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Review Article

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Coagulopathy and D-Dimer Level Changes Among Yemeni Patients with Chronic Liver Disease and Cirrhosis

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ABSTRACT

Background: The liver is the largest organ in the body; Chronic liver disease consists of chronic hepatitis and cirrhotic epatic. The liver has a cardinal role in the haemostatic system. Liver synthesizes plasma proteins including many coagulation proteins e.g., Factor I, II, V, VII, VIII, IX, X, XI, XII, XIII, many natural anticoagulants like protein C & S. Chronic or acute liver diseases frequently have an intense impact on the haemostatic system Bleeding in liver disease could be due to decreased plasma levels of haemostatic proteins synthesized by the liver. It could also be due to thrombocytopenia, coagulopathy, enhanced fibrinolysis or portal hypertension. Recent studies have shown that patients with liver disease also develop deep venous thrombosis and pulmonary artery embolism at rates between 0.5%-1.9%

Aims: The aims of this study are to evaluate the coagulopathy status and D-dimer level changes in context of severity of CLD and cirrhosis including their correlation with disease progression and severity.

Patients and methods: Observational, cross-sectional study. any patient aged ≥ 18 years old, confirmed clinically and para-clinically had CLD either with or without liver cirrhosis, and attended to Al-Sadaqah hospital-Taiz for treatment and follow up, through 1st January, 2021 to 30th December, 2022.

Results: One hundred fourteen patients classified according to Child Paugh score. Of total, A, B and C and were 10.5%, 26.3%, and 63.2%; 63.2% was male. 3.5%, 31.6%, 14%, 33.3%, 10.5% and 7% was fallen in < 20, 20-29, 30-39, 40-49, 50-59 and ≥60 years old; all patients were Khat hewers while only 17.5% were active smokers, all of active smokers found in Child-Pugh C. Autoimmune hepatitis followed by HBV, Bilharziasis and HCV found in 36.8%, 21.1%, 12.3% and 7% of total patients respectively, 22.8% were of unknown etiology. All patients presented with current history of increased fatiguability. Distended abdomen, discoloration of the body, GIT bleeding, Change OC and Anuria and accounting of 89.5%, 70.2%, 56.1%, 52.6% and 3.5% of total patients respectively. Vital signs were taken in ER on arrival, systolic blood pressure, diastolic blood pressure and heart rate were recorded for all patients. Of note, there is a difference of statistically significance among Child-Pugh groups regarding their blood pressure and heart rate, sustainable hypotension was found in C and B while tachycardia was recorded in all A and some of B and little of C. S platelets count ranged between 26-216(130.5), 115-198(174), 56-163(131), and 26- 216(129) of total, Child-Pugh A, B and C respectively. All thrombolytic patients below 50k found in Child-Pugh C, bellow 100k found in C and B. PT (seconds) ranged between 15-50(18), 17-18(18), 15-18(16.5), and 17-50(23.75) and INR (%) ranged between 1.13-3.8(1.4), 1.2-1.4(1.4), 1.13-1.4(1.4), and 1.3-3.8(1.8) for total, Child- Pugh A, B, and C respectively. D-dimer ranged between 320-10000(5127), 320- 560(460), 950-8870(1800), and 1143-10000(6200) for total, Child-Pugh A, B, and C respectively. of note, D-dimer of Child-Pugh patients found within normal cut off point of 500.

Conclusion: Coagulopathy and bleeding tendency in direct proportion with severity of chronic liver diseases defined by Child-Pugh score. D dimer correlated well with advanced stages of liver disease even in absence of thrombotic events.

Introduction

The liver is the largest organ in the body, weighs approximately 1.5 kg, contributing about 2 % of the total body weight, in the average adult human. Chronic Liver Disease (CLD) consists of chronic hepatitis and cirrhotic hepatic. The morbidity and mortality of this disease has significantly increased in developing countries primarily due to viral hepatitis, especially hepatitis B and C and physical damage, alcohol, drugs, others

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viral infections, toxins, and autoimmune reactions. The Child-Pugh score is an internationally accepted system for grading the severity of chronic liver disease such as cirrhosis

The liver has a cardinal role in the haemostatic system. Liver synthesizes plasma proteins including many coagulation proteins e.g., Factor I, II, V, VII, VIII, IX, X, XI, XII, XIII, many natural anticoagulants like protein C & S. Chronic or acute liver diseases frequently have an intense impact on the haemostatic system. Bleeding in liver disease could be due to decreased plasma levels of haemostatic proteins synthesized by the liver. It could also be due to thrombocytopenia, coagulopathy, enhanced fibrinolysis or portal hypertension. Recent studies have shown that patients with liver disease also develop deep venous thrombosis and pulmonary artery embolism at rates between 0.5%-1.9% [1-3].

A large population-based study done by Sogaard KK et al., also showed an increased risk for development of venous thrombosis in patients with liver disease as compared with healthy persons. This thrombotic tendency has been attributed to decreased plasma levels of the natural anticoagulants, protein C, S and antithrombin. Therefore, it is evident that patients with liver disease may experience both bleeding complications as well as thrombotic episodes [4].

Yemen is one of the developing countries, where hepatitis with its chronic sequels is frequently encountered in daily practice. This usually due to viral, Khat related, autoimmune, toxins or even of unknown cause. Coagulopathy and Elevated D-dimer level among chronic and cirrhotic liver disease patients were observed in the last years in proportion with severity of CLD.

Objectives

General Objectives

To study the coagulopathy status and D Dimer level of Yemeni patients with CLD and cirrhosis at Al-Sadaqah Hospital- Taiz, through 1st January, 2021 to 30th December, 2022.

Specific Objectives

To study the demographical characters of patients such as age, age groups, gender, special habits, marital status, residency and jobs.

To study the clinical and paraclinical manifestations and their correlations with D- dimer level changes.

To investigate the correlation of D-dimer level and severity of liver diseases as measured by Child-Pugh score.

To assess the utility of D-dimer as a prognostic indicator or diagnostic tool for prediction complications of CLD and cirrhosis. To explore the potential factors influencing the coagulopathy and D-dimer level in patients such as disease etiology, comorbidity.

Patients and method

Study Design

Observational, cross-sectional study.

Inclusion Criteria

One hundred fourteen patients (114), aged ≥ 18 years old, regardless of their gender, confirmed clinically and Para-clinically had have CLD either with or without cirrhosis, attended to Al-Sadaqah hospital for treatment and follow up, either in compensated or decompensated state with coagulation profile including D-dimer level measurement.

Exclusion Criteria

Patients who were less than 18 years old, with acute hepatitis, hepatic tumors either primary or secondary, isolated biliary disorders as obstructive jaundice, hematological or bleeding disorders or on anticoagulant therapy, chronic kidney disease, uncontrolled diabetes mullites, advanced cardiovascular disease, obvious recently diagnosed arterial or venous thrombosis, or incompletely investigated or refused to be enrolled in the study was excluded.

Patient, Place and Time

Any patient met the inclusion criteria that mentioned above and attend to Al-Sadaqah hospital in Taiz, through 1st January, 2021 to 30th December, 2022 for management and follow up.

Sample, Size and Calucation

Sample size was calculated using expected prevalence rate of the coagulopathy among CLD patients which was found in similar studies of 7%. So, the total expected sample size was 114 patients by Epi info program calculator.

Sampling Process

During the period of study, -because of small number of attended patients to Al- Sadaqah hospital-, patient was selected consecutively according to their flow by the chance unless excluded by criteria so sampling bias was avoided

Data Collectio

Data was collected during face-to-face interviews using already prepared questionnaire for those purposes and included in this study, some data was collected from patients' files, rechecked with the participants or their close relatives after explaining to them the study nature, goals and taking their verbal permission and agreement to participates. History, clinical examinations, anthropometrics as weight, height was taken by help of board candidates in the place. Investigations (Blood samplings will be collected at admission for measurement of: routine and specific investigations as hematological and biochemical (CBC, ESR, CRP, LFT, RFT, PTT, PT/INR and D-dimer and etc.), imaging (abdominal US was standardized done by highly qualified consultant radiologist. These results were gathered during visits and through a system of telephone communication at regular intervals of follow up. Hypertension defined as either Khat chewing in Yemen was defined as regular, daily chewing Khat plant leaflets for equal to 3 hours or more.

Data Processing

Statistical Analyses

The categorical variables were expressed as numbers and percentages, and continuous variables as the mean ± SD. The variables were compared using the chi- square test for categorical variables and independent samples t-test for continuous variables with equal variance. For continuous variables with unequal variance, the nonparametric Mann–Whitney U test was used for comparison. Statistical significance was accepted for all P values ≤ 0.05.

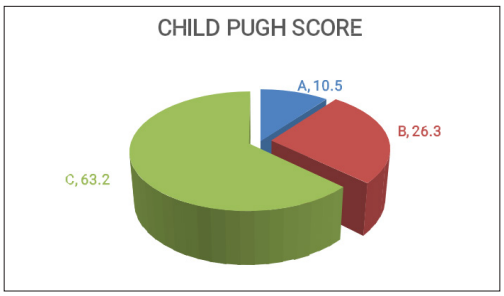

Figure 1: The distribution of patients according to Child Pugh score.

Results

In this study, coagulopathy and D-dimer level in patients with CLD and cirrhosis was evaluated. The total number of participants were 114 patients. Patients were classified according to Child-Pugh score into A, B and C and were encountered in 12(10.5%), 30(26.3%), and 72(63.2%) of total patients respectively. Figure (1).

Regarding to their age, it was ranged between18 -68 years with mean 39± 9.3 years of total patients. This was classified into 6 age groups: < 20, 20-29, 30-39, 40-49, 50-59 and ≥60 years old accounting of 4(3.5%), 36(31.6%), 16(14%), 38(33.3%), 12(10.5%) and 8(7%) of total patients respectively with a statistically significant differences among Child-Pugh groups and age groups (P-value < 0.001**). Of note, the majority of patients in Child-Pugh C were younger- < 40 years old- than in A and B whom were > 40 years old. table (1)

Table 1: The distribution of patients according to their age group.

Age group (Yrs)	Total= 114(100%)		Child-Pugh Score						P Value
			A = 12 (10.5%).		B = 30 (26.3%).		C = 72 (63.2%).		
	No	%	No	%	No	%	No	%	
< 20	4	3.5	0	0	0	0	4	5.6	<0.001**
20-29	36	31.6	0	0	4	13.3	32	44.4	
30-39	16	14	0	0	0	0	16	22.2	
40-49	38	33.3	4	33.3	18	60.1	16	22.2	
50-59	12	10.5	4	33.3	4	13.3	4	5.6	
> 60	8	7	4	33.3	4	13.3	0	0	

Regarding to patients' gender, male was 72(63.2%) while female 42(36.8%) of total patients. There is no difference of statistically significant among Child-Pugh groups and gender. table (2) and figure (2).

Table 2: The distribution of patients according to their gender.

Gender	Total= 114(100%)		Child-Pugh Score						P Value
			A = 12 (10.5%).		B = 30 (26.3%).		C = 72 (63.2%).		
	No	%	No	%	No	%	No	%	
Male	72	63.2	8	66.7	20	66.7	44	61.2	0.8
Female	42	36.8	4	33.3	10	33.3	28	38.9	

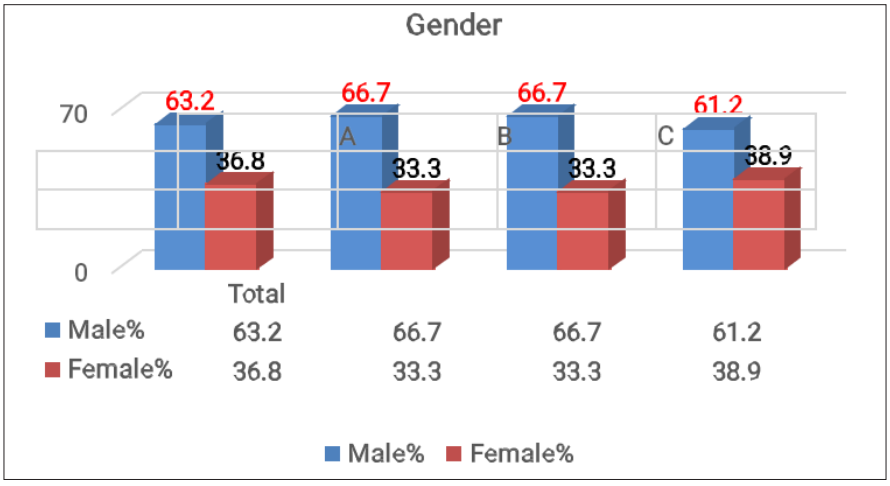

Figure 2: The distribution of patients according to their gender.

All patients were from Yemen, most of them were workers and followed by housewives and farmers accounting of 43(37.7%), 38(33.4%) of total sample respectively. Table (3).

Table 3: The distribution of patients according there to Occupation.

Occupation	Total= 114(100%)		Child-Pugh Score						P Value
			A = 12 (10.5%).		B = 30 (26.3%).		C = 72 (63.2%).		
	No	%	No	%	No	%	No	%	
Worker	43	37.7	8	66.7	18	60	17	23.6	
Farmer	25	21.9	0		2	6.7	23	31.9	
Housewife	38	33.4	4	33.3	10	23.3	24	33.3	
Driver	4	3.5	0	0	0	0	4	5.6	
Soldier	4	3.5	0	0	0	0	4	5.6	

Regarding to patients' marital state, the majority of patients were married accounting of 106(93%), the others were single and accounting of 8(7%) of total. table 4

Table 4: The distribution of patients according to their marital state.

Marital stare	Total= 114(100%)		Child-Pugh Score						P Value
			A = 12 (10.5%).		B = 30 (26.3%).		C = 72 (63.2%).		
	No	%	No	%	No	%	No	%	
Married	106	93	12	100	30	100	64	88.9	0.8
Single	8	7	0	0	0	0	8	11.1	

Of total patients, all patients were Khat chewers while only 20(17.5%) were active smokers with differences of statistically significance among Child-Pugh scores regarding smoking habits, all active smokers were found in Child-Pugh C. (P-value 0.001*). table (5).

Table 5: The distribution of patients according to their special habits.

Habits	Total= 114(100%)		Child-Pugh Score						P Value
			A = 12 (10.5%).		B = 30 (26.3%).		C = 72 (63.2%).		
	No	%	No	%	No	%	No	%	
Active smokers	20	17.5	0	0	0	0	20	27.8	0.001*
Khat chewers	114	100	12	100	30	100	72	100	1

Although, causes of CLD and cirrhosis were known among most of patients: autoimmune hepatitis followed by HBV, Bilharziasis and HCV accounting of 41(36.8%), 24(21.1), 14(12.3%) and 8(7%) of total patients respectively, however 26(22.8%) of total patients were surprisingly of unknown etiology. table (6) and figure (3).

Table 6: The distribution of patients according to Etiology of CLD and cirrhosis.

Causes of CLD	Total= 114(100%)		Child-Pugh Score						P Value
			A = 12 (10.5%).		B = 30 (26.3%).		C = 72 (63.2%).		
	No	%	No	%	No	%	No	%	
HBV	24	21.1	4	33.3	8	26.7	12	16.7	<0.001**
HCV	8	7	0	0	2	6.7	6	8.3	
AIH	42	36.8	0	0	6	20	36	50	
Bilharziasis	14	12.3	6	50	4	13.3	4	5.6	
Unknown	26	22.8	2	16.7	10	33.3	14	19.4	

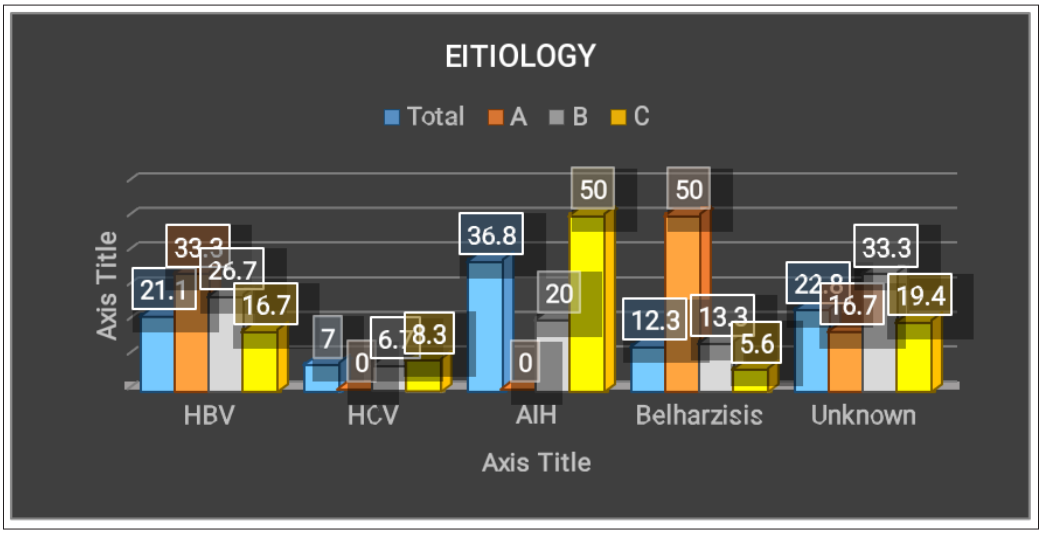

Figure 3: The distribution of patients according to the etiology of CLD and cirrhosis. On arrival to ER, all patients were undergoing a comprehensive evaluation according to local policy of hospital, clinically and laboratorial. All patients were presented with current history of increased fatiguability. Others presented symptoms were, Distended abdomen, Discoloration of the body, GIT bleeding, change Level of Consciousness (LOC) and Anuria and accounting of 102(89.5%), 80(70.2%), 64(56.1%), 60(52.6%) and 4(3.5%) of total patients respectively. table (7).

Table 7: The distribution of patients according to clinical state of presentation.

Symptoms	Total= 114(100%)		Child-Pugh Score						P Value
			A = 12 (10.5%).		B = 30 (26.3%).		C = 72 (63.2%).		
	No	%	No	%	No	%	No	%	
Increased Fatiguability	114	100	12	100	30	100	72	100	1
Distended abdomen	102	89.5	4	33.3	26	86.7	72	100	<0.001**
Discoloration of the body	80	70.2	0	0	8	26.7	72	100	<0.001**
GIT bleeding	64	56.1	2	16.7	10	33.3	52	72.2	<0.001**
Change LOC	60	52.6	0	0	0	0	60	83.3	<0.001**
Anuria	4	3.5	0	0	0	0	4	5.6	0.2

Vital signs were taken in ER on arrival, systolic blood pressure, diastolic blood pressure and heart rate were recorded for all patients. Of note, there is a difference of statistically significance among Child-Pugh groups regarding their blood pressure and heart rate, sustainable hypotension was found in C and B while tachycardia was recorded in all A and some of B and little of C. table (8).

Table 8: The distribution of patients according to blood pressure and heart rates.

	BP and HR	Total= 114(100%)		Child-Pugh Score						P Value
				A = 12 (10.5%).		B = 30 (26.3%).		C = 72 (63.2%).		
		No	%	No	%	No	%	No	%	
SBP	<90 mmHg	20	17.5	0	0	4	13.3	16	22.2	0.01*
	<90 mmHg	94	82.5	12	100	26	86.7	56	77.8	
DBP	<60 mmHg	20	17.5	0	0	4	13.3	16	22.2	0.01*
	<60 mmHg	94	82.5	12	100	26	86.7	56	77.8	
HR	>100 bpm	36	31.6	12	100	12	40	12	16.7	<0.001**
	60-100	78	68.4	0	0	18	60	60	83.3	

Initial investigations were started in ER lab during stabilization of the patients, CBC, serum creatinine, LFTs, basal PTT and PT/INR, Serum electrolytes and CRP are routinely evaluated table (9).

Table 9: The distribution of patients according to their laboratory investigation.

Investigations		Total= 114(100%)	Child-Pugh Score			P Value
			A = 12 (10.5%).	B = 30 (26.3%).	C = 72 (63.2%).	
Hb	Min - Max (Median)	7.2-20(10.5)	9.1-11.2(11)	7.2-16(11)	9-20(10)	0.7
	Mean±SD	10.5±2.22	10.7±0.76	11.1±2.22	10.73±2.39	
WBC	Min – Max (Median)	2140-13300(4900)	4500-6010(6010)	2900-7140(3500)	2140-13300(5150)	0.007*
	Mean±SD	5617±2728	5573±656	4319±1508	6165±3135	
Neutrophils	Min – Max (Median)	1134-9908(3077)	2800-4747(4098)	1566-5785(1978)	1134-9908(3082)	0.005*
	Mean±SD	4202±2648	4098±959	2915±1539	4756±3006	
Plateletes	Min – Max (Median)	26-216(130.5)	115-198(174)	56-163(131)	26-216(129)	0.02*
	Mean±SD	121±53.77	167±27	129±35	111±59	
SGOT	Min – Max (Median)	19-265(45)	22-34(23.5)	19-265(42)	19-234(54.5)	0.02*
	Mean±SD	73.78±69.5	26.9±5.2	68.5±78.96	83.8±68.2	
SGPT	Min – Max (Median)	12-310(36)59.5+64.1	13-33(22)	12-310(26)	16-240(48)	0.8
	Mean±SD	59.5±64.1	21.1±5.8	66.9±98	62.8±48.2	
T Bilirubin	Min – Max (Median)	0.4-8.5(2.7)	0.5-1.8(0.85)	0.4-2.8(1.8)	2.3-8.5(3.85)	<0.001**
	Mean±SD	3.2±1.9	1±0.44	1.7±0.7	4.12±1.7	
PTT	Min – Max (Median)	25-77(43)	39-45(43)	26-47(28)	25-77(45)	0.001*
	Mean±SD	42.2±12.3	42.3±1.9	34±7.7	45.5±13.3	
PT	Min – Max (Median)	15-50(18)	17-18(18)	15-18(16.5)	17-50(23.75)	<0.001**
	Mean±SD	21.8±7.6	17.6±0.6	16.8±0.9	24.7±8.3	
INR	Min – Max (Median)	1.13-3.8(1.4)	1.2-1.4(1.4)	1.13-1.4(1.4)	1.3-3.8(1.8)	<0.001**
	Mean±SD	1.7±0.6	1.3±0.09	1.3±0.09	1.9±0.6	
D Dimer	Min – Max (Median)	320-10000(5127)	320-560(460)	950-8870(1800)	1143-10000(6200)	<0.001**
	Mean±SD	4744±4141	440±86	3708±3338	5893±2497	
Albumin	Min – Max (Median)	2-3.8(2.6)	3.2-3.8(3.6)	2.7-3.6(3.25)	2-3.2(2.3)	<0.001**
	Mean±SD	2.72±0.55	3.52±0.24	3.22±0.3	2.38±0.32	
T Bilirubin	Min – Max (Median)	0.4-8.5(2.7)	0.5-1.8(0.85)	0.4-2.8(1.8)	2.3-8.5(3.85)	<0.001**
	Mean±SD	3.2±1.9	1.01±0.45	1.7±0.7	4.11±1.7	
S. K	Min – Max (Median)	2.3-5.3(3.8)	3.5-4(3.8)	3.1-4.8(3.4)	2.3-5.3(3.7)	0.2
	Mean±SD	3.87±0.8	3.8±0.2	3.68±0.6	3.98±0.9	
S Creatinine	Min – Max (Median)	0.24-3.6(0.7)	0.32-0.7(0.7)	0.3-1.1(0.9)	0.2-3.6(0.5)	0.4
	Mean±SD	0.7±0.44	0.6±0.1	0.75±0.2	0.7±0.5	

On ultrasonographical imaging, features of liver diseases chronicity were established and confirmed in all patients. table (10).

Table 10: The distribution of patients according to the result of abdominal ultrasonography.

Abdominal USG		Total= 114(100%)		Child-Pugh Score						P Value
				A = 12 (10.5%).		B = 30 (26.3%).		C = 72 (63.2%).		
		No	%	No	%	No	%	No	%	
Spleen size	Min - Max (Median)	12-20(15.5)		12-14(12)		12-16.5(14)		10-20(17.25)		<0.001**
	Mean±SD	15.4±2.7		12.7±0.98		14.2±2.02		16.3±2.82		
PV Diameter	Min - Max (Median)	10-22(12)		10-13(10)		10-18(14)		10-22(12.4)		0.05*
	Mean±SD	12.8±2.9		11±1.48		12.8±2.73		13.2±3.03		

Ascites		102	89.5	4	33.3	26	86.7	72	100	<0.001**
Feature of chronicity		114	100	12	100	30	100	72	100	1
Splenomegaly		88	77.2	4	33.3	20	66.7	64	88.9	<0.001**

Esophageal varices were identified in 102(89.5%) of total patient. Of note there is a difference of statistically important regarding Child-Pugh groups and varices, esophageal varices were identified in 12(100%), 30(100%) and 60(83.3%) of Child- Pugh A, B and C patients respectively. while 33.3 % of Child-Pugh C had have varices grade 2 to 3, all others groups had grades 3 to 4. table (11).

Table 11: The distribution of patients according to their UGIT endoscopy finding.c

Abdominal USG		Total= 114(100%)		Child-Pugh Score						P Value
				A = 12 (10.5%).		B = 30 (26.3%).		C = 72 (63.2%).		
		No	%	No	%	No	%	No	%	
Esophageal varices		102	89.5	12	100	30	100	60	83.3	0.02**
Grades	2 to 3	20	19.6	0	0	0	0	20	33.3	<0.001**
	3 to 4	82	80.4	12	100	30	100	40	66.7	

The D-dimer positively correlated with bilirubin, ascites and Child-Pugh points (R=0.44, P value = 0.009*; R=0.372, P value <0.001**; and R =0.401, P value <0.001** respectively). On the other hand, it negatively correlated with albumin (R=0.415, P value < 0.001**). Surprisingly, there were no correlations between D dimer and PT, INR and platelets count. table (12) and figures (4-6).

Table 12: The correlation of D-dimer with some clinical and paraclinical parameters

Correlation		Albumin	Bilirubin	Ascites	Child-Pugh points	PT	INR	Platelets count
D dimer	R	0.415	0.44	0.372	0.401	0.11	0.07	0.07
	P value	<0.001**	0.009*	<0.001**	<0.001**	0.23	0.4	0.4
	Direction	Negative	Positive	Positive	Positive	Negative	Negative	Negative

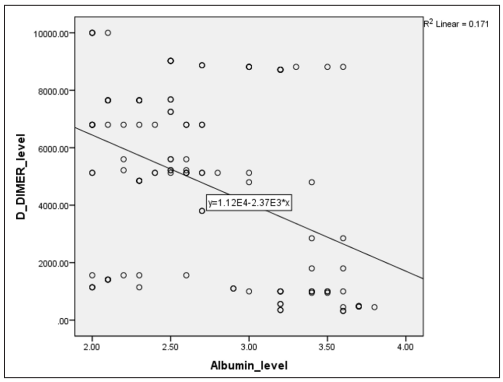

Figure 4: Shows correlation of D-Dimer with serum albumin level

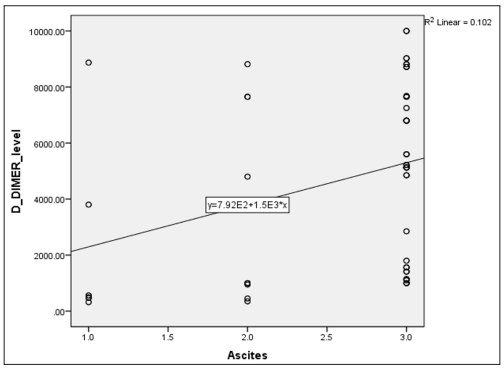

Figure 5: Shows correlation of D-Dimer with ascites

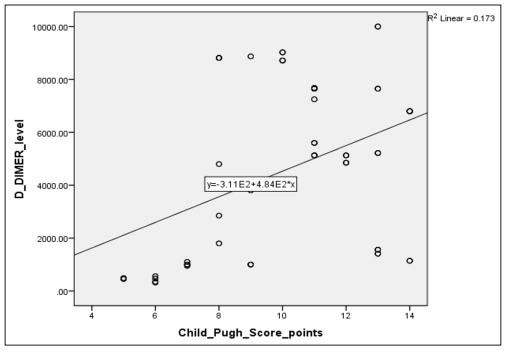

Figure 6: Shows correlation of D-Dimer with Child-Pugh Score points

Discussion

Coagulopathy and D-dimer level among 114 patients with CLD and cirrhosis were evaluated in this study. they were classified according to Child-Pugh score into A, B and C; and encountered in 10.5%, 26.3%, and 63.2% of total patients respectively. by the way, Baker et al. studied Child-Pugh score as predictor of short-term prognosis in Bangladesh, 2021 and found the incidence of Child-Pugh score A, B, and C was 8%, 28%, and 64% respectively [5] while Kumar, et al., studied Child-Pugh score as a better predictor of mortality than MELD in Karachi, 2018 among 165 patients, and reported that, Child's Class A, B, and C showed in 1.21% 38.65%, and 60.60% respectively [6]

In this study, male more affected than female, 63.2% vs 36.8% of total patients and this came in concordance with 68.5% vs

31.5% reported by Kumar et al, and 56.7% vs 43.3% reported by Siddiqui et al [6,7]. However, gender-specific distribution of patients among Child-Pugh score were nearly equal and as a reflection of their total percentages.

The age 40 years divided the affected patients into two halves. And, 72.2% of Child- Pugh C patients were younger (< 40 years old). On the other hand, 100% of Child- Pugh A, 86.7% of Child-Pugh B patients were 40 years old or older (P Value < 0.001**). By comparison, Siddiqui et al reported that 53.8% were older than 45 years old with male affected more than female.

All patients were Khat chewers. Khat chewing is unique habits for Yemeni and some African nations such as Ethiopian and Somalian. In this scope, Khat induced hepatitis is considered more recently as unique entity, in others words, disease per se and still in scope of research, however, some postulate that Khat triggers hepatitis either from toxin effect or drugs abuse or in just an immune susceptible patient and by the way, AIH relapse recurrent by Khat Chewing [8,9].

In this study, 17.5% of total patients were active smokers with a difference of statistically significance among Child-Pugh scores regarding smoking habits, all active smokers were in Child-Pugh C (P value 0.001*). in literature review, A history of smoking is observed in approximately 40% of patients with liver disease. Clinical evidence indicates that cigarette smoking negatively impacts the incidence and severity of CLD at multiple levels: cigarette smoking promotes hepatocarcinogenesis, represents a hepatic fibrogenic stimulus, exacerbates metabolic fatty liver diseases and negatively impacts liver-related outcomes at cellular, histologic, systemic, and clinical layer respectively [9-12].

Etiology of CLD and cirrhosis were known among most of our patients: autoimmune hepatitis, HBV, Bilharziasis, HCV accounting of 36.8%, 21.1%, 12.3% and 7% of total patients respectively. However, 22.8% of total patients were surprisingly of unknown etiology. By combining of AIH and Unknown etiology together, they constituted more than 50% of causes and hence we can recall Khat chewing effects as previously detailed and supported by many published papers. By the way, while viral hepatitis either B or C or coinfection were recognized as the main cause of CLD by Siddiqui et al, 10% was of unknown cause and AIH was not reported. This is indirectly going with the effect of Khat chewing in countries where chewing Khat habit well recorded.

Increased fatiguability was in every patient. Others presented symptoms were, Distended abdomen (ascites and splenomegaly), Discoloration of the body (jaundice), GIT bleeding (hematemesis and melena), Change LOC (encephalopathy), and Anuria. accounting of 89.5%, 70.2%, 56.1%, 52.6% and 3.5% of total patients respectively.

In context of distended abdomen, abdominal USG confirmed the presence of ascites in 89.5%, and splenomegaly in 77.2% of total patients. These percentages in our study were a higher than 53.8%, and 66.1% which reported by Siddiqui et al respectively. US is operator depended machine and the aim of each study may stand beyond these slight differences. Of note, presence of ascites and splenomegaly incrementally proportionated with Child-Pugh score; The higher score hence severity of disease, the higher percentage of ascites and splenomegaly, (P-vale < 0.001**). By the same side, Jaundice and encephalopathy recognized among 70.2% and 52.6% which were higher than 48.5%, and 30.4% of total patients reported by Siddiqui et al respectively. on the opposite side, GI bleeding found among 56.1%of total in this study which was slightly lower than 71.9% which reported by [7].

Although bleeding events found in direct proportion with stage of liver disease, - the higher stage then severity, the higher bleeding events-, esophageal varices of grade 3 to 4 discovered in all patients of Child-Pugh A and B while only in 83.3% of Child-Pugh C of them 66.7% in the same grade. So, GIT bleeding rather than presence of esophageal varices of any grade responsible of decompensation and severe stage of CLD. High portal pressure, thrombocytopenia, decrease production of coagulation factors (elevated PT/INR) and increased tissue plasminogen level are factors come in favors of bleeding tendency (Valla et al., 2014). In this context, platelets count ranged between 26-216(130.5), 115-198(174), 56-163(131), and 26-216(129) of total, Child-Pugh A, B and C respectively. All thrombocytic patients below 50k found only in Child-Pugh C, while those who had platelets count bellow 100k but > 50k found in C and B. This result in consistent with most previously mentioned studies in the literature [13]. Many pathophysiological mechanisms can explain thrombocytopenia in CLD such as increased splenic pooling, shortened life span due increased splenic destruction, increased antibody mediated platelet destruction, relative bone marrow insufficiency, and decreased thrombopoietin secretion [14].

Similarly, PT (seconds) prolonged among 94.7% of total patients and it ranged between 15-50(18), 17-18(18), 15-18(16.5), and 17-50(23.75) and INR (%) ranged between 1.13-3.8(1.4), 1.2-1.4(1.4), 1.13-1.4(1.4), and 1.3-3.8(1.8) for total, Child- Pugh A, B, and C respectively. So, it was clear that, the median of PT/INR in Child- Pugh C patients were prolonged/elevated while that of Child-Pugh A and B were slightly elevated or nearly normal. Although 90.6% of GIT bleeding had prolonged PT/INR and 9.4% had normal PT/INR values, the last presented in decompensated stages B and C. So, advanced CLD stages may predict bleeding events even with normal PT/INR value, this agreed with Tripodi et al [15,16].

However, many factors come in favors of thrombotic tendency Low portal venous blood flow, Immobilization-related venous stasis, Increased vW factor level, increased high molecular weight vW factor levels (decreased ADAMTS13 levels) Decreased antithrombin, protein C and protein S level, Increased factor VIII levels, decreased plasminogen, factor XIII, a2 antiplasmin and TAFI levels, and Increased PAI-1 levels [14]. These factors D-dimer was measured and found in direct proportion with stage of liver disease, the higher stage then severity of liver disease, the higher D-dimer level. D-dimer ranged between 320-10000(5127), 320-560(460), 950-8870(1800), and 1143 -10000(6200) for total, Child-Pugh A, B, and C respectively. of note, D-dimer of Child- Pugh patients based on normal cut off point of 500. On the other hand, patients in Child-Pugh B and C groups showed high D-dimer levels. furthermore, there were strong positive correlation between elevated D-dimer and severity of the disease. In the context, elevated D-dimer among

CLD and cirrhotic liver is well known in literatures, Primignani et al. (2017), Dhanunjaya et al. Wesam A. Ibrahim, Sara Abdelhakam et al. in 2011, Spadero et al. and [17].

Moreover, Dhanunjaya et al, found that was to be strongly increased significantly with severity of liver disease. on the other hand, A part of high D-dimer levels and the time of sample recruitment for this study which was during 1st pandemic episode of COVID-19, there was no thrombotic event, however the possibility of infection with and effect of COVID-19 can't be excluded. Our study showed a statistically significant negative correlation of D dimer levels with albumin level R-Value (-0.415) P-Value < 0.001**. And positive correlation with bilirubin level R-Value (0.44) P-Value=0.009**, ascites R-Value (0.372) P-Value < 0.001** and Child-Pugh points R-Value (0.401) P-Value < 0.001**. These correlations came in concordance withSurprisingly there were no statistically significant D-dimer correlations with platelets count, Prothrombin time and INR in patients with CLD and this disagree with Wesam A. Ibrahim, Sara Abdelhakam et al [18].

Conclusion

Coagulopathy and bleeding tendency in direct proportion with severity of CLD defined by Child-Pugh score. D-dimer correlated well with advanced stages of CLD even in absence of clear evidence of thrombotic events [19-21].

Limitation

- Poverty of similar study in our country and Arabic regions.
- The availability of certain laboratory tests for evaluation of coagulopathies was one of critical obstacle issues.

Recommendation

- Adoption and promotion of research activities of higher quality and good evidence in the same subject to explore, develop and validate new diagnostic and prognostic criteria and tools that integrate traditional with novel biomarkers including D-dimer.
- Establishment of specialized hepatic research center on the level of our country and governorates.
- Highlight on the effect of Khat chewing and smoking on liver either establishment or evolving its severity by different national medias.

Data Availability

All data are available including:

- Patients' history and physical examination files
- Patients' investigations files
- Imaging files
- All statistical raw data
- Others supplementary files

Author Contribution

1.Abdo Ali Hezam is the Main Author
He collects, analyses and interpret the data
He also writes and coordinates the whole research.
2.Khalid Alqubati is the Supervisor Author
He supervises, guide, follow and contribute in data analysis and discussion.

Conflict to the Interests

No interest of conflict

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Ethical Statement

Ethical and Research committee in faculty of medicine, Taiz university approved this proposal formally before starting to collect the cases.

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