



General Medicine

D-DIMER AS A BIOMARKER FOR ASSESSMENT OF COVID-19 PROGNOSIS: D-DIMER LEVELS ON ADMISSION AND ITS ROLE IN PREDICTING DISEASE OUTCOME IN HOSPITALIZED PATIENTS WITH COVID-19.

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*Corresponding Author**ABSTRACT****Introduction:** Coronavirus Disease 2019 is a primarily respiratory illness that can cause thrombotic disorders. Elevation of D-dimer is a potential biomarker for poor prognosis in COVID-19.**Methods:** Clinical and laboratory parameters and outcomes of confirmed COVID-19 cases admitted to Alluri Sitarama Raju Academy of Medical Sciences, Eluru, from April 2020 to September 2020 were retrospectively analyzed. Admitted COVID-19 cases with recorded D-dimer and definitive outcomes were included consecutively.**Results:** 182 patients were included in the study out of which 34(18.7%) died during the hospital stay. The mean admission D-dimer among surviving patients was 1.067 $\mu\text{g/ml}$ ($\pm 1.705 \mu\text{g/ml}$), whereas that among patients who died was 3.208 $\mu\text{g/ml}$ ($\pm 2.613 \mu\text{g/ml}$). ROC curve for D-dimer and mortality gave an area under the curve of 0.807 (95% CI 0.728–0.886, $p < 0.001$). Optimal cutoff value for D-dimer was 1.5 $\mu\text{g/ml}$ (sensitivity 70.6%, specificity 78.4%). On Cox proportional hazards regression analysis, the unadjusted hazard ratio for high D-dimer was 6.809 (95% CI 3.249–14.268, $p < 0.001$), and 5.862 (95% CI 2.751–12.489, $p < 0.001$) when adjusted for age.**Conclusion:** D-dimer value on admission is an accurate biomarker for predicting mortality in patients with COVID-19. 1.5 $\mu\text{g/ml}$ is the optimal cutoff value of admission D-dimer for predicting mortality in COVID-19 patients.**KEYWORDS :****INTRODUCTION:**

Corona virus disease 2019 (COVID-19), caused by the Severe acute respiratory syndrome corona virus 2, was first recorded in Wuhan, the capital of Hubei province of China in December 2019. While COVID-19 is primarily a respiratory illness, it can affect multiple organ systems including gastrointestinal, hepatic, cardiac, neurological, and renal systems. Thrombotic complications and coagulopathies including Disseminated intravascular coagulopathy are common in COVID-19, likely reflecting activation of the coagulation cascade due to viremia or cytokine storm, or possibly due to super infection and organ dysfunction.

D-dimer is a fibrin degradation product, widely used as a biomarker for thrombotic disorders. A D-dimer value less than 0.5 $\mu\text{g/mL}$ is usually considered normal, and values increase with increasing age and in pregnancy. Following the outbreak of the COVID-19 pandemic, D-dimer has been identified as a potential indicator for its prognosis in COVID-19 patients.

MATERIALS AND METHODS:

This retrospective study was conducted in Alluri Sitarama Raju Academy of Medical Sciences, Eluru, which was a designated hospital for COVID-19 patients.

The sample size was calculated using the methodology described by Buderer, with an expected sensitivity of 92.3% and an expected specificity of 83.3% taken from a reference study. The mortality rate was estimated at 20% based on a review of hospital records. The precision and confidence interval were fixed at 10% and 95% respectively. The estimated sample size for sensitivity and specificity was calculated to be 137 and 67 respectively, and the larger value of 137 was selected.

Inclusion Criteria:

COVID 19 RT-PCR positive patients admitted in Alluri Sitarama Raju Academy of Medical Sciences from April 2020 to September 2020.

RESULTS:

A total of 182 eligible candidates were enrolled in the study, among which 113 (62.1%) were male and 69 (37.9%) were female. The mean age of enrolled participants was 58.16 years (± 15.65 years).

34 (18.7%) patients died during hospital stay. One patient was

discharged on the patient's request and one patient left against medical advice. The area under the curve for receiver operating characteristic (ROC) curve for D-dimer values on admission against patient outcome was 0.807 (95% CI 0.728–0.886, $P < 0.001$). The optimal cut-off value of D-dimer to predict in-hospital mortality was determined by minimizing the Euclidian distance from the curve to (0,1), i.e., by measuring the shortest distance from the top-left corner of the ROC plot. The optimal cut-off value was found to be 1.5 $\mu\text{g/ml}$ with a sensitivity of 70.6% and a specificity of 78.4.

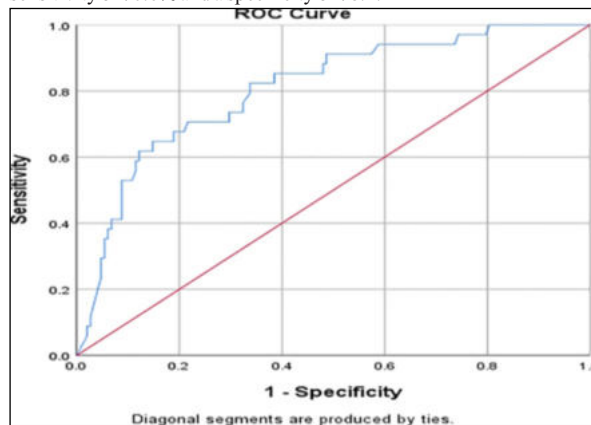


Fig 1. ROC Curve For D-dimer As A Predictor Of In-hospital Mortality.

Based on the cut-off value of 1.5 $\mu\text{g/ml}$ all patients were categorized into two groups for comparison, summarized in Table 1. Among patients with admission D-dimer less than 1.5 $\mu\text{g/ml}$, 59 had underlying medical conditions (Hypertension 38, Diabetes Mellitus 32, hypothyroidism 9, COPD 3, chronic kidney disease 1, depression 2, dyslipidemia 1, anxiety 1, coronary artery disease 1, asthma 1). Similarly, among patients with admission D-dimer more than 1.5 $\mu\text{g/ml}$, 28 patients had comorbidities (Diabetes mellitus 18, Hypertension 17, COPD 4, hypothyroidism 3, Atrial fibrillation 2, dyslipidemia 2, CKD 1, depression 1, hyperthyroidism 1). A significant difference was observed between the groups in age, whereas comorbidities did not show a statistically significant difference.

Table: 1

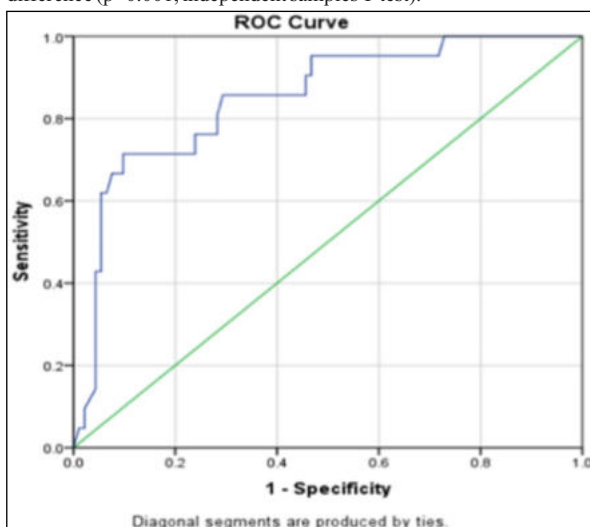
variables	Total	d-dimer <1.5mcg/ml N=126	d-dimer >1.5mcg/ml N=56	P value
Age(mean+/-SD)	58.16+/-15.65	55.67+/-15.89	63.75+/-13.63	0.001
Age>60years (n)	90	53	37	0.003
Pts with underlying conditions	87	59	28	0.692
Diabetes mellitus	50	32	18	0.347
hypertension	55	38	17	0.979
COPD	7	3	4	0.204
Hypothyroidism	12	9	3	0.758
Death n(%)	34	10	24	<0.001
Discharged n(%)	148	116	32	
D-dimer (mean+/-SD)	1.48+/-2.08	0.44+/-0.36	3.83+/-2.42	
D-dimer (range)	0.002->10	0.02-1.48	1.52->10	
Mean duration of stay in days (mean+/-SD)	10.59+/-6.53	10.03+/-5.54	12.65+/-9.18	0.165

The mean D-dimer values on admission by age and sex are summarized in Table: 2.

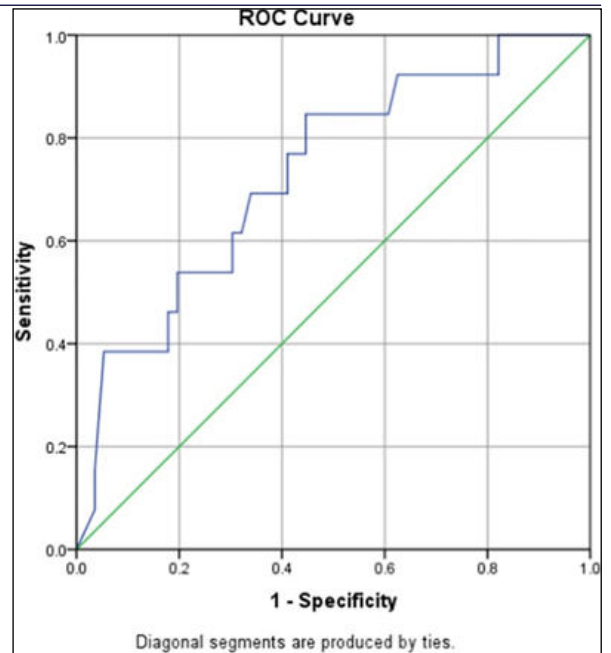
Variables	Mean admission D-dimer(mcg/ml)
Age<60 years	1.01+/-1.50
Age>=60years	1.96+/-2.46
Male	1.29+/-1.84
Female	1.79+/-2.40

126 out of 182 patients had D-dimer on admission less than 1.5 µg/ml, out of which 10 patients (7.9%) died during hospital stay and 116 were discharged (including one discharge on patient request). Of the 56 patients who, on admission, had D-dimer of 1.5 µg/ml and above, 24 (42.9%) died and 32 were discharged (including one against medical advice).

The mean admission D-dimer among patients who survived was 1.067 µg/ml (±1.705 µg/ml), whereas that among patients who died was 3.208 µg/ml (±2.613 µg/ml). This is a highly statistically significant difference ($p < 0.001$, independent samples T-test).

**Fig 2:** ROC Curve For D-dimer As A Predictor Of In-hospital Mortality In Males.

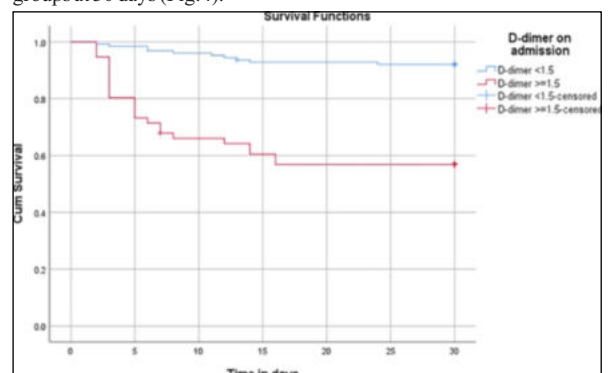
Subgroup analysis of male and female patients showed different optimal cutoff values; 1.90 (0.759–0.94) with sensitivity of 71.4% and specificity of 90.2% for males and 1.46 (0.583–0.880) with sensitivity of 69.2% and specificity of 66.1% for females (Figs 2 and 3).

**Fig 3:** ROC Curve For D-dimer As A Predictor Of In-hospital Mortality In Females.

The peripheral oxygen saturation measured via pulse oximeter at the presentation to the hospital and D-dimer levels at hospital admission were analyzed for presence of any correlation. The Pearson correlation between the two was found to be -0.134 with alpha level set to 0.05 and a p-value of 0.085. This demonstrates that there is no correlation between oxygen saturation and D-dimer at admission.

Comparison of duration of hospital stay between the two groups using Mann-Whitney U test did not show a statistically significant difference ($p = 0.236$). Among the 146 patients who recovered and were discharged routinely (excluding discharge against medical advice), 113 had D-dimer at the time of admission of less than 1.5 µg/ml, while 31 had D-dimer on admission higher than 1.5 µg/ml. A separate analysis of these patients, who were discharged routinely, included in Table 1, again failed to show a significant difference ($p = 0.165$).

30-day survival of patients was analyzed using the Kaplan-Meier procedure, which showed a significant difference (Log-rank (Mantel-Cox) of 0.00) in survival between the low D-dimer and high D-dimer groups at 30 days (Fig:4).

**Fig 4:** Survival Analysis Using The Kaplan Meier Procedure.

The results of univariate Cox regression, as shown in Table 3, performed using high admission D-dimer (higher than 1.5 µg/ml), age, sex, and major comorbidities (hypertension, diabetes mellitus, chronic kidney disease) are summarized in Table 3. Only admission D-dimer and age had significant hazard ratios when analyzed separately. When adjusted for age, the hazard ratio for high D-dimer was 5.862 (2.751–12.489 at 95% CI, $p < 0.001$), whereas when adjusted for age, sex, presence of hypertension, diabetes mellitus, and chronic kidney disease, the hazard ratio for D-dimer was 6.823 (3.105–14.991 at 95% CI, $p < 0.001$).

Table 3: Univariate Cox Regression Analysis.

variable	Unadjusted hazard ratio	95.0%CI		Significance
		lower	upper	
Age	1.033	1.010	1.057	0.005
Sex	1.003	0.502	2.003	0.994
D dimer on admission	6.809	3.249	14.268	<0.001
Diabetes mellitus	0.948	0.442	2.030	0.890
Hypertension	1.280	0.633	2.586	0.492
Chronic kidney disease	3.200	0.437	23.447	0.252

Further analysis among the deceased cases was done taking into consideration the laboratory parameters including hemoglobin, WBC with lymphocyte, platelet count, C- reactive protein, prothrombin time (PT) and activated partial thromboplastin time (aPTT) as shown in Table 4. These variables have a role in determining coagulopathy in the patients. CRP and aPTT showed statistically significant elevation among deceased cases with high D- dimer values.

Table 4: Basic Laboratory Values Among High And Low D-dimer Groups.

	Mortality among High D-Dimer cases	Mortality among Low D-Dimer cases	p-value
	Hemoglobin(10/19)	Hemoglobin (5/9)	
Mean+/-SD	12.2+/-1.5635	12.78+/-1.8939	0.538
	WBC(15/19)	WBC(8/9)	
Mean+/-SD	7290+/-4382.305	9950+/-3450.329	0.535
	Platelets(10/19)	Platelets(5/9)	
Mean+/-SD	179090+/-18722	241000+/-101126.159	0.338
	Lymphocyte (15/19)	Lymphocyte(8/9)	
Mean+/-SD	0.1448+/-0.6757	0.15325+/-0.503	0.566
	CRP(15/19)	CRP(7/9)	
Mean+/-SD	137.38+/-82.035	60.013+/-31.255	0.025
	PT(10/19)	PT (4/9)	
Mean+/-SD	16.25+/-2.55	12.75+/-1.6623	0.626
	aPTT(10/19)	aPTT (5/9)	
Mean+/-SD	47.38+/-20.34	42.32+/-13.5717	0.028

Table 5: Treatment Received And Immediate Cause Of Death Among Patients With High And Low D-dimer Values.

Mortality among high D-Dimer

Total patients	24	Immediate cause of death	
Received LMWH	21	Severe respiratory failure leading to cardiac arrest	16
Mechanical ventilation	11	ARDS documented among severe respiratory failure cases	4
Non-invasive ventilation	7	sepsis	1
Received plasma therapy	8		

Mortality Among Low D-Dimer

Total patients	10	Immediate cause of death	
Received LMWH	9	Severe respiratory failure leading to cardiac arrest	1
Mechanical ventilation	2	ARDS	1
Non-invasive ventilation	6	sepsis	2
Received plasma therapy	4	Multiorgan failure	1

DISCUSSION:

The current study included 182 cases admitted to the hospital with a diagnosis of COVID-19 from March to December 2020, which was in the relatively early phase of the pandemic in ASRAM. Cases were managed in the hospital-based on available resources and guidelines, the latter of which were not established early on and evolved with time. D-dimer was usually measured on admission, and serial D-dimer measurement was not part of routine management. Treatment during the study period was largely symptomatic, consisting of antipyretics, analgesics, and supplemental oxygen when required. LMWH was given prophylactically to all patients without contraindications.

This study found that a higher D-dimer value on hospital admission was significantly associated with in-hospital mortality in patients of COVID-19.

CONCLUSION:

D-dimer value on admission is an accurate biomarker for predicting mortality in patients with COVID-19 and 1.5 µg/ml is the optimal cut off value of admission D-dimer for predicting mortality in COVID-19 patients, with good sensitivity and specificity. D-dimer can thus be an

easy to perform and inexpensive laboratory indicator for COVID-19 prognosis.

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