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Study of Diagnostic Value of D-Dimer Serum Level as a Marker in Neonatal Sepsis

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ABSTRACT

Background: Neonatal septicemia is widely recognized around the world. A prominent cause of infant mortality and morbidity. Folinolysis in sepsis causes a rise in the D-dimer marker, which is generated when cross-linked fibrin breaks down.

Objective: The goal of this work was to evaluate the clinical significance of D-Dimer level for diagnosis of neonatal sepsis.

Patients and Methods: Our study was done on 90 neonates divided into two groups: 45 septic neonates as cases and 45 healthy controls. A complete medical history, clinical examination, and diagnostic tests were performed for all newborns (CBC, CRP, blood culture, D-dimer).

Results: Most of blood cultures were negative (42.2%) and the other positive cultures showed that klebsiella was the most common organism (22.2%), E-coli was 15.5%, Pseudomonas was 8.89%, Staph. Aureus was 6.67% and the less common was GBS (4.4%). CRP and D-dimer levels were significantly elevated in neonatal sepsis cases compared to controls. D-dimer at a cutoff point higher than 2 had 97.8% accuracy for detection of neonatal sepsis with 100.0% sensitivity and 95.6% specificity. D-dimer levels were significantly higher in infant sepsis patients who died compared to those who survived (5.5 ± 1.3 versus 3.2 ± 1.4) respectively indicating that D-dimer increased with increased severity of cases who had bad prognosis.

Conclusion: D-dimer had 97.8% accuracy for detection of neonatal sepsis with 100.0% sensitivity and 95.6% specificity. So it may be used as a marker in neonatal sepsis.

Keywords: D-Dimer, CRP, Neonatal sepsis.

INTRODUCTION

Sepsis is still a critical challenge in pediatric critical care medicine, in spite of continued advances in neonatal medicine [(1)]. Neonatal sepsis mortality has dropped from 87% in 1928 to 3% in 2003, yet it remains a major cause of illness and mortality in newborns [(2)]. Neonatal sepsis is a phrase used to describe a systemic bacterial, viral, or fungal infection that causes hemodynamic abnormalities and other clinical symptoms as well as significant morbidity and death in the newborn population. Severe neonatal sepsis can be characterized as either early or late onset, based on the age and time of the sepsis episode [(3)]. Neonatal sepsis causes some nonspecific symptoms and signs, involving jaundice, hypnosis, bradycardia, apnea, tachycardia, respiratory distress, hypotonia, bulging fontanel, feeding difficulties, seizures, long capillary refill time and temperature instability [(4)].

Neonatal sepsis can only be accurately diagnosed by a blood culture, which is the gold standard in this field. It is possible to miss the causative agent due to technical issues like as poor blood sample or antibiotic use by the mother [(5)].

Neonatal sepsis is associated with a high incidence of coagulation malfunction, which might appear clinically or subclinically in the setting of DIC. When the clotting system is overactive, it leads to an increase in fibrin deposition and a decrease in clotting factor and platelet consumption, which is known as DIC [(6)]. Chronic inflammation causes intravascular deposition of fibrin and a prothrombotic condition, which in turn causes microvascular thrombosis, which in turn causes various organs to be damaged by anoxic injury [(7)]. When fibrin is broken down, a molecule called D-dimer is created, and this molecule's concentration rises in sepsis as a result of fibrinolysis. D-dimer is also elevated in DIC, which indicates that the coagulation mechanism has been activated [(8)].

The goal of this work was to evaluate the clinical significance of D-Dimer level for diagnosis of neonatal sepsis.

PATIENTS AND METHODS

Ninety newborns hospitalized at Zagazig University Hospitals, in the Neonatal Intensive Care Unit between February 2020 and August 2021 served as the subjects for this cross-sectional trial. The neonates were divided into two groups. **Group 1 (Study group)** that included 45 neonates diagnosed to have sepsis. **Group 2 (control group)**, which included 45 newborns, all of the same age and gender. They were gathered from the resuscitation room and found to be in good health.

Inclusion criteria: For septic group, all established newborns with sepsis-related symptoms, and signs at the time of admission or who contracted sepsis during their hospital stay. For control group, to be non-septic clinically and laboratory.

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Exclusion criteria: (1) Neonatal surgical problems. (2) Congenital anomalies. (3) Parental disapproval to participate in the study.

Ethical approval:

Zagazig University's Research Ethics Council approved the study as long as all participants' parents signed informed consent forms that were submitted to ZU-IRB#6285. We adhered to the Helsinki Declaration, which is the ethical form for human testing established by the World Medical Association.

All the participants in this research were subjected to the following:

History: The patient's age, sex, gender, maternal risk factors, gestational age, prenatal and natal history were all recorded in a thorough medical history.

Clinical examination: Weight of a newborn, Suckling and Moro reflexes (Moro) were performed on the newborns as well as vital parameters such as heart rate and respiration rate. Spotting the early indications of sepsis: Restlessness, sleepiness, pallor, and mottled skin characterise the infant's condition, and a fluctuation in temperature, either hyperthermia or hypothermia and problem with the respiratory system.

Laboratory evaluation: When sepsis was suspected, blood samples were collected. Four centimeters of blood were collected by applying antiseptic to the skin. For the CBC, 1 cm of blood was injected into the culture bottle, whereas 2 cm of blood were taken in a simple test tube for the CRP. Complete blood count was analysed by sysmex 21-kx cell counter for hemoglobin level, red blood cell count, RDW, hematocrit value, platelet count and white blood cell (WBC) count (Total and differential). Results of CBC were interpreted using Hematological scoring system by **Rodwell *et al.* [(9)].**

Quantitative C-reactive protein (CRP): Turbox plus was used to separate serum after centrifuging for 10 minutes at 1500 rpm with 1cm of blood in a plain test tube. Results were considered positive when they exceeded 6 mg/l.

Blood culture: Using automated BACT/ALERT 3D 60 (Biomerieux).

D-dimer: D-dimer test was done using automated chemistry analyzer Cobas 6000, Roche diagnostics.

Statistical analysis

The independent t-test (t) and Mann-Whitney (MW) test were employed to compare parametric and non-parametric data, respectively, in the analysis of the differences between the groups. When there was a difference between two groups of non-parametric data, the Kruskall-Wallis test (KW) was employed. Proportions were compared using the Chi-square test (x^2). Diagnostic and prognostic utility in newborn sepsis were evaluated using Receiver Operating Characteristics (ROC) analysis and cut-off points and their associated values. P value ≤ 0.05 was considered statistically significant (S). It was judged highly significant (HS) when the P value was 0.001 and non-significant (NS) when the P value was > 0.05.

RESULTS

Table (1) showed that there were statistically significant lower gestational age and higher preterm rates among cases than controls, whereas there were no statistically significant differences between the case and control groups regarding age, weight, and sex.

Table (2) showed that not doing well was the commonest clinical characteristics followed by respiratory distress, poor suckling then hepatomegaly and pallor and lastly jaundice.

Table (3) showed that most of blood cultures were negative (42.2%) and the other positive cultures showed that klebsiella was the most common organism (22.2%), E-coli was (15.5%), Pseudomonas was (8.89%), Staph. Aureus was (6.67%) and less common was GBS (4.4%).

CRP and D-dimer levels were significantly elevated in neonatal sepsis cases compared to controls [(58.5 ± 57.7 versus 5.8 ± 3.5) and (4.24 ± 1.6 versus 1.02 ± 0.6) respectively].

Table (4) showed that in newborn sepsis cases, CRP and D-dimer levels were statistically significantly higher than in the control group [(58.5 ± 57.7 versus 5.8 ± 3.5) and (4.24 ± 1.6 versus 1.02 ± 0.6) respectively].

Table (5) showed that D-dimer and CRP levels were found to have a statistically significant positive connection with hospital length of stay and statistically significant positive correlation with WBCs. A statistically significant link between D-dimer level and RBCs/platelets count was found to exist. Otherwise, other variables had no statistically significant association.

Table (6), Figure (1) showed that the D-dimer at a cutoff point higher than 2 had 97.8% accuracy for detection of neonatal sepsis with 100.0% sensitivity and 95.6% specificity. While, CRP at a cutoff point higher than 6 had 90.2% accuracy for detection of neonatal sepsis with 85.0% sensitivity and 70.3% specificity. Figure (2) showed that 89 % of the cases recovered while 11% died.

Table (7) showed that D-dimer levels were much higher in severely newborn sepsis cases that died compared to those that recovered, a statistically significant difference (5.5 ± 1.3 versus 3.2 ± 1.4 respectively) indicating that D-dimer increased with increased severity of cases who had bad prognosis.

Table (1): Patients' demographic and clinical information was gathered for the study

Demographic data	Case (N = 45)	Control (N = 45)	Test	P-value (Sig.)
	Mean ± SD (Range) median	Mean ± SD (Range) median		
Weight (kg)	3.1 ± 0.4 (2 - 4) 3	3.1 ± 0.3 (2.3 - 3.9) 3	0.4*	0.6 (NS)
Age (days)	5.7 ± 3.3 (1 - 15) 5	6.2 ± 2.6 (1 - 14) 6	1.6*	0.07 (NS)
Gestational age (weeks)	36.1 ± 1.3 (35 - 40) 36	38.7 ± 0.5 (38 - 40) 38	2.7*	0.03 (Sig.)
	No. **%**	**No.** **%**		
Sex				
Male	23 51.1	18 40	1.1•	0.3 (NS)
Female	22 48.9	27 60		
Hospital length of stay (days) Mean ± SD (Range) median		8.8 ± 5.4 (3-27) 7		

Table (2): Clinical characteristics of the case (septic) group

Variables	The Case group	
	No (45)	**%**
Not doing well	37	82.2%
Respiratory distress	35	77.8%
Poor suckling	32	71.1%
Hepatomegaly	19	42.2%
Pallor	17	37.8%
Jaundice Yes	14	31.1%

Table (3): Blood culture results in the case group

Blood culture results	The case group	
	No (45)	**%**
Klebsiella	10	22.2%
E-Coli	7	15.5%
Pseudomonas	4	8.89%
Staph. Aureus	3	6.67%
GBS	2	4.4%
No growth	19	42.2%

Table (4): Comparing CRP and D-dimer between case and control groups

Variable	Case (45)	Control (45)	Test	p-value
CRP mean ± SD median	58.5±7.7 46	5.8±1.5 3.3	M.W 6.1	**0.001****
D-dimer mean ± SD median	4.24±1.6 4.2	1.02±0.2 0.9	M.W 13.5	**0.001****

Table (5): Correlation between D-dimer level with patient investigations and patient characteristics among the case group

Variable	*D-dimer level* r	^ p	SIG
Age	0.2	> 0.05	NS
Weight	-0.1	> 0.05	NS
RBCs	**-0.2**	**0.03***	**S**
WBCs	**0.3**	**0.04***	**S**
HB(g/dl)	0.04	> 0.05	NS
Platelets	**-0.2**	**0.03***	**HS**
CRP	**0.7**	**0.001****	**HS**
Hospital stay	**0.8**	**0.001****	**HS**

Table (6): ROC curve Analysis of CRP and D-Dimer as diagnostic tool for neonatal sepsis

Cut-off	SN % (95%CI)	SP % (95%CI)	PPV % (95%CI)	NPV% (95%CI)	Acc. (95%CI)	AUC (95%CI)	P-value
D-dimer (0 – 0.5 ug/ml)							
> 2	100%	95.6%	95.7%	100%	97.8%	0.98	< 0.001 (HS)
CRP (1 - 5 mg/ml)							
> 6	85%	70.3%	69.1%	85%	90.2%	0.872	< 0.001 (HS)

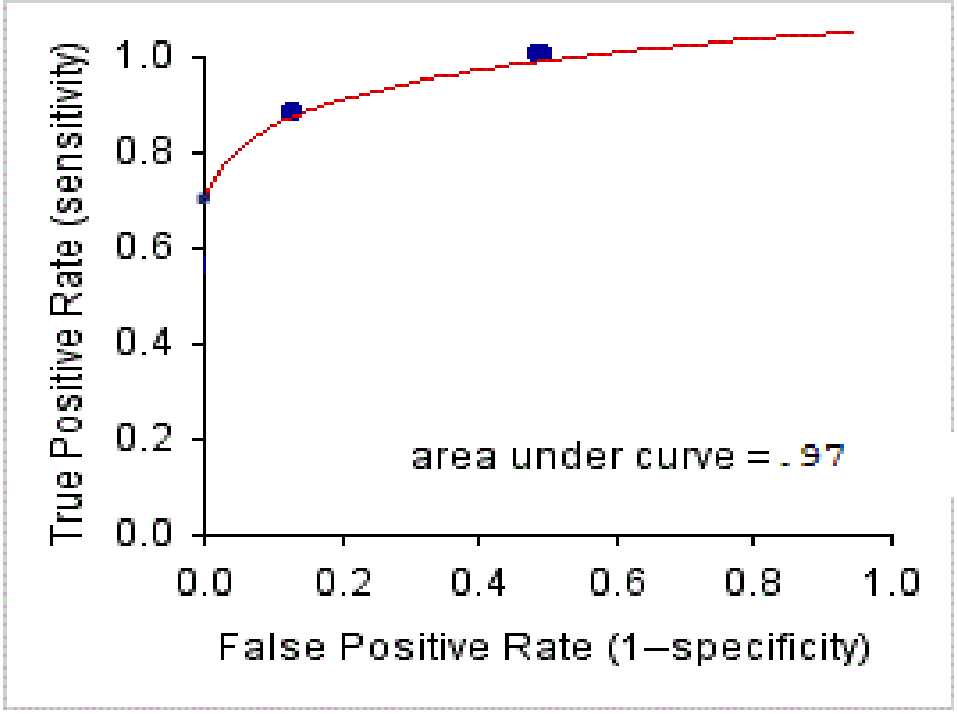

Figure (1): ROC curve analysis of CRP in diagnosis of sepsis

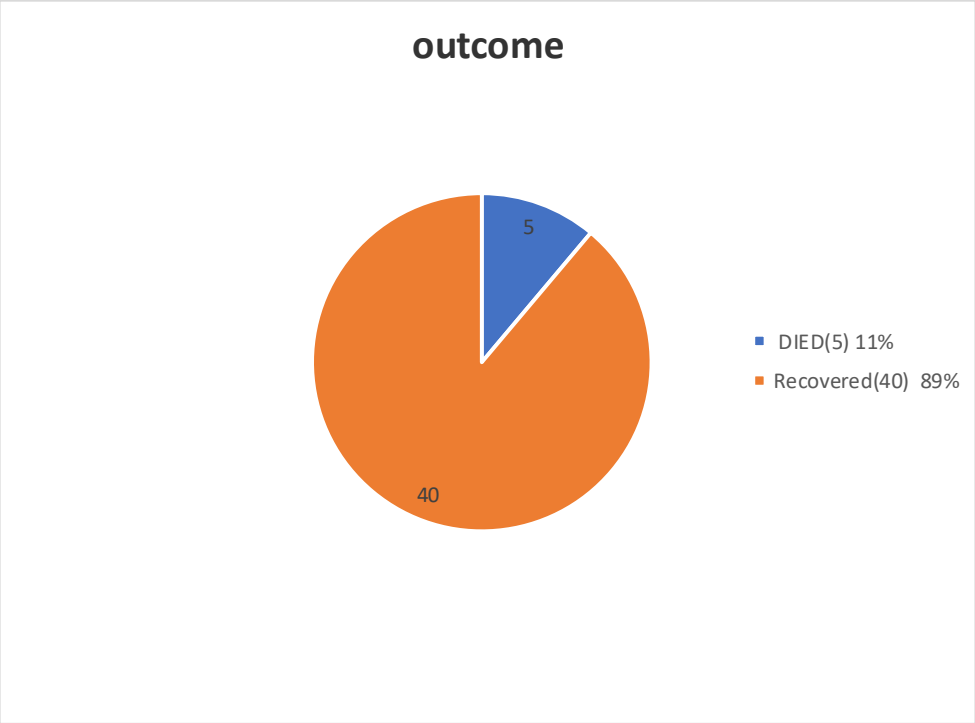

Figure (2): Outcome in the case group

Table (7): Comparison of D-dimer level as regard outcome among patient with sepsis in the case group

D-dimer level	Recovered (N =40)	Died (N = 5)	Test	p-value
mean ± SD (Range) median	3.2 ± 1.4 (1.9 - 4.7) 3.5	5.5 ±1.3 (3.9 - 7.4) 5.4	4.2*	0.001 (HS)

DISCUSSION

As a life-threatening illness brought on by an infection, sepsis accounts for 45% of all newborn emergencies and is the most common cause of neonatal morbidity as well as mortality [(10)]. Fibrinolysis function decreases in sepsis despite persisting coagulation activity, causing greatly increased fibrin formation and eventually microvascular thrombosis. Fibrinolysis activity can be assessed by D-dimer measurement [(11)].

Our study showed that 23 (51.1%) were males and 22 (48.9%) were females in the case group while 18 (40%) of the control group were males and 27 (60%) were females with no significant difference between them [(12)]. Also **Kumar *et al.*** [(7)] agrees with this result as sex distribution was almost equal between septic and control neonates with no statistically difference.

Our study showed that mean age was 6.2 ± 2.6 and 5.7 ± 3.3 in control and cases successively with no significant difference between them. This is almost the same result for **Kumar *et al.*** [(7)] who showed that the average age of the study group was 5.58 days while the average age of the control group was 5.62 days.

In the current study, mean of birth weight was 3.1 ± 0.4 and 3.1 ± 0.3 kg in the case and control groups respectively with no significant difference between them. According to **Belachew *et al.*** [(13)], the chances ratio of low birth weight newborns developing neonatal sepsis was 1.42 times greater than the odds ratio of normal-weight born babies developing the condition.

In the current study, not doing well was the commonest clinical presentation (82.2%) followed by respiratory distress (77.8%), poor suckling (71.1%) then hepatomegaly (42.2%) and pallor (37.8%) and lastly jaundice (31.1%). In the study of **Khinchi *et al.*** [(14)] Tachycardia or respiratory distress (75%) and fever (74%) were the most common neonatal complaints. While, **Lim *et al.*** [(15)] showed that apnea, bradycardia, and/or cyanosis were the most common signs of sepsis (104/158; 65.8%), followed by lack of activity (77/158; 48.7%), and increased respiratory effort (68/158; 43.0%).

In our study, most of blood cultures were negative (42.2%) and the other positive cultures showed that klebsiella was the most common organism (22.2%), E-coli was 15.5%, Pseudomonas was 8.89%, Staph. Aureus was 6.67% and less common was GBS (4.4%). While in study done by **Karne *et al.*** [(16)] where in 16 of the 40 cases, Pseudomonas aeruginosa was shown to be the pathogen (40%), followed by Staph.

Aureus (17.5%), Candida (15%), klebseilla (10%) and less common was acinobacter and E-coli.

In the current study, CRP and D-dimer levels were significantly elevated in neonatal sepsis cases compared to controls [(58.5 ± 57.7 versus 5.8 ± 3.5) and (4.24 ± 1.6 versus 1.02 ± 0.6) respectively]. This agrees with **Saleh *et al.*** [17] who found that all of the healthy controls had normal CRP levels, although statistically significant differences (P 0.001) were seen in all of the cases where CRP was increased. Also, **Younis *et al.*** [18] discovered that the mean CRP level in patients with sepsis was considerably greater than in controls. Another study by **Mohsen *et al.*** [19] in newborns with sepsis showed that CRP levels were found to be considerably elevated. While for D-dimer results this agrees with **Peker *et al.*** [20] who revealed that D-Dimer levels of the patient group were significantly higher than those of the control group.

D-dimer levels had a statistically significant positive link with CRP and hospital stay, as well as a statistically significant positive correlation with WBCs, according to the findings of the current study. D-dimer levels were found to be negatively correlated with RBC and platelet counts in a statistically meaningful way. A statistically significant relationship with any other factors was not found. This comes in agreement with **Peker *et al.*** [20] where there was a statistically significant difference in the levels of D-dimer, CRP, and TLC between the patients and the control group (P0.05). **Decembrino *et al.*** [21] also showed in their study, significant elevation of D-dimer, WBCs in septic neonates than in non-septic with results of D-dimer (mg/L) 2.69 ± 2.98, and WBCs 13.4 ± 16.5, while showed lower levels of platelets in septic neonates 92± 84. This disagree with **Anggraini *et al.*** [22] who found in their study that coagulation activity in sepsis patients showed that platelets count was still in the normal range while D-dimer levels were increased.

In the current study, there was statistically highly significant increase in D-dimer among severely neonatal septic cases that died than recovered cases (5.5±1.3 versus 3.2±1.4 respectively) indicating that D-dimer increased with increased severity of cases who had bad prognosis. This comes in agreement with **Hao *et al.*** [23] who showed in their study that plasma D-dimer levels in the extremely critical and critical groups were significantly higher than in the control group. The extremely critical group had significantly higher DD levels than the critical group, and the critical group had significantly higher DD levels than the non-critical group.

In the current study, the D-dimer at a cutoff point higher than 2 had 97.8% accuracy for detection of neonatal sepsis with 100.0% sensitivity and 95.6% specificity. Also, D-dimer had a high predictive ability for detection of neonatal sepsis with positive predictive value of 95.7% and negative predictive value of 100%. While, CRP at a cutoff point higher than 6 had 90.2% accuracy for detection of neonatal sepsis with 85.0% sensitivity, specificity of 70.3%, positive predictive value of 69.1%, and negative predictive value of 85%. This comes in agreement with **Kumar *et al.*** [7] where they reported a sensitivity of 90%, specificity of 58%, positive predictive value of 69%, and a negative predictive value of 84.4% for the D-dimer. This study found that CRP was 80.8%, specificity was 74.4%, positive predictive value was 69.5%, and negative predictive value was 80.4%. While **Brahmana** [24] found that D-dimer had a sensitivity value of 28%, specificity of 70%, positive predictive value of 40%, and negative predictive value of 58%.

Due to the recruitment in India by **Kumar *et al.*** [7] study being done in all infants with positive blood culture results, there are discrepancies between these trials, while in **Brahmana** [24] study all infants with clinical sepsis were treated without waiting for the results of blood cultures.

CONCLUSION:

In neonatal septicemia D-dimer has 97.8% accuracy for detection of neonatal sepsis with 100.0% sensitivity and 95.6% specificity. So, it might be used as a marker in neonatal sepsis. D-dimer increased with increased severity of cases who had bad prognosis, so it can be used for prognostic purposes in neonatal sepsis or early prediction of severe sepsis rather than the early diagnosis of neonatal sepsis.

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