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Study of the Role of D-dimer in The Prediction of Hepatorenal Syndrome in Cirrhotic Egyptian Patients

Hadeer Mahmoud Alkharkhisy [1]*, Mona Mahrous Abdelaty [1], Noha Elsayed Esheba [1], Amira Yousef Abd-Elnaby [2], Ahmed Motawea Elsefy [1]

[1] Internal Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt

[2] Clinical Pathology Department, Faculty of Medicine, Tanta University, Tanta, Egypt

*** Corresponding author:** Hadeer Mahmoud Alkharkhisy, **Email:** Hadeeralsayed65@gmail.com, **Phone:** +20 1019431743

ABSTRACT

Background: Unless they undergo liver transplantation or early therapy, most patients with hepatorenal syndrome (HRS), especially type 1, die within a few weeks after the beginning of renal impairment. In this investigation, we sought to determine if plasma D-dimer might be used to predict the HRS-AKI type in liver cirrhosis patients.

Methods: Cross-sectional observational research was conducted on 60 adult patients with type 1 HRS and liver cirrhosis who were ≥ 18 years old at a single centre. The patients who were part of our study were split up into three equal groups: Patients with type 1HRS (HRS/AKI), patients with child A (compensated cirrhosis), and patients with child B or C (decompensated cirrhosis). **Results:** Males represented 63.3% of the study participants. Patients with Child A had significantly lower D-dimer levels and a higher estimated glomerular filtration rate (eGFR). D-dimer was an independent risk factor for HRS-AKI development with OR (CI 95%):1.965 (1.156 – 4.763) and p-value, 0.006 in the compensated cirrhotic group and 2.632 (1.795-6.746) and p-value, 0.023 in the decompensated group. D-Dimer also could be a good prognostic factor for survival at a specific cutoff value.

Conclusion: The D-dimer may not only be a marker of hypercoagulability and hemostatic alteration but can be considered as a simple and available marker for the prediction of HRS-AKI type, which might provide early detection and rapid treatment for those patients to improve their outcome.

Keywords: D-dimer, Hepatorenal syndrome, Cirrhosis, Acute kidney injury.

INTRODUCTION

Globally, liver cirrhosis is linked to considerable morbidity and death. The most prevalent conditions in Middle Eastern nations, including Egypt, are non-alcoholic fatty liver disease (NAFLD) and chronic viral hepatitis B/C [1, 2]. A considerable number of cirrhotic patients suffer from many complications, such as portal hypertension and hepatocellular carcinoma (HCC), and about one-third of them may develop hepatorenal syndrome (HRS) [3].

One of the several possible causes of acute kidney injury (AKI) in individuals with acute or chronic liver disease is HRS, which affects 20–40% of patients with severe cirrhosis and portal hypertension and is linked to a dismal prognosis if managed [4]. Two forms of HRS are defined according to the rapidity of renal function decline; the most serious type with rapid renal injury is HRS-AKI or type 1 HRS, and the less severe form, diuretic-resistant ascites or (type 2HRS) [5].

The decline in renal perfusion secondary to splanchnic vasodilation and a decrease in systemic vascular resistance, which can be precipitated by different causes, including bleeding or infections, is considered the most accepted mechanism for HRS [5, 6].

AKI in critically sick patients is influenced by coagulopathy and haemostatic instability linked to cirrhosis, according to some publications. Reduced platelet aggregation, coagulation system activation and prothrombotic alterations, reduced levels of fibrin stabilising factor XIII (FXIII), and rapid fibrinolysis have all been linked to AKI in patients with decompensated cirrhosis [7, 8]. Renal blood flow may decrease as a result of intravascular coagulation brought on by this disruption of the haemostatic system [9].

Plasma D-dimer is a fibrin breakdown product and one of the hemostatic markers that usually increases in patients with thromboembolic events, reflecting overactive coagulation and fibrinolysis [10].

During fibrinolysis, D-dimers, which are byproducts of crosslinked fibrin breakdown, emerge. They serve as a proxy for coagulation and the ensuing thrombus lysis. In the intricate cascade of coagulation and fibrinolysis, three active enzymes, factor IIa (thrombin), factor XIIIa, and plasmin, are required for the synthesis of d-dimer [11]. Fibrin monomers (factor Ia) are created when factor IIa (thrombin) acts on the E domain of fibrinogen (factor I). These monomers then combine to form fibrin polymers. They are affected by factor XIIIa, which is triggered by thrombin and forms crosslinked fibrin polymers. Ultimately, fibrin degradation products, such as d-dimers, are produced when plasmin-induced breakdown of the crosslinked polymers occurs [12]. Patients with liver cirrhosis have elevated D-dimer levels, which are associated with the degree of liver dysfunction [13]. D-dimer has recently been found to be an early indicator of AKI in both pregnant women and patients receiving percutaneous coronary intervention [14]. Nevertheless, there hasn't been enough research done on how elevated D-dimer levels affect the onset of HRS-AKI in individuals with severe cirrhosis. The purpose of this study was to assess if plasma D-dimer could be used to predict the HRS-AKI type in liver cirrhosis patients.

PATIENTS AND METHODS

Between January 2023 and June 2023, sixty adult patients with liver cirrhosis who were assessed and monitored at the Internal Medicine Department of Tanta

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University Hospital, Egypt were included in single-center cross-sectional observational research. Using established laboratory, radiographic, and clinical criteria, liver cirrhosis was diagnosed.

Inclusion criteria: Participants in our study were adults over the age of eighteen who had been diagnosed with cirrhosis for whatever reason, as well as those who had type 1 HRS (compensated, decompensated liver cirrhosis and Hepatorenal syndrome) based on imaging, laboratory results, clinical judgement, and history.

Exclusion criteria: Individuals with diagnoses of HCC or other current cancers were not allowed, nor were those with liver diseases other than cirrhosis. Pregnant females, patients with a history of recent thromboembolic events or received anticoagulants within the last 3 months, and those with a previously known renal disease were also excluded from our study. Since acute liver failure is a unique illness with unique haemostatic properties, patients with this condition were not included. Any individuals who got liver or kidney transplants before the research period were not included.

The patients who took part in the trial were split up into three equal groups: patients with type 1HRS (HRS/AKI), patients with child A (compensated cirrhosis), and patients with child B or C (decompensated cirrhosis).

Study definitions: Based on KIDIGO criteria, AKI was identified in our patients as a rise in serum creatinine of 0.3 mg/dL or higher within 2 days or a 50% increase in baseline creatinine within 7 days [15]. The International Club of Ascites-Acute Kidney Injury (ICA-AKI) criteria were used to define HRS/AKI. AKI causes include shock, recent exposure to nephrotoxic agents, diuretic withdrawal in cirrhosis patients, failure to improve kidney function after volume expansion with intravenous albumin for at least 48 hours, and the absence of structural renal disease signs such as proteinuria, haematuria, or abnormal radiological findings [16].

Data collection: The baseline data about age, sex, clinical evaluation for vital signs, presence of ascites, consciousness level, and urine output were documented. A pelvis-abdominal ultrasound was done to confirm radiological signs of cirrhosis and the presence of ascites. Laboratory investigations were measured initially and repeated when indicated, including complete blood count, liver and renal function tests with calculation of e-GFR, prothrombin time and activity, and INR. Plasma D-dimer was measured for all patients in the three groups and was compared to the other clinical and laboratory data. For those who received a transfusion of platelets, cryoprecipitate, or fresh frozen plasma in the past 3 days before screening, we repeated the hemostatic profile after another 3 days to avoid the interference of transfusion with the results. Plasma D-Dimer was analyzed using an enzyme-linked immunosorbent assay (ELISA) on Japanese Tosoh AIA1800.

Sampling: 3 ml blood samples were withdrawn under complete aseptic conditions using sterile syringes, put in a tube containing sodium citrate, and then centrifugated for 15 minutes at 3400 rpm. The serum was separated in Eppendorf and used for the D-dimer test.

Sample size: The statistical program EpI-Info 2002, created by the CDC and WHO, was used to calculate the sample size. The following factors were taken into account while calculating the sample size: A recent research [17] found that the sensitivity of D-Dimer in HRS prediction was 87.3% with a 95% confidence level and a ± 10% confidence limit. To combat dropout, eight instances were introduced. As a result, we planned to hire sixty cases.

Ethical considerations: The study was done after being accepted by The Research Ethics Committee, Tanta University. All patients provided written informed consents prior to their enrolment. The consent form explicitly outlined their agreement to participate in the study and for the publication of data, ensuring protection of their confidentiality and privacy. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The statistical analysis was conducted using IBM©, Chicago, IL, USA's SPSS version 27. Quantitative parametric data were analysed with an ANOVA (F) test and a post-hoc test. The results were provided as mean ± SD. Quantitative non-parametric data were compared between each group using the Mann Test and the Kruskall-Wallis test. The data were reported as the median and interquartile range (IQR). The Chi-square test was used to analyse qualitative variables. The Pearson moment correlation equation was used to correlate several variables. To determine the link between a dependent variable and several independent factors, both univariate and multivariate regression studies, were employed. ROC curve was utilised for evaluation of diagnostic performance sensitivity, specificity, and predictive value. A P-value ≤ 0.05 was deemed statistically noteworthy.

RESULTS

Tables (1 and 2) provided a description of the research participants' baseline characteristics and investigations. A total of sixty adult patients with liver cirrhosis with and without AKI were included in the study; the mean age was 60.10±11.42 years in the compensated cirrhosis group versus 62.25±9.48 and 65.95±9.65 years in the decompensated and HRS groups respectively. There was no statistically significant difference in the proportion of male patients between the three groups. Ascites and hepatic encephalopathy were significantly more common in the HRS group, and patients with compensated cirrhosis had significantly higher median systolic and diastolic blood pressures (122.50±13.32 and 79.50±9.45 mmHg) compared to the HRS group's values of 103.75±24.22 and 68.50±15.31 mmHg (Table 1).

Table (1): Sociodemographic characteristics, ascites, encephalopathy and vital signs of the studied groups

		Compensated group (n=20)	Decompensated group (n=20)	HRS group (n=20)	P
Age (years)		60.10±11.42	62.25±9.48	65.95±9.65	0.196
		P1=0.509, P2=0.076, P3=0.257			
Sex	**Male**	12(60.0%)	13(65.0%)	13(65.0%)	0.931
	Female	8(40.0%)	7(35.0%)	7(35.0%)	
		P1=0.744, P2=0.744, P3=1.0			
Ascites		0(0.0%)	17(85.0%)	20(100.0%)	**<0.001***
		P1=0.001*, P2<0.001*, P3=1.0			
Encephalopathy		0(0.0%)	3(15.0%)	16(80.0%)	**<0.001***
		P1=0.106**, P2<0.001*, P3<0.001***			
Vital signs	**SBP (mmHg)**	122.50±13.32	115.50±17.31	103.75±24.22	**0.009***
		P1=0.245, **P2=0.003*,** P3=0.053			
	DBP (mmHg)	79.50±9.45	74±12.31	68.50±15.31	**0.028***
		P1=0.172, **P2=0.008*,** P3=0.158			
	MAP (mmHg)	93.80±10.29	87.85±13.49	80.20±17.88	**0.014***
		P1=0.192, **P2=0.004*,** P3=0.095			

Data are presented as mean ±SD or frequency (%). * Significant P value <0.05, p1: significant between compensated & decompensated group, p2: significant between compensated & HRS group; P3: significant between Decompensated & HRS group, HRS: Hepatorenal syndrome, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial blood pressure.

The hemostatic markers were significantly higher in the HRS group, with a mean D-dimer level of 2.763±0.995 µg/ml versus 0.526±0.257 and 0.901±0.377 µg/ml in the compensated and decompensated cirrhosis groups, respectively. In addition, compared to the other two groups, patients in the HRS group had substantially greater prothrombin time and INR as well as lower albumin levels. The blood urea and serum creatinine levels in the compensated and decompensated groups did not significantly differ from one another, while we found significantly higher urea and creatinine levels and lower e-GFR among patients in the HRS group (Table 2).

Table (2): Comparison of serum D-dimer level, coagulation profile, liver and kidney function tests and CBC between studied groups

	Compensated group (n=20)	Decompensated group (n=20)	HRS (n=20)	P
D-dimer (µg/ml)	0.526±0.257	0.901±0.377	2.763±0.995	**<0.001***
	P1=0.012*, P2<0.001*, P3<0.001*			
INR	1.1(1.0-1.425)	1.6(1.35-1.92)	2.09(1.74-3.75)	**<0.001***
	P1<0.001*, P2<0.001*, P3=0.007*			
PT (seconds)	13.0(12.25-14)	18(17-20)	31.65(18.95-61.25)	**<0.001***
	P1<0.001*, P2<0.001*, P3=0.001*			
Albumin (g/dl)	3.98±0.268	2.89±0.424	2.33±0.411	**<0.001***
	P1<0.001*, P2<0.001*, P3<0.001*			
Total Bilirubin (mg/dl)	1.23±0.34	7.85±1.46	9.81±2.86	**<0.001***
	P1=0.001*, P2<0.001*, P3=0.107			
AST (IU/L)	50.5(40-67)	53.5(28.25-81)	41.5(22.75-84.5)	0.578
	P1=0.665, P2=0.323, P3=0.490			
ALT (IU/L)	45(31.25-76)	35.5(18.25-52)	24.25(15.75-46.5)	0.134
	P1=0.184, P2=0.121, P3=0.330			
Creatinine (mg/dl)	0.922±0.09	0.895±0.207	3.82±1.04	**<0.001***
	P1=0.888, **P2<0.001*, P3<0.001***			
Urea (mg/dl)	33(29-38.75)	38.5(29-43)	177(131-210)	**<0.001***
	P1=0.128, **P2<0.001*, P3<0.001***			
eGFR (ml/min/1.73m ^{2})	95.5(80-122.5)	92.5(77.75-107.5)	19(14.5-22.5)	**<0.001***
	P1=0.350, **P2<0.001*, P3<0.001***			
CBC				
TLC (×10^3/cmm)	7.25(4.35-9.10)	5.85(4.15-9.28)	9(6.8-10.88)	0.061
	P1=0.978, **P2=0.029*,** P3=0.058			
Platelet count (×10^3/cmm)	190(173.5-287.5)	146(101.25-211.75)	103.0(67.75-134.75)	**<0.001***
	P1=0.002*, P2=0.001*, P3=0.02*			
Hb (gm/dl)	10.89±2.16	10.04±1.78	9.80±1.07	0.121
	P1=0.126, P2<0.063, P3=0.662			

Data are presented as mean ±SD or median (IQR). * Significant P <0.05, p1: significant between compensated & decompensated group, p2: significant between compensated & HRS group; P3: significant between Decompensated & HRS group, HRS: Hepatorenal syndrome, INR: international normalised ratio, PT: prothrombin time, AST: aspartate aminotransferase, ALT: Alanine aminotransferase, eGFR: estimated glomerular filtration rate, CBC: complete blood count, TLC: Total leucocyte count, Hb: hemoglobin.

The univariate analysis identified the following as risk factors for the development of HRS-AKI in patients with compensated and decompensated cirrhosis: The presence of hepatic encephalopathy, low platelet count and high D-dimer, extended prothrombin time, and INR. Using the multivariate analysis, D-dimer was the sole independent risk factor and predictor for HRS-AKI in both groups, with (OR 4.521, CI 95%; 2.639-8.642, p-value 0.001) and OR 4.531, CI95% 1.963 – 9.856, p-value =0.001) in the compensated and decompensated cirrhosis groups respectively (Tables 3 and 4).

Table (3): Univariate and multivariate analysis for predictors of decompensated cirrhosis versus compensated cirrhosis

	Univariate analysis		**Multivariate analysis**		
	P	**COR (95%CI)**	**β**	**P**	**AOR (95%CI)**
Ascites	**0.003***	9.33(2.18-39.96)	2.36	**0.004***	**9.10(2.11-30.65)**
Encephalopathy	0.852	0.459 (0.324 – 0.652)			
SBP (mmHg)	0.277	0.621(0.263-1.47)			
DBP (mmHg)	0.267	0.396(0.077-2.03)			
MAP (mmHg)	0.285	3.85(0.326-45.41)			
D-dimer (µg/mL)	**0.001***	27.25(10.45-35.6)	7.92	**0.001***	30.25(8.56-40.12)
INR	0.109	25.31(0.488-39.89)			
PT (seconds)	0.124	1.36(0.919-2.02)			
Albumin (g/dl)	**0.018***	0.02(0.001-0.210)	-43.57	**0.352**	0.002(0.0004-8.4)
Bilirubin (mg/dl)	0.789	0.886(0.364-2.16)			
AST (IU/L)	0.245	0.853(0.265-1.295)			
ALT (IU/L)	0.174	0.944(0.902-3.987)			
Creatinine (mg/dl)	0.856	0.524(0.01-25.8)			
UREA (mg/dl)	0.074	1.12(0.990-1.26)			
eGFR (ml/min/1.73m^2)	0.295	1.02(0.979-1.07)			
TLC (×10^3/cmm)	0.719	1.04(0.858-1.25)			
Platelet count (×10^3/cmm)	**0.018***	0.986(0.975-0.998)	**-0.014**	**0.035***	0.986(0.973-0.99)
Hb (gm/dl)	0.309	0.828(0.576-1.19)			

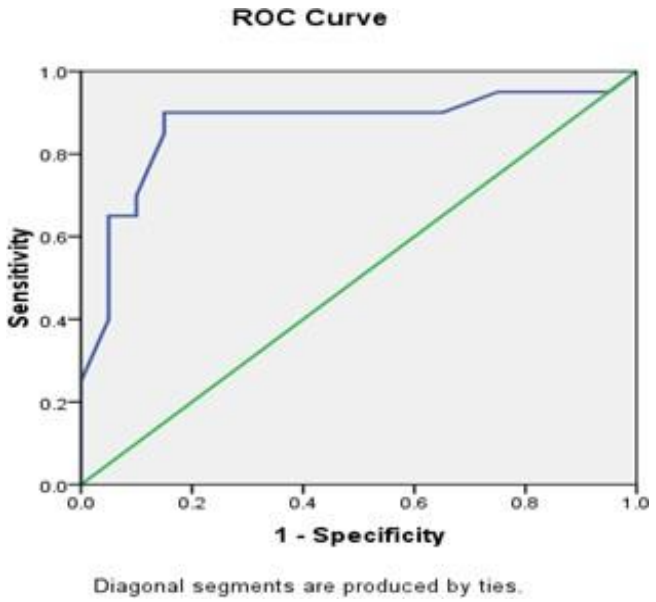
* Significant p value <0.05. HRS: Hepatorenal syndrome, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial blood pressure, AOR: Adjusted odds ratio, COR: Crude odds ratio, INR: international normalised ratio, PT: prothrombin time, AST: aspartate aminotransferase, ALT: Alanine aminotransferase, eGFR: estimated glomerular filtration rate, CBC: complete blood count, TLC: Total leucocyte count, Hb: hemoglobin.

Table (4): Univariate analysis for predictors of HRS versus compensated and decompensated

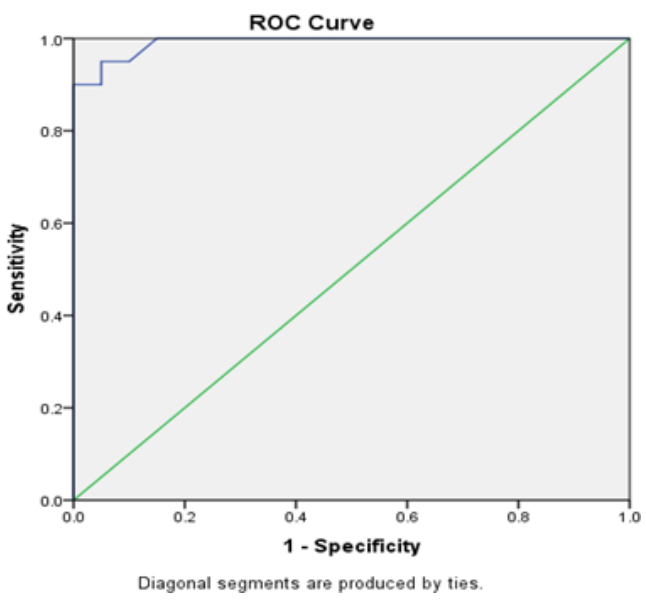
	Univariate analysis			
	P	**COR (95%CI)**	**P**	**COR (95%CI)**
	Compensated		**Decompensated**	
Ascites	**0.009***	4.333 (2.148-8.742)	**0.851**	2.416 (0.586 – 6.831)
Encephalopathy	**0.021***	0.167 (0.068 – 0.408)	**<0.001***	22.67(4.37-117.47)
SBP (mmHg)	**0.01***	0.950(0.913-0.988)	0.094	0.972(0.941-1.01)
DBP (mmHg)	**0.017***	0.933(0.881-0.988)	0.215	0.971 (0.926-1.01)
MAP (mmHg)	**0.012***	0.937(0.890-0.986)	0.138	0.969 (0.929-1.01)
D-dimer (µg/mL)	**0.001***	4.521 (2.639 – 8.642)	**0.001***	4.531 (1.963 – 9.856)
INR	**0.004***	20.18(2.66-153.27)	**0.05***	2.83(1.001-7.99)
PT (seconds)	**0.008***	1.48(1.11-1.99)	**0.02***	1.18(1.02-1.36)
Albumin (g/dl)	0.532	0.263 (0.129 – 2.634)	**0.004***	0.016(0.001-0.256)
Bilirubin (mg/dl)	0.171	2.39(0.687-8.29)	0.102	1.32(0.16-1.87)
AST (IU/L)	0.754	0.963 (0.478 – 5.631)	0.673	0.856(0.756-0.931)
ALT (IU/L)	0.574	0.586 (0.039 – 3.563)	0.586	0.912(0.875-0.976)
Creatinine (mg/dl)	0.359	1.452 (0.745 – 2.854)	0.992	1.853 (0.064 – 3.523
UREA (mg/dl)	0.995	1.81(0.002-18.95)	0.995	1.88)0.563 – 3.214)
eGFR (ml/min/1.73m^2)	0.991	0.048(0.002-16.5)	0.985	0.004 (0.002 – 0.032)
TLC (×10^3/cmm)	0.054	1.27(0.996-1.61)	0.337	1.08(0.919-1.27)
Platelet count (×10^3/cmm)	0.003*	0.969(0.949-0.990)	**0.04***	0.988(0.977-0.999)
Hb (gm/dl)	0.004*	0.433(0.244-0.768)	**0.018***	0.527(0.311-0.894)

* Significant p value <0.05. HRS: Hepatorenal syndrome, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial blood pressure, AOR: Adjusted odds ratio, COR: Crude odds ratio, INR: international normalised ratio, PT: prothrombin time, AST: aspartate aminotransferase, ALT: Alanine aminotransferase, eGFR: estimated glomerular filtration rate, CBC: complete blood count, TLC: Total leucocyte count, Hb: hemoglobin.

The sensitivity and specificity of D-dimer in the prediction of HRS-AKI between the three groups were detected by the ROC curve (Figure 1).



(A)



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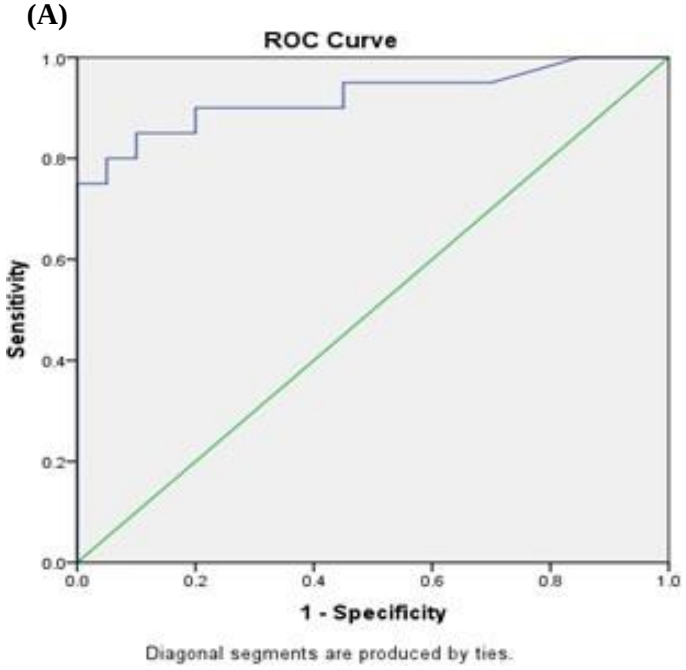

(C)

Figure (1): ROC curve of D-dimer in differentiating between (A) compensated & decompensated cirrhosis, (B) compensated cirrhosis & HRS and (C) decompensated cirrhosis & HRS.

The D-dimer test was valid in differentiation between compensated and decompensated cirrhosis groups with a sensitivity of 85% and specificity of 80% at a cutoff point of 0.595 µg/ml, also D-dimer test was valid in differentiation between compensated group and HRS group with a sensitivity 90% and specificity 85% at a cutoff point 1.5 µg/ml and between decompensated group and HRS with a sensitivity 95% and specificity 90% at a cutoff point 2.5 µg/ml. Based on the Child-Pugh score, D-dimer significantly positively correlated with the severity of cirrhosis in all patients. Conversely, in the HRS and compensated cirrhosis groups, D-dimer exhibited a strong negative connection with albumin levels and e-GFR respectively (Table 5).

Table (5): Multivariate analysis for predictors of HRS versus compensated and decompensated

	Multivariate analysis					
	B	**P**	**AOR (95%CI)**	**B**	**P**	**AOR (95%CI)**
	Compensated			**Decompensated**		
Ascites	0.864	0.142	2.563 (0.859 – 5.426)			
Encephalopathy	0.065	0.138	0.754 (0.328 – 2.453)	3.17	**0.002***	23.87(3.74-75.68)
SBP (mmHg)	0.284	0.565	1.33(0.505-3.49)			
DBP (mmHg)	0.732	0.466	2.08(0.290-14.93)			
MAP (mmHg)	-1.02	0.493	0.359(0.019-6.71)			
D-dimer (µg/mL)	5.63	**0.006***	1.965 (1.156 – 4.763)	1.65	**0.023***	2.632 (1.795 – 6.746)
INR	0.568	0.569	1.76(0.250-12.47)	0.504	0.716	1.65(0.109-25.11)
PT (seconds)	0.141	0.07	1.15(0.989-1.34)	0.151	0.190	1.16(0.928-1.46)
Albumin (g/dl)				-5.78	0.06	0.003(0.001-1.27)
Platelet count (×10^3/cmm)	0.001	0.912	1.001(0.983-1.02)	-0.007	0.279	0.993(0.981-1.01)
Hb (gm/dl)	-0.718	0.138	0.488 (0.189-1.26)	-0.499	0.084	0.607(0.345-1.07)

Significant p value <0.05. HRS: Hepatorenal syndrome, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial blood pressure, AOR: Adjusted odds ratio, COR: Crude odds ratio, INR: international normalised ratio, PT: prothrombin time, AST: aspartate aminotransferase, ALT: Alanine aminotransferase, eGFR: estimated glomerular filtration rate, CBC: complete blood count, TLC: Total leucocyte count, Hb: hemoglobin.

In compensated cirrhosis group, there was a significant positive correlation of D-dimer with INR, PT, creatinine, ascites and child-Pugh score. On the other hand, D- dimer showed a significant negative correlation with albumin. In decompensated cirrhosis group, there was a significant positive correlation of D-dimer with Child-Pugh score. In compensated cirrhosis group, there was a significant positive correlation of D-dimer with ALT, creatinine, urea and Child-Pugh score. On the other hand, D-dimer showed a significant negative correlation with eGFR (Table 6).

Table (6): Correlation between d-dimer and clinical findings & laboratory findings in compensated cirrhosis, decompensated cirrhosis and HRS

	D-dimer		**D-dimer**		**D-dimer**	
	r	**p**	**r**	**P**	**r**	**P**
	Compensated cirrhosis		**Decompensated cirrhosis**		**HRS**	
INR	**0.700***	**0.001***	-0.153	0.519	0.435	0.055
PT (seconds)	**0.633***	**0.003***	0.093	0.696	0.123	0.607
Albumin(gm/dl)	**-0.660***	**0.002***	0.261	0.266	-0.191	0.420
bilirubin(mg/dl)	0.223	0.345	0.033	0.890	0.371	0.107
AST (mg/dl)	-0.117	0.622	-0.245	0.298	0.214	0.365
ALT (mg/dl)	-0.246	0.295	-0.367	0.112	**0.461***	0.041
Creatinine(mg/dl)	**0.475***	**0.034**	0.226	0.339	**0.621***	0.013
urea(mg/dl)	0.156	0.511	-0.149	0.532	**0.713***	0.001
eGFR(ml/min/1.73m^2)	-0.398	0.083	-0.210	0.374	0.563	**-0.024***
TLC (×10^3/cmm)	0.245	0.298	0.124	0.603	-0.008	0.972
PLT (×10^3/cmm)	-0.419	0.066	-0.435	0.055	-0.145	0.542
Hb(gm/dl)	-0.007	0.976	-0.309	0.185	-0.129	0.588
Age (years)	0.278	0.236	0.017	0.944	-0.093	0.696
SBP (mmHg)	0.266	0.256	-0.067	0.780	-0.130	0.584
DBP (mmHg)	0.091	0.704	0.090	0.706	-0.184	0.436
MAP (mmHg)	0.199	0.401	0.020	0.934	-0.180	0.448
Sex	0.213	0.367	-0.073	0.759	-0.220	0.351
Ascites	**0.636***	**0.003**	0.153	0.520	0.164	0.489
Encephalopathy	--	--	0.012	0.959	--	--
Child pugh score	**0.583***	**0.024**	**0.597**	**0.021***	**0.735**	**0.001***

. r: Spearman correlation co-efficient *statistically significant <0.05, INR: International normalized ratio, PT: Prothrombin time, eGFR: estimated glomerular filtration rate; TLC: Total leucocytic count. Hb: Hemoglobin, SBP: Systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure.

Survival analysis using the D-dimer level:

It was found that patients presented with HRS-AKI who had low D-dimer levels (below 2.5 mg/L) demonstrated significantly better survival when compared to HRS-AKI patients with higher D-dimer (Figure 2).

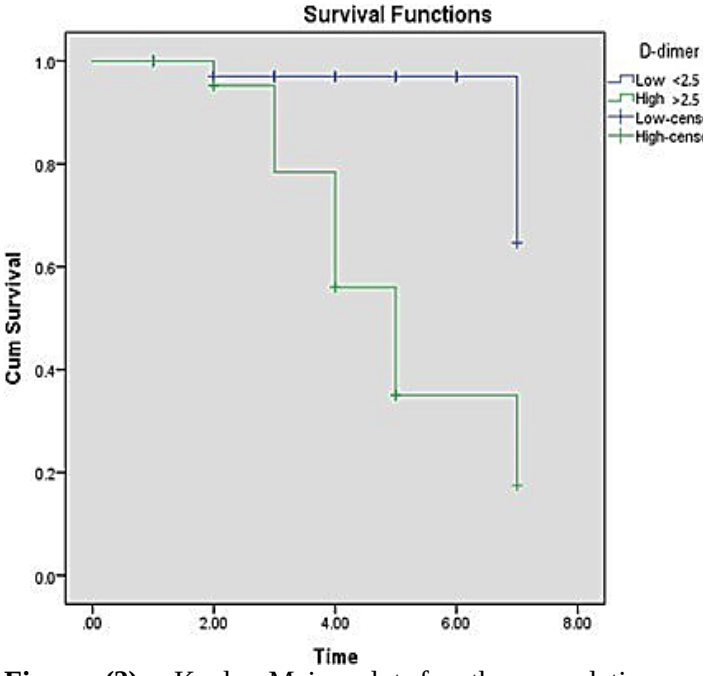

Figure (2): Kaplan-Meier plot for the cumulative survival in hepatorenal syndrome patients according to the two stratifications of D-dimer (Log-Rank, p=0.007*).

DISCUSSION

Only individuals with severe cirrhosis have HRS-AKI, which is uniquely linked to a poor prognosis and a reduced quality of life for affected individuals and their families in the absence of prompt treatment [18]. The diagnosis of HRS-AKI is made when all other potential causes of acute or subacute kidney injury have been ruled out. Few investigations reported varying findings of certain markers, such as serum Cystatin C and Urinary NGAL, in separating HRS-AKI from other causes of renal damage in cirrhotic individuals [19]. However, the high cost and unavailability of these markers in a standardized lab at the time of the study limit their use.

Classically, it is caused by circulatory dysfunction that occurs in cirrhosis. Nevertheless, the development of AKI in liver cirrhosis may also be influenced by additional pathogenic abnormalities, such as systemic inflammation and haemostatic dysfunctions, which worsen with the severity of liver disease [20-22]. Currently, there is a lack of comprehensive studies assessing the impact of coagulopathy and hemostatic markers on the prediction of HRS-AKI type in individuals with cirrhosis. This study aimed to investigate the significance of D-dimer as an indicator of hemostatic changes associated with the onset of HRS-AKI in patients suffering from liver cirrhosis, as well as its implications for survival outcomes.

Our findings indicated that patients in the HRS group exhibited statistically significant elevations in D-dimer levels, prothrombin time, and INR when compared to other patient cohorts. Notably, in the multivariate analysis, elevated D-dimer levels emerged as the sole independent risk factor for the onset of HRS in cirrhotic patients. Furthermore, D-dimer levels demonstrated a positive correlation with the Child-Pugh score and a negative correlation with e-GFR in patients with HRS, with higher D-dimer concentrations being linked to poorer survival outcomes in this population. Recent research by **Volkanovska** [23] and colleagues, who performed a prospective study on 50 patients to evaluate plasma D-dimers in patients with different degrees of liver dysfunction, noted similar results as they revealed a favourable relationship between the degree of liver disease and D-dimer levels. A different investigation conducted by **Li Y *et al.*** [24] discovered a strong correlation between D-dimer and the Child-Pugh score and the Model for End-Stage Liver Disease (MELD) in cirrhosis patients. It was also a predictor of in-hospital mortality, which aligns with our results.

Elevated D-dimer was reported in recent studies as a risk factor for AKI and poor outcomes in different conditions [25]. Some authors [26, 27] reported extensive crosstalk between inflammation, coagulation, and vascular endothelium damage. Particularly in individuals with cirrhosis, D-dimer is strongly linked to endothelial dysfunction and inflammatory activity, which can reduce renal blood flow and worsen renal function. In our investigation, we discovered that greater D-dimer levels were linked with a nearly twofold increase in the probabilities of advancing to HRS-AKI in cirrhotic patients, and levels higher than 2.5 mg/L were correlated with higher fatality rates.

Park J *et al.* [28] reported that investigation of the significance of D-dimer in predicting acute kidney injury (AKI) among liver transplant recipients yielded comparable findings. Specifically, elevated D-dimer levels (greater than 1.1 mg/L) were linked to a four-fold increase in the risk of developing AKI when contrasted with patients exhibiting lower D-dimer levels.

In a recent retrospective analysis conducted by **Chen and colleagues** [29], which included 108 cirrhotic patients both with and without AKI, it was observed that D-dimer levels were markedly higher in patients suffering from hepatorenal syndrome (HRS) compared to those experiencing other forms of renal injury. This elevation in D-dimer was correlated with adverse survival outcomes, demonstrating a sensitivity of 87.3% and specificity of 72.9% at a threshold of 3.7 mg/L (FEU), which is aligning with our own research findings.

It is important to acknowledge that the increase in fibrin and fibrinogen degradation products in liver cirrhosis, resulting from diminished clearance of plasma D-dimer and hyperfibrinolysis, may restrict the utility

of D-dimer levels in assessing coagulant status in cirrhotic patients. Numerous studies [30-32] have employed D-dimer to investigate various pathological conditions in cirrhotic individuals, including spontaneous bacterial peritonitis, hepatocellular carcinoma (HCC), and the prognosis of hepatitis B virus-related liver failure, as well as to exclude thromboembolic events. These authors propose that D-dimer may serve as a valuable predictive marker, albeit with higher cutoff values than those typically applied in non-cirrhotic populations.

Limitations: The sample size was relatively small, and we didn't follow up on the D-dimer levels after treatment for survivors. This may be explained by the short follow-up period after improvement. Also, some patients were missed after discharge. Despite these limitations, our study was the first prospective study conducted from our center on this concern. To assess the ability of D-dimer to distinguish HRS-AKI from other kidney injury that may affect cirrhotic patients, we advise larger studies evaluating the effect of different comorbidities on D-dimer levels, the effect of treatment on D-dimer levels, and the inclusion of patients with other types of renal insult.

CONCLUSION

High D-dimer levels were associated with liver cirrhosis progression and development of HRS-AKI, confirming the relationship between hemostatic disorders and the severity of cirrhosis and can be used as a significant predictor for HRS-AKI type in cirrhotic patients with high sensitivity and specificity. This can help in early detection and management of this serious complication.

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