

D-dimer as a Prognostic Marker in Predicting Sepsis Severity in ICU

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Abstract

Background : Sepsis is a medical emergency and is one of the major causes of mortality and morbidity across the world. The present study was conducted to evaluate the correlation between D-dimer level and other prognostic markers of Sepsis like APACHE II, SOFA scores, and serum lactate levels in predicting sepsis severity in ICU patients.

Method : This prospective observational study was conducted at Department of Emergency Medicine, J. J. M Medical College, Davanagere, Karnataka from August 2021 to October 2021. A total of 40 patients with clinical and laboratory findings of sepsis admitted at the Emergency Medicine department, who met the inclusion and exclusion criteria were enrolled. Patients' demographic data, vital signs viz. heart rate (HR), respiratory rate (RR), blood pressure (BP), and white blood cell (WBC) count were evaluated and recorded in proforma datasheet. D-dimer was measured by a Turbidimetric immunoassay and values below 500 ng/mL were considered normal. Serum lactate levels were measured using standardised kit based assay methods. Sepsis severity was scored by APACHE II, SOFA scores, and serum lactate levels. Patient's length of hospital stay, ventilator support and mortality were recorded. The primary outcome was to evaluate the relationship of D-dimer level in predicting Sepsis severity based on APACHE II, SOFA scores and serum lactate levels.

Results : Results revealed that majority of the study subjects i.e, 27.50% each were in the group of 41-50 years with male predominance i.e, 65% as compared to females i.e, 35%. Spearman partial correlation analysis was performed to analyze correlations between D-dimer levels and APACHE II, SOFA scores and serum lactate levels in predicting sepsis severity. The findings revealed that D-dimer levels significantly correlated with APACHE-II ($r=0.543$, $p = 0.000$), SOFA ($r=0.618$, $p = 0.000$), and serum lactate levels ($r = 1.000$). In conclusion, our study demonstrated that D-dimer levels could be used as a prognostic marker in predicting sepsis severity.

Conclusion : Our study demonstrated that D-dimer levels of > 1000 ng/dl was associated with higher mortality. Hence, D-dimer levels could be used as a prognostic marker in predicting Sepsis severity and mortality.

Keywords: Sepsis, Severity, D-Dimer, APACHE II, SOFA, Lactate.

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I. Introduction

Sepsis is a major cause of mortality and morbidity in patients admitted in intensive care unit. According to the Third International Consensus definitions for Sepsis and Septic shock, (Sepsis-3), Sepsis is considered as "a life threatening organ or system dysfunction caused by a dysregulated host response to infection"¹. As Sepsis severity increases, a multifactorial series of events lead to impairment in oxygen delivery, secondary to macro- and microvascular malperfusion as well as direct cellular damage secondary to inflammation. Hemostasis derangement is very frequently associated with Sepsis among all types of dysregulations². There is an inappropriate activation of coagulation system resulting in intravascular thrombin formation, small vessel thrombosis and consumption of clotting factors and platelets eventually leading to multiorgan dysfunction. Simultaneous activation of fibrinolytic system results in breakdown of clots and subsequent bleeding.

The disease burden is a true catastrophe especially in children, elderly and immunocompromised patients.¹⁻⁴ Most studies have defined sepsis as a disease caused by acute inflammatory response with a proven or suspected microbial source.⁵ This suspicion is made clinically but the gold standard for diagnosis has conventionally been blood cultures. The main limitation of blood cultures is the long duration usually required for their definite results.⁶ Alternatively, several Sepsis biomarkers are used for early diagnosis and prognosis. These biomarkers include Procalcitonin, CRP, antithrombin-III, protein C and S, thrombomodulin, ferritin, interleukin, D-dimer etc.⁷⁻⁹

Severe sepsis is a frequently fatal condition and is associated with multiorgan failure.¹⁰ It is known that the most common results of severe organ dysfunction are acute respiratory distress syndrome, acute kidney failure, and extensive intravascular coagulation.¹¹ Scoring systems are used worldwide to predict disease severity and mortality in patients diagnosed with Sepsis. These scoring systems are also useful for standardizing research and comparing patient care quality in ICUs. The Acute Physiology and Chronic Health Evaluation 2 (APACHE-2) scoring system is the most used scoring system in the world.¹² It consists of three parts: acute physiology score, age, and chronic health assessment. Accordingly, the acute and chronic health status of the patient is evaluated. It is applied within 24 hours of admission of patient to ICU. Higher APACHE-2 scores correspond to more severe disease and higher risk of death. The sequential organ failure assessment (SOFA) scoring is another commonly used method in predicting the clinical outcomes of critically ill patients. SOFA uses simple measurements of major organ dysfunction to calculate a severity score, and it does not contain any parameters related to the patient's chronic health status.¹³ The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, neurologic, coagulation and renal systems. Regardless of the initial score, the mortality rate is at least 50% when the score is increased in the first 96 hours of admission while the mortality is 27-35% if the score remains unchanged and less than 27% if the score is reduced.¹⁸⁻¹⁹

D-dimer is a specific degradation product of crosslinked fibrin unlike fibrin/fibrinogen degradation products (FDP's). Therefore higher D-dimer levels reflect ongoing activation of both hemostatic and thrombolytic system and as a result it is significantly increased during sepsis.¹⁴ D-dimer has been used as a marker of sepsis severity and most studies revealed that D-dimer is a potent predictor of mortality in sepsis and it is well related to sepsis severity similar to acute physiology and chronic health evaluation score (APACHE 2).¹⁵⁻¹⁷ Some studies have demonstrated that patients with Sepsis with D-dimer levels in the normal range had 4-fold higher mortality rate as compared to those with higher values revealing that prognostic value of D-dimer in Sepsis to be either poor or modest. Confirmatory evidence is required to define prognostic significance of measuring D-dimer levels in Sepsis as well as its potential clinical and laboratory correlation. Prognostication is an important part of management of any critically ill patients. With this scenario, present study was designed with the main aim to determine the correlation between D-dimer level and other prognostic markers of Sepsis like APACHE II, SOFA scores, and serum lactate levels in predicting sepsis severity in ICU patients.

II. Materials and Methodology

Study design : This prospective observational study was conducted at Department of Emergency Medicine, J. J. M Medical College, Davangere, Karnataka from August 2021 to October 2021. The study was approved by the institutional ethics committee of J. J. M Medical College. The study aim was explained to the patients and informed written consent was obtained from all the participants.

Study subjects : A total of 40 patients who satisfy criteria for Sepsis admitted at the emergency medicine department fulfilling the following inclusion and exclusion criteria were enrolled.

Inclusion criteria:

- Patients who are above 18 years of age.
- Patients who satisfy criteria for diagnosis of Sepsis.
- Patients or relatives who have given written informed consent

Exclusion criteria:

- Patients with age less than 18 years
- Patients with prior thromboembolic events
- Pregnant women
- Patients with chronic liver disease
- Patients with malignancy
- Patients with the history of recent trauma or surgery within 3 months
- Patients with hematological disorders

Patient’s demographic data, vital signs *viz.* heart rate (HR), respiratory rate (RR), blood pressure (BP), and white blood cell (WBC) count were evaluated and recorded in proforma datasheet. D-dimer was measured by a Turbidimetric immunoassay in an ACL Elite coagulometer using a Hemosil kit and values below 500 ng/mL were considered normal. D-dimer was measured within 1 hour of patient admission. Serum lactate levels were measured using standardised kit based assay methods. Sepsis severity was scored by APACHE II, SOFA scores, and serum lactate levels. Patients length of hospital stay, ventilator support and mortality were recorded. Our primary outcome was to determine the relationship of D-dimer level in predicting Sepsis severity based on APACHE II, SOFA scores and serum lactate levels.

D-dimer levels were categorised into 3 groups and given score 1, 2 and 3 for statistical analysis as shown below:

Score	Values (ng/dl)
1	<500
2	500-1000
3	>1000

Statistical analysis

The collected data was analysed using statistical package for social sciences (SPSS) IBM, version 20. The data are presented as frequency, mean and standard deviation and median as appropriate. Pearson partial correlation coefficient analysis was done to determine the correlation between numerical variable (APACHE II, SOFA, Serum lactate levels, D-dimer and mortality). $p < 0.005$ was considered statistically significant.

III. Results

Majority of the study subjects *i.e.*, 27.50% were in the group of 41-50 years followed by 25% in the age group of 51-60 years and 20% each belonged to age group of 31-40 and 61-70 years of age. The mean age of study subjects was found to be 52.20 ± 12.44 with minimum of 32 years and maximum of 84 years. Male predominance *i.e.*, 65% was observed as compared to females *i.e.*, 35% (Table 1).

Table 1: Distribution of study subjects based on demographics

Variables	Frequency	Percentage
Age		
31-40 yrs	8	20.00
41-50 yrs	11	27.50
51-60 yrs	10	25.00
61-70 yrs	8	20.00
71-80 yrs	2	5.00
81-90 yrs	1	2.50
Mean \pm S.D	52.20 ± 12.44	
Minimum	32	
Maximum	84	
Gender		
Male	26	65.00
Female	14	35.00

The mean HR, RR, body temperature, and WBC count of study subjects in our study was found to be 108.98, 30.75, 36.8, and 13399 respectively (Table 2).

Table 2: Descriptive statistics of vital parameters of study subjects

Variables	Minimum	Maximum	Mean	S.D.
HR	64	132	108.98	15.258
RR	20	46	30.75	6.109
Body Temperature (°C)	35.0	38.5	36.800	1.2598
WBC (cells/cu. mm)	1620	28270	13399.25	6562.428

The comparison of study variables viz. D-dimer levels, APACHE II score, SOFA score and serum lactate levels according to mortality is represented in Table 3. The median values depicted that APACHE II score, SOFA score and serum lactate levels did not have a normal distribution.

Table 3: Comparison of the study variables according to mortality

Parameters	Survived	Expired	DAMA
	Median (95% CI)	Median (95% CI)	Median (95% CI)
APACHE II Score	12.50 (9.89-16.93)	23.00 (18.78-29.36)	16.00 (3.67-31.83)
SOFA Score	6.00 (4.39-7.52)	13.00 (9.19-14.38)	8.50 (2.91-14.09)
Lactate Levels (mmol/L)	2.00 (1.45-2.01)	3.00 (2.65-3.07)	-
D-DIMER	2(1.74-2.53)	3(2.21-3.07)	2.50(0.73-3.77)

Pearson partial correlation analysis was performed to analyze correlations between D-dimer levels and prognostic markers of sepsis like APACHE II, SOFA and Lactate levels. The results revealed that D-dimer levels correlated with APACHE-II ($r=0.543$, $p = 0.000$), SOFA ($r=0.613$, $p = 0.000$), and serum lactate levels ($r = 1.000$) (Table 4).

Table 4: Correlations of D-dimer levels with APACHE II, SOFA scores and lactate levels

Parameters	Pearson correlation (r-value)	p-value
APACHE II Score	0.543	0.000
SOFA Score	0.618	0.000
Lactate Levels (mmol/L)	1.000	NA

NA-Not applicable

IV. Discussion

Despite the improvements in the diagnosis and treatment of Sepsis, it is still one of the major causes of morbidity and mortality in most emergency departments. The annual incidence of sepsis ranges from 300 to 1000 cases/ 100,000 persons.²⁰ Various biochemical markers have been explored to determine the prognosis of septic patients, but different results have been obtained. Hence, present study was aimed at evaluating the correlation between D-dimer levels and other prognostic markers like APACHE II, SOFA scores, and serum lactate levels in predicting sepsis severity in ICU patients.

In our study majority of the study subjects i.e., 27.50% were in the group of 41-50 years with male predominance i.e., 65% was observed as compared to females i.e., 35%. The mean HR, RR, body temperature, and WBC count of study subjects in our study was found to be 108.98, 30.75, 36.800, and 13399. 25 respectively. The median values depicted that APACHE II score, SOFA score and serum lactate levels did not have a normal distribution.

Our main objective of conducting this study was to evaluate the relationship between D-dimer level and other prognostic markers of Sepsis like APACHE II, SOFA scores, and serum lactate levels in predicting sepsis severity in ICU patients. Hence, Spearman partial correlation analysis was performed to analyze correlations between D-dimer levels and sepsis severity. The results revealed that D-dimer levels significantly correlated with APACHE-II ($r=0.543$, $p = 0.000$), SOFA ($r=0.618$, $p = 0.000$), and serum lactate levels ($r = 1.000$). The APACHE II and SOFA scoring systems have been widely validated and used by many ICUs to classify sepsis severity and predict hospital mortality.^{12,13} In our study, APACHE II and SOFA scores significantly correlated with D-dimer levels. These findings were in accordance with various other studies reported in the literature wherein the prognostic value of biomarkers screened for sepsis has been compared with APACHE II and SOFA scoring systems.²¹⁻

According to various literature, there are multiple reports that show the relationship between the elevation of serum lactate and the occurrence of septic states.²⁴⁻²⁶ This is due to the presence of an imbalance

between the production and clearance of serum lactate. It is proposed that there is a state of critical tissue hypoperfusion that affects the synthesis of ATP by blocking the pyruvate dehydrogenase enzyme due to hypoxia, resulting in conversion of pyruvate to lactate.²⁷ In a previous study, 830 patients admitted to an emergency ward, with a diagnosis of severe sepsis, were classified into three groups based on the serum lactate levels. They were low risk with a level of lactate less than 2, intermediate risk from 2 to 3.9 and high risk with levels greater than 4. At day 28 post-admission, mortality was 15.4%, 37% and 46.9%, respectively for the three defined lactate levels. In contrast, in patients who did not present with shock, mortality was 8.7%, 16.4% and 31.8%, respectively.²⁸ In the present study, serum D-dimer level and the presence of elevated serum lactate levels ($r = 1.000$) showed a direct relationship in predicting sepsis severity and hence correlating with previous studies.²³ The present study also showed that D-dimer levels with score 3 [>1000 ng/dl] was associated with higher mortality rate. This correlated with many previous studies which showed that higher D-dimer levels were associated with higher mortality.

In summary, the findings of our study demonstrated that D-dimer level could be considered as a prognostic marker in predicting Sepsis severity and mortality. Apparently, serum levels of D-dimer can be affected by various known and unknown factors during patients's hospitalization. Further research is required to answer the above questions.

V. Conclusion

Based on our study findings, it was demonstrated that D-dimer levels significantly correlated with other prognostic markers of Sepsis like APACHE-II, SOFA, and serum lactate levels. Our study also demonstrated that D-dimer levels of > 1000 ng/dl was associated with higher mortality. Hence, D-dimer levels could be used as a prognostic marker in predicting Sepsis severity and mortality.

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