SERODIAGNOSIS OF EARLY NEONATAL SEPSIS IN EGYPTIAN NEONATES

By

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ABSTRACT

Background: *Neonatal sepsis is a life-threatening disease. Early diagnosis is essential, but no single marker of infection has been identified. Sepsis activates a coagulation cascade with simultaneous production of the D-dimers due to lysis of fibrin. D-dimer test reflects the activation of the coagulation system.*

Aim and objectives: *the main aim of this study was to evaluate the level of D-dimer in neonatal sepsis as a diagnostic test and if has a role in the severity or complications of neonatal sepsis.*

Subjects and methods: *This was cross-sectional study that conducted in the tertiary care NICU of Bab El-sheria and Al- Hussein University Hospitals, Al-Azhar University. This study was conducted on 40 septic newborns (Patients group), and 40 non-septic newborns served as Control group.*

Results: *There was high positive significant correlation between D-dimer and mortality ($r=0.858$, $P<0.001$), and there was high positive significant correlation between D-dimer and I/T ratio and high negative significant correlation with PLT.*

Conclusion: *D-dimer is a sensitive predictor of sepsis in neonates with sensitivity 80%, specificity 96%, negative predictive value 88.9% and positive predictive value 92.3%. Hence, it should be included in the septic screening of newborns.*

Keywords: *D-dimer; Neonates; Screen; Sepsis*

INTRODUCTION

Neonatal sepsis defines the systemic condition that arises from the bacterial, viral or fungal origin, associated with hemodynamic changes and clinical findings causing severe morbidity and mortality, its incidence varies depending on the definition of the case and the population studied and is between 1 and 5 in 1000 live births

(American Academy of Pediatrics, 2018).

Neonatal sepsis causing some nonspecific systemic signs and symptoms, including temperature instability, respiratory distress, cyanosis, apnea, bradycardia or tachycardia, feeding difficulties, hypotonia, lethargy, irritability, seizures, bulging fontanel, long capillary refill time, paleness, mottled skin, abdominal distention, and jaundice **(Shah BA et al., 2014)**.

Blood culture remains the gold standard for confirmation of sepsis but it is limited by low sensitivity and duration of time before a culture is determined to be positive (often around 24 to 72 hours). Fastidious organisms, maternal antibiotics, and small sample collection limit the sensitivity of blood cultures. False positives may occur due to inadequate skin antisepsis prior to sample collection **(Ershad, M et al., 2019)**.

While the growth of the microorganism in blood culture is diagnostic in the neonatal period, the failure to produce it does not exclude the diagnosis **(Odabasi IO, Bulbul A, 2020)**.

D-dimer (DD) as well as other biomarkers related to coagulation is significantly increased during sepsis and especially when developing disseminated intravascular coagulation (DIC) **(Joaquín R. Rodelo. et al., 2012)**.

Coagulation dysfunction is one of the complications of neonatal sepsis that can manifest clinically or sub clinically in disseminated intravascular coagulation, D-dimer one of degradation of cross-linked fibrin is increased in disseminated intravascular coagulation **(Ishikura, H., et al., 2014)**.

Aims of the Work

To evaluate the level of D-dimer in neonatal sepsis as a diagnostic test and if has a role in the severity or complications of neonatal sepsis.

Ethical considerations:

1. An informed consent was taken from all parents before getting involved in study.
2. Confidentiality of all data was ensured.
3. The study was done after approval of ethical committees of Pediatrics department & faculty of medicine for Al-Azhar University.
4. The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Sample size:

The sample size will be calculated using the following formula:

Where:

$$n = 2\left[\frac{(Z_{\alpha/2} + Z_{\beta}) * \sigma}{\mu_1 - \mu_2}\right]^2$$

n = sample size

$Z_{\alpha/2}$ = 1.96 (The critical value that divides the central 95% of the Z distribution from the 5% in the tail)

Z_{β} = 0.84 (The critical value that separates the lower 20% of the Z distribution from the upper 80%)

σ = the estimate of the standard deviation of neonates with D-dimer level in the lowest quartile = 1.47

μ_1 = mean of neonates with D-dimer level in the lowest quartile was = 27.9

μ_2 = mean in of neonates with D-dimer level in the other quartiles follow up = 9.2

So, by calculation, the sample size will be equal to 80 patients in total.

PATIENTS AND METHODS

This was a cross-sectional study conducted on 40 septic newborns (Patients group) admitted to the tertiary care NICU of Bab El-Sheria and Al- Hussein University Hospitals, Al-Azhar University and control group on 40 non-septic incubated due to causes other than sepsis during the period from May 2021 to November 2021, they were selected by simple random method, both patients and controls were divided into 2 groups (septic group and control group).

Inclusion criteria:

1. Preterm and term infants less than 28 days of life.
2. Presence of neonatal sepsis risk factors which include: Low birth weight (<2500 grams), prematurity (<37 weeks of gestation age).
3. Febrile illness in the mother within 2 weeks prior to delivery, foul smelling discharge and/or meconium-stained amniotic liquid and suspected chorioamnionitis, prolonged rupture of membranes >18 hours, prolonged labor (sum of 1st and 2nd stage of labor > 24 hrs.).
4. Neonatal infants who have one or more of the following criteria of sepsis: Lethargy, an

increase in the number or severity of apneic spells, feeding intolerance, temperature instability and an increase in ventilator support.

Exclusion criteria:

1. Post neonatal period.
2. Neonates with major congenital anomalies and any
3. Neonates with other diagnosis e.g., Hypoxic ischemic encephalopathy and Cong. Heart diseases, inborn error of metabolism (IEM).

Tools of Assessment: The including neonates subjected to the following:

- Full history taking (Perinatal, natal & postnatal)
- Clinical examination: including gestational age, Apgar score, Ballard score, general and local examination.
- Routine Investigations: Complete blood count with differential leucocytic count: using sysmex Kx 21N, CRP by enzyme-linked immunosorbent assay (ELISA), blood cultures, D- dimer level by D-DI2 (Tina-quant D-Dimer Gen.2) "Cobas c 311" and chemistry by "Cobas c 311", all the collecting data was statistically analyzed, compared and discussed.

Statistical analysis of the data: Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean and standard deviation. Significance of the obtained results was judged at the 5% level.

The used tests were:

- **Chi-square test:** For categorical variables, to compare between different groups.
- **Student t-test:** For normally quantitative variables, to compare between two studied groups.
- **Mann Whitney test:** For abnormally quantitative variables, to compare between two studied groups.

RESULTS

Table (1): Descriptive data of studied cases

	patient Group (n = 40)	Control Group (n = 40)	Test of Sig.	P Value
Gestational Age (weeks)				
Min.-Max.	32-39	32-40	U=658.50	0.166
Mean± S. D	34.20±2.334	34.93±2.347		
Delivery type				
VD	8(20.0%)	11(27.5%)	X^2=0.621	0.600
CS	32(80.0%)	29(72.5%)		
Baby Sex				
Male	23(57.5)	19(47.5%)	X^2=0.802	0.502
Female	17(42.5%)	21(52.5%)		
Baby weight (gm)				
Min.-Max.	1115-3720	1140-3720	U=671.00	0.214
Mean± S. D	1711.17±682.761	1873.68±709.077		

X2: Chi-square test, t: T-student test, U: Mann- Whitney test, p: p value for comparing between the two studied groups
*: Statistically significant at P <0.05

Tables (1) this table shows no statistically significant differences between the two studied groups.

Table (2): Comparison between the studied groups regarding to duration on NICU and outcome

	Patient Group (n = 40)	Control Group (n = 40)	U	P Value
Days in NICU				
Min.-Max.	6-33	3-10	530.50	0.009*
Mean± S. D	16.53±6.972	3.5±3.9		
Outcome				
Survive	31(77.5%)	40(100%)		0.002*
Died	9(22.5%)	0		

Table (2) shows highly statistically significant differences between both groups regarding the duration of incubation and outcome with mortality rate in patient group equal to 22.5%.

Table (3): Comparison between two groups as regard to CBC

	Patient Group (n = 40)	Control Group (n = 40)	Test of sig.	P Value
WBC				
Min.-Max.	1.2-37.0	5.2-22.4	t=1.325	0.189
Mean± S. D	13.97±8.303	11.94±4.599		
HGB				
Min.-Max.	8.1-20.3	10.1-19.6	t=1.626	0.108
Mean± S. D	13.20±3.039	16.29±2.929		
PLT				
Min.-Max.	20-477	155-685	U=312.50	<0.001*
Mean± S. D	148.56±110.021	284.90±120.076		
LYM (%)				
Min.-Max.	8.6-64.0	2.7-60.0	t=3.502	0.001*
Mean± S. D	31.59±15.963	36.73±13.451		
NEUT (%)				
Min.-Max.	27.00-82.02	5.2-73.0	t=1.998	0.049*
Mean± S. D	53.28±17.49	43.40±14.355		
I/T ratio				
Min.-Max.	0.15-0.36	0.10-0.30	U=92.50	<0.001*
Mean± S. D	0.27±0.06	0.16±0.042		

Table (3) shows highly statistical significant difference between both groups regarding neutrophil count, I/T ratio and Platelets.

Table (4): Comparison between the studied groups regarding to coagulation profile and D-dimer

	Patient Group (n = 40)	Control Group (n = 40)	Test of sig.	P Value
PT				
Min.-Max.	11.60-31.00	10.10-17.80	U=545.50	0.014*
Mean± S. D	15.69±4.280	13.63±2.125		
PTT				
Min.-Max.	20.0-465.10	12.80-67.00	U=567.50	0.025*
Mean± S. D	81.21±89.703	39.13±10.825		
INR				
Min.-Max.	0.88-19.00	0.76-1.40	U=434.00	0.001*
Mean± S. D	1.68±2.833	1.03±0.158		
D-dimer				
Min.-Max.	580-2100	125-547	U=0.00	<0.001*
Mean± S. D	1344.28±477.419	352.13±111.048		

Table (4) shows significant increasing in PT, PTT, INR and D-dimer levels in septic group when compared to control group with highly significant statistical difference.

Table (5): Correlation between D-dimer and days on NICU and mortality

	D-dimer	
	R	**P**
Days in NICU	0.224	0.052
Mortality	0.481	<0.001*

Table (5) shows positive correlation between D-dimer level and days on NICU incubation time and mortality ($r=0.858$, $P<0.001$).

Table (6): Correlation between D-dimer and CBC

	D-dimer	
	R	**P**
WBC	0.153	0.186
HGB	-0.098	0.398
PLT	-0.319	0.005*
LYM (%)	0.225	0.051
NEUT (%)	-0.049	0.677
I/T ratio	0.761	<0.001*

Table (6) shows high positive significant correlation between D-dimer and I/T ratio (r=0.761, P<0.001) while there was high negative significant correlation between D-dimer and PLT (r=-0.319, P=0.005).

Table (7): Correlation between D-dimer and CRP and ESR

	D-dimer	
	R	**P**
CRP	0.494	0.001*
ESR	0.659	<0.001*

Table (7) shows high positive significant correlation between D-dimer and each of CRP (r=0.494, P=0.001), ESR (r=0.659, P<0.001).

Table (8): Correlation between D-dimer and liver and kidney functions

	D-dimer	
	R	**P**
AST	0.284	0.013*
ALT	0.167	0.148
Urea	0.462	<0.001*
Creatinine	0.209	0.070

Table (8) shows high positive significant correlation between D-dimer and each of AST (r=0.284, P=0.013) and urea (r=0.462, P<0.001).

Table (9): Correlation between D-dimer and coagulation profile

	D-dimer	
	R	**P**
PT	0.285	0.013*
PTT	0.257	0.025*
INR	0.278	0.016*

Table (9) shows correlation between D-dimer and laboratory investigations and it show positive significant correlation between D-dimer and each of PT (r=0.285, P=0.013), PTT (r=0.257, P=0.025) and INR (r=0.278, P= .016)

Table (10): Blood culture results in patient group

Blood Culture	**Patient Group (n = 40)**	
	No.	**%**
Negative	27	67.5
Positive	13	32.5
E-coli	4	10.0
KLEPSILLA	6	15.0
Staph epidermidisa	2	5.0
Pseudomonas	1	2.5
Total	40	100

Table (10) shows Blood Cultures in Patient Group and it show that 27(67.5%) were negative and 13(32.5%) were positive.

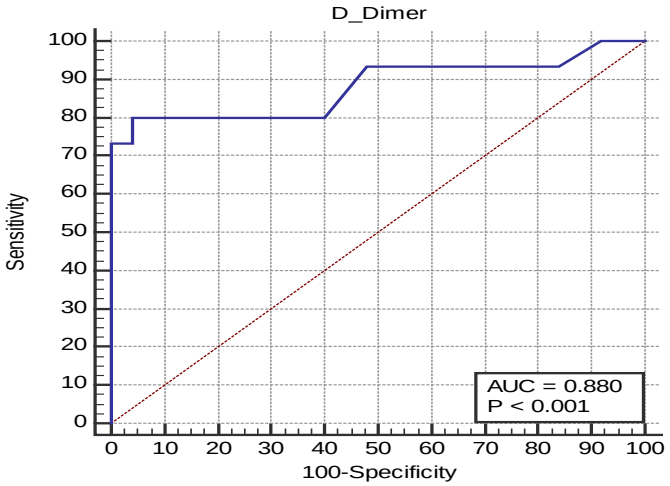

Figure (1): ROC curve analysis between blood culture and D-dimer

Figure (1) ROC curve shows that at cut off value >1547 it can predict blood culture with sensitivity 80.0% and specificity 96.0% and AUC = 0.880 with accuracy 94.45%.

DISCUSSION

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 **(Wynn, J L., 2016)**.

Biomarkers for diagnosis of neonatal sepsis have been investigated that help in the early diagnosis of neonatal sepsis, before the onset of clinical manifestation so that early treatment of sepsis can be started and neonate can be properly managed.

The current study showed that there were no statistically significant differences between patient and control groups as regard gestational age, delivery type, sex and birth weight.

In line with **El-Shahat et al., 2022** who found that there were no statistically significant differences between the case and control groups regarding age, weight, and sex.

But in our study the percent of males in patient group (57.5%) is higher than females (42.5%) but still statistically insignificant (P Value = 0.502).

This not agreed by **Saleh et al., 2017** which reported that females were higher among cases than controls, without statistical significance.

As regard Maternal risk factors, our study showed that the maternal risk factors of infection are significantly higher in patient groups compared with the controls (p value < 0.001) but there is no statistical difference between the two studied groups as regard to maternal chronic diseases (HTN and DM).

In agreement with **Noah et al., 2022** who reported that the cesarean section is a prevalent risk factor for early onset neonatal sepsis, followed by maternal infections.

Also, in agreement with our results **Gebremedhin et al., 2016** who reported that the possible risk factors of neonatal sepsis include history of maternal urinary tract infection.

Our study showed that admission in NICU was much longer in the patient group when compared with controls.

Mortality rate in our patient groups was significantly higher (22.5%) in comparison with the control group in which the mortality rate was (0%).

This agree with **Manandhar et al., 2021** who reported that the NICU stay were significantly longer in Sepsis neonates in comparison to non-Sepsis neonates, however mortality rate was non-significantly higher in Sepsis neonates (22%) than controls (18%).

Also, **Araújo & Guimarães., 2020** reported that the length of NICU stay was significantly longer in Sepsis neonates in comparison to non-Sepsis neonates.

The study by **El-Shahat et al., 2022** reported that the mortality was 11% of neonates with Sepsis, While, the study by **Ellahony et al., 2020** reported 38% mortality rate.

Regarding the correlation between D-dimer and days on NICU and MV, and outcome, the current study showed that there was high level of D-dimer in patient group with prolonged NICU admission.

This was in agreement with the study by **El-Shahat et al., 2022** who reported that D-dimer levels were increased with increased severity of sepsis and had bad prognosis.

Also, in our patient group we found that the incidence of death was higher in patients with high

D-dimer level when compared with the patients with low level.

Side by side with **El-Shahat et al., 2022** who reported that D-dimer levels were much higher that died compared to those that recovered.

Our results were coincide with study of **Hiroyasu Ishikura et al., 2022** as they reported that platelet count was significantly lower in sepsis group than non-sepsis group (p value <0.001).

Furthermore, **Shalaby et al., 2017** found that platelets count of the septic group was significantly lower than that of the control group.

Also, our present study agreed with **HAMAM et al., 2019** who found that there was no significant difference between sepsis and control group (p-value >0.05) as regard Total Leucocytic Count.

Also, the study by **El Shimi et al., 2017** reported that the (I/T ratio) is significantly high >0.2 in septic patient group when compared to controls.

C-reactive protein (CRP) is an acute phase reactant, produced in the liver which has a half –life of 24 to 48 hours. It is a commonly used marker to diagnose neonatal sepsis but as it takes 10 to 12 hours to respond to an infection, it is not reliable **(Ganesan, P et al., 2016)**.

The current study showed that as regard comparison between the studied groups regarding inflammatory markers. It was noticed that the levels of CRP and ESR were significantly higher in septic patients group compared to control group (p<0.001).

In accordance with our results, **Mondal et al., 2012** reported that CRP and ERS levels were significantly higher in septic group compared to control group.

Also, **Chatterjee et al., 2017** revealed that the serum C-reactive protein (CRP) level was significantly raised in the clinically suspected neonatal sepsis groups than the control groups which are consistent with other studies.

As regard to chemistry, we found that there was significant increase in urea and AST levels in septic patient group when compared to controls

Also, there was high positive significant correlation between D-dimer and each of AST (r=0.284, P=0.013) and urea (r=0.462, P<0.001).

This can be supported by **Li et al., 2021** who reported that neonates with sepsis and severe sepsis had a higher level of blood

urea nitrogen (BUN). The prevalence of neonates with severe sepsis was dramatically increased according to BUN level. Correlation analysis showed that BUN levels were positively correlated with the levels of infection marker procalcitonin (PCT) and high-sensitivity C-reactive protein (hsCRP).

Regarding the coagulation profile and D-dimer, the current study showed that there was significant increase in PT, PTT, INR and D-dimer levels in septic patient when compared to the control group.

In accordance with our results **Sharma et al., 2018** reported that the difference was statistically significant (P<0.01). PT and APTT were significantly (P<0.01) higher in patients compared with the controls.

Also, we found that the D-dimer level is significantly high in patient group when compared with control group (P<0.001).

In agreement with the current study **El-Shahat et al., 2022** reported that D-dimer level was significantly elevated in neonatal sepsis cases compared to controls. Also, PT and APTT were significantly (P<0.01) higher in patients group compared with the controls.

Regarding blood culture, Klebsiella pneumoniae were the most common organism found (15%) followed by E-coli (10%) and staph epidermidisa (5%) in our study.

Our results were supported with study of **Fahmey & Mostafa, 2019** as they reported that as regard the microorganisms identified in blood cultures; Klebsiella pneumoniae was the most common organism (26/60) followed by coagulase-negative Staphylococci (12/60).

Also, in the study of **HAMAM et al., 2019** the most prevalent organism was Klebsiella (37.25%) followed by staphylococcus aureus (17.65%).

Regarding the correlation between D-dimer and CBC, we found that the level of D-dimer is high in patient with high I/T ratio > 0.2 (r=0.761, P<0.001) while in patient group with high D-dimer level there were low PLT number when compared to those with low level (r=-0.319, P=0.005).

This coincides with the current study **El-Shahat et al., 2022** who reported that the patient group with low PLT number had significant higher level of D-dimer (r=-0.2, P=0.03).

But there was no statistically significant link between D-dimer level and RBC and WBC count.

As regard to correlation between D-dimer and CRP and ESR our results showed that in septic group with high CRP and ESR level the level of D-dimer was significant positive correlation between CRP (r=0.494, P=0.001), ESR (r=0.659, P<0.001) respectively.

In agreement with **El-Shahat et al., 2022** reported that there was high positive significant correlation between D-dimer and CRP (r=0.7, P=0.001).

Regarding the correlation between D-dimer and coagulation profile, our results showed that there was positive correlation between D-dimer and increased levels of PT (r=0.285, P=0.013) and PTT (r=0.257, P=0.025).

ROC curve analysis between blood culture and D-dimer showed that at cut off value >1547 ng it can predict positive blood culture with sensitivity 80% and specificity 96% and AUC = 0.918 with accuracy 94.45%, NPV of 88.9% and PPV 92.3 %.

This can be supported by **El-Shahat et al., 2022** who reported that D-dimer at a cutoff point higher than 2000 ng 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 92.3% and negative predictive value of 88.9%.

While **Brahmana., 2019** found that D-dimer had a sensitivity value of 28%, specificity of 70%, positive predictive value of 40%, and negative predictive value of 58% for early detection of sever sepsis.

CONCLUSION

In neonatal septicemia D-dimer has 94.45% accuracy for detection of neonatal sepsis with 80% sensitivity and 96% 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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القيمة التشخيصية لمستوى (دى-دايمر) في الأطفال حديثي الولادة المصابين بالإنتان الوليدي

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تسمم الدم في حديثي الولادة هو رد فعل التهابي جهازي شديد لعدوى مجرى الدم مع ارتفاع معدلات المراضة والوفيات خلال فترة حديثي الولادة. يعد التشخيص المبكر والسليم لتسمم الدم في حديثي الولادة أمرًا بالغ الأهمية للمضادات الحيوية التي يتم تناولها في الوقت المناسب، ويقلل من مدة الإقامة في المستشفى، ويحسن الإنذار، وخاصة النتيجة النمائية العصبية.

نظرًا لأن تسمم الدم هو حالة سريرية ناتجة عن التفاعل بين العامل الجرثومي والاستجابات المناعية والالتهابية والتجلط للمضيف، فقد أظهرت بعض الدراسات تغيرات في بروتينات التخثر المنتشرة مقترنة بضعف نشاط تحلل الفبرين في المرضى الذين يعانون من تسمم الدم المؤكد.

يحدث ارتفاع دي دايمر ومنتجات تحلل الفيبرينوجين بسرعة بعد بدء التخثر المنتشر داخل الأوعية، والذي قد ينشأ كمضاعفات لتسمم الدم. يساهم تنشيط التخثر المنعكس من خلال الزيادة في مستويات دي دايمر بشكل كبير في نتيجة الإنتان.

كان الهدف الرئيسي من هذه الدراسة هو تقييم مستوى دي دايمر في تسمم الدم في حديثي الولادة كاختبار تشخيصي وإذا كان له دور في شدة أو مضاعفات تسمم الدم في حديثي الولادة.

كانت هذه دراسة مقطعية أجريت في وحدة العناية المركزة لحديثي الولادة في مستشفى باب الشعرية ومستشفى الحسين الجامعي بجامعة الأزهر. أجريت هذه الدراسة على 40 من الأطفال حديثي الولادة المتعفنين (مجموعة المرضى)، و40 من الأطفال حديثي الولادة الأصحاء غير المتعفنين خدموا كمجموعة تحكم.

أظهرت النتائج الرئيسية للدراسة ما يلي:

- كانت هناك فروق ذات دلالة إحصائية عالية بين المجموعات وفقا لعدوى الأمهات، ولكن انتشار الأمراض المصاحبة للأمهات كان متماثلا في كلا المجموعتين.
- لم تحدد أي من الدراسات المسترجعة أي عوامل خطر وليدية لتسمم الدم في حديثي الولادة.
- كانت هناك فروق ذات دلالة إحصائية عالية بين المجموعات وفقًا لعدد الأيام في العناية المركزة لحديثي الولادة، تظهر النتائج فروق ذات دلالة إحصائية عالية بين المجموعتين مع معدل وفيات في مجموعة الدراسة يساوي 22.5٪.

- أظهـــرت الدراســـة الحاليـــة أن هنـــاك علاقـــة ارتبـــاط موجبـــة عالية بين دي دايمر والنتيجة.

- كـــان هنـــاك ارتبـــاط معنـــوي إيجـــابي مرتفـــع بـــين دي دايمـــر وI/T، بينمـــا كـــان هنـــاك ارتبـــاط ســـلبي مرتفـــع بـــين دي دايمـــر والصفائح الدموية.

- كـــان هنـــاك ارتبـــاط معنـــوي إيجـــابي مرتفـــع بـــين دي دايمـــر وكـــل من البروتين التفاعلي سي.

- كانـــت هنـــاك فـــروق ذات دلالـــة إحصـــائية بـــين المجموعـــات وفقا ل وقت البروثرومبين ومعامل التجلط ودي دايمر.

- أظهـــرت مزرعـــة الـــدم فـــي مجموعـــة الدراســـة أن 27 (67.5٪) كانت سلبية و13 (32.5٪) كانت إيجابية.

- أظهـر تحليـل منحنـى الـروك بـين مزرعـة الـدم ودي دايمـر أنـه عنـد قيمـة القطـع> 1547 يمكنـه التنبـؤ بإيجابيـة مزرعـة الـدم بحساســـية 80٪ ونوعيـــة 96٪ ومنطقـــه تحـــت المنحنـــي = 0.880 بدقة 94.45٪.

بنـاءً علـى النتـائج التـي توصـلنا إليهـا، نوصـي بـإجراء مزيـد مـن الدراســات حــول حجــم العينــة الأكبــر وعلــى نطــاق أوســع للتأكيــد على استنتاجنا.