy, weak suckling reflex, abdominal distention, bradycardia, mottling, hypotension, poor perfusion, feeding intolerance, and hepatomegaly. According to ELMeneza et al.[9] the signs and symptoms are nonspecific and involve cyanosis, respiratory distress, apnea, feeding difficulties, lethargy or irritability, seizures, hypotonia, bulging fontanel, bleeding problems, poor perfusion, abdominal distention, hepatomegaly, unexplained jaundice, or, most importantly, simply an unappealing look. This study showed that sclerema was found to be significantly greater in EOSG than in LOSG.

In this study regarding HS-CRP, it has been found to be significantly greater in EOSG and in LOSG compared to the control group and also significantly greater in EOSG than in LOSG. C-reactive protein is an acute-phase reactant that is synthesized by the liver within 6 hours of the onset of tissue necrosis and inflammation. The C-reactive protein test has gained popularity due to its rapid synthesis, brief half-life, and quick decline with recovery, as well as a correlation between greater elevations and serious infections with bacteria.[11]

Regarding the sensitivity of antibiotics, this study revealed that the most sensitive antibiotics in EOSG were Colistin (33.3%), Gentamycin (26.7%), Vancomycin (26.7%), and Ciprofloxacin (16.7%). While the most sensitive antibiotics in LOSG were Colistin (70%), Minocycline (20%), and Cefepime (10%).

According to HS-CRP, there were no statistically significant relations among the level of highly sensitive C-reactive protein and any complications of sepsis or the outcome in EOSG or LOSG. These results agreed with El Shahat et al.[12] who stated that a statistically insignificant relation has been observed among CRP level and severity of cases or mortality rate.

The present investigation showed a statistically significant negative association between D-dimer level and gestational age (weeks), body weight, and body length. El Shahat et al.[12] agreed with these results; they found high levels of D-dimer in low birth weight and preterm babies.

In this study, a significant positive association has been observed among the level of D-dimer in EOSG and the Silverman score, Downes score, and Tollner score. This agreed with the results of Meini et al.[13] who stated that the D-dimer level could predict the severity and severe invasive infections course.

In the present investigation, a significant negative association has been observed between D-dimer and platelet count in EOSG and LOSG. Platelets play an active role in the defense mechanisms of the host as they can perform phagocytosis. Platelets direct toxic injury, megakaryocytic suppression, elevated peripheral consumption as in DIC, or the presence of immune component because of elevated levels of platelet-associated immunoglobulins.[14]

In this study, we found a significant positive correlation between D-dimer levels and PT and APTT levels in LOSG. This agreed with a study concluded by Ebar et al.[15] that prothrombin time, activated partial thromboplastin time, fibrinogen, and D-dimer have been significantly elevated in cases with sepsis.

The cutoff point for the D-dimer level to diagnose the EOS has been found to be > 1.42 (90.0% sensitivity and 96.7% specificity). Also, the cutoff point for the D-dimer level to diagnose the LOS was found to be > 1.62 with (100.0%) sensitivity and (96.7%) specificity.

Al-Biltagi et al.[3] and El Shahat et al.[12] agreed with us and reported that D-dimer could be utilized as an adjunct to other sepsis markers to elevate the specificity and sensitivity for diagnosis of neonatal sepsis. The cutoff point in the Al-Biltagi study for D-dimer in neonatal sepsis was a sensitivity of 72.7% and a specificity of 86.7%. El Shahat's study revealed that D-dimer at a cutoff point had an accuracy of 97.8% for the identification of neonatal sepsis with a sensitivity of 100.0% and specificity of 95.6%.

The cutoff point for HS-CRP level for diagnosis of EOS was found to be > 1.8 with (100.0%) sensitivity and (100.0%) specificity. At the same time, the cutoff point for HS-CRP level for diagnosis of LOS was found to be > 1.5 with (100.0%) sensitivity and (100.0%) specificity.

4. Conclusion

HS-CRP in the present study has been shown to be more specific and sensitive for the identification of neonatal sepsis in preterm infants than D-dimer; however, D-dimer elevated with elevated severity of cases who had bad prognosis, so it could be utilized for prognostic purposes in neonatal sepsis.

Disclosure

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