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Coagulopathies in Patients with Liver Cirrhosis Presenting to DHQ Teaching Hospital, Dera Ismail Khan

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ABSTRACT

The liver develops fibrosis and nodules due to persistent damage, altering its natural lobular organization, known as cirrhosis. Various assaults such as toxic substances, viral infections, autoimmunity, or genetic disorders can damage the liver. Each lesion leads to fibrosis, or scar tissue formation, initially maintaining its functionality. **Objective:** To determine the frequency of coagulopathies occurring in patients with liver cirrhosis. **Methods:** This descriptive cross-sectional study was conducted in the General Medicine department at DHQ Teaching Hospital, D.I Khan, from June 12, 2022, to December 12, 2022. A total of 240 patients were recruited using non-probability consecutive sampling to determine the frequency of coagulopathies occurring in patients with liver cirrhosis. Coagulation tests, including prothrombin time and activated partial thromboplastin time, were performed. Data on age, gender, diabetes mellitus, hypertension, smoking status, and coagulopathies were recorded on a pre-designed proforma. Analysis was done using SPSS 20.0. Means and standard deviations were calculated for age and frequencies and percentages for categorical variables. Coagulopathies were stratified by gender, diabetes, hypertension, and smoking status to assess effect modifications. Post-stratification chi-square tests were applied, with $P < 0.05$ as significant. **Results:** The mean age was 45.56 ± 3.357 years. Males comprised 127 (52.9%) and females 113 (47.1%). Age distribution was 12.9% (20-30 years), 24.6% (31-40 years), 47.5% (41-50 years), and 15.0% (51-60 years). Coagulopathies were present in 74 (30.8%) patients, while 166 (69.2%) had none. Ninety patients (37.5%) had normal PT, lasting less than 15 seconds (mean + SD = 11.28 ± 2.02 sec), while 121 patients (50.4%) had prolonged PT (mean + SD = 22.94 ± 5.93 sec) and indicates a statistically significant difference of PT. **Conclusions:** Patients with cirrhosis had significantly higher and prolonged PT and APTT values, indicating an increased risk of coagulopathies.

INTRODUCTION

Liver cirrhosis is a severe condition where healthy liver tissue is replaced by scar tissue, impairing liver function [1]. One of the essential functions of the liver is the production of proteins responsible for blood clotting. In liver cirrhosis, the production of these clotting factors is decreased, leading to an increased risk of bleeding [2]. This condition results from various etiologies, including viral infections, autoimmune diseases, alcohol abuse, and genetic predispositions [3]. In the Global Burden Disease Study 2017, the estimated number of people with compensated cirrhosis was 112 million worldwide, corresponding to an age-standardized global prevalence of compensated cirrhosis of 1,395 cases per 100,000 populations [4]. The global incidence of liver cirrhosis is 2.4% of global deaths in 2021, highlighting regional differences in disease burden and risk factors, including hepatitis B and C infections, prevalent in many Asian countries and Pakistan [5, 6]. Data from the Southeast Asia region are similarly limited. In one study, the most common etiology among 4,413 patients with cirrhosis from 11 hospitals was alcohol consumption (34%), followed by other causes (29%), HBV infection (18%), HCV infection (17%) and NAFLD (2%) [7]. However, among 192 people with cirrhosis who underwent endoscopic band ligation in a

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hospital in Pakistan, cirrhosis was attributed to HCV infection in 63% and to HBV infection in 19% [8]. Understanding the pathophysiology of cirrhosis involves multiple cellular interactions, including hepatocytes, Kupffer cells, sinusoidal endothelial cells, and hepatic stellate cells. Chronic liver injury triggers inflammatory responses and oxidative stress, promoting fibrogenesis and disrupting liver architecture. Portal hypertension and hyperdynamic circulation are common complications, contributing to increased morbidity and mortality in cirrhotic patients [9]. Recent studies from 2019 to 2024 have highlighted various findings regarding coagulation abnormalities in liver cirrhosis. For instance, research by Ren W et al., in 2020 identified a high prevalence of prolonged Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) in cirrhotic patients, indicating significant impairments in clotting function [9-11]. Moreover, recent advancements in understanding coagulopathies in cirrhosis have emphasized the complex interplay between hemostasis and thrombosis. For example, research by La Mura V et al., in 2022 explored the paradoxical presence of both hypercoagulable and hypercoagulable states in cirrhotic patients, complicating clinical management strategies [10, 12]. Knowing the specific clotting abnormalities present in a patient with liver cirrhosis is crucial for guiding treatment decisions. For instance, depending on the type of coagulopathy, doctors may prescribe medications like vitamin K or blood products to prevent or manage bleeding complications Coagulopathies are significant clinical concerns in cirrhosis management, characterized by both decreased synthesis of clotting factors and platelet dysfunction. This study aimed to investigate the prevalence and characteristics of coagulopathies in cirrhotic patients at DHQ Teaching Hospital, D.I Khan, providing insights into tailored treatment strategies and improving patient care outcomes. The presence and severity of coagulopathies can also be an indicator of the overall health status and prognosis of patients with liver cirrhosis. Focusing on patients with liver cirrhosis presenting at the District Head Quarter Hospital MTI, D.I Khan provides valuable data on the prevalence and characteristics of coagulopathies in this specific patient population. This information can help tailor treatment strategies and identify areas for improvement in patient care at this facility. To determine the frequency of coagulopathies occurring in patients with liver cirrhosis presenting to District Head Quarter Hospital MTI, D.I Khan.

METHODS

This descriptive cross-sectional study was done at the Department of General Medicine, District Head Quarter Hospital MTI, Dera Ismail Khan (D.I. Khan) from 12th June 2022 to 12th December 2022. The sample size was 240, calculated using a 20% prevalence of hypocoagulability, with a 95% confidence interval and a 5% margin of error using the WHO Sample Size Calculator [13]. The sampling technique used was nonprobability consecutive. The inclusion criteria adopted were patients with liver cirrhosis, aged 20-60 years, with or without diabetes mellitus, hypertension, or smoking history, were included. Patients having co-morbidities such as chronic kidney disease and ischemic heart disease and pregnant women were excluded from the study. Before starting the study, Ethical approval was taken from the institutional review board under the approval No. 201 /DMR/ADR of Gomal Medical College D.I Khan. The aim and the objective of the study were conveyed to all the patients and written informed consents were taken. All patients were subjected to conventional coagulation testing; such as prothrombin time (PT), and Activated Partial Thromboplastin Time (aPTT). The prothrombin was divided as normal range (2-15 sec) and prolonged as (>15 sec). And Partial Thromboplastin Time was divided as Normal (30-40 sec) and Prolonged (>40 sec). Information such as age, gender, diabetes mellitus, hypertension, smoking status, and coagulopathies was recorded on a separate proforma. Data were entered and analyzed in SPSS version 20.0. Mean ± SD were calculated for numerical variables like age. Frequencies and percentages were calculated for quantitative variables. Coagulopathies were stratified according to gender, diabetes mellitus, hypertension, and smoking status promthombintime and Partial Thromboplastin Time to see effect modifications. Post-stratification chi-square tests were applied keeping P value < 0.05 as significant.

RESULTS

According to age-wise distribution, 20-30 years were 31(12.9%), 31-40 years was 59(24.6%), 41-50 years were 114(47.5%) and 51-60 years were 36 (15.0%). According to gender distribution, males were 127(52.9%) and females were 113(47.1%). There were 74(30.8%) patients having coagulopathies and 166(69.2%) were having no coagulopathies. There were 64 (26.7%) diabetic and 176 (73.3%) non diabetic patients. Out of 240 patients, 92 (38.3%) were smokers and 148 (61.7%) were nonsmokers. 78 (32.5%) were having hypertension and 162 (67.5%) were having normal blood pressure. Stratification of coagulopathies according to age and gender was shown in table no.1 with significant p values of 0.001. Stratification of coagulopathies according to DM and hypertension and smoking was shown in table no.2 with only significant p value of 0.001 for hypertension while p values for diabetes mellitus (0.023) and smoking statues (0.034) were insignificant.

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Table 1: Stratification of Coagulopathies According To Age and Gender(n=240)

Age	Coagulopathies N (%)		Total N (%)	p-Value
	Yes	No		
20-30 Years	24 (77.4%)	7 (22.6%)	1 (100%)	0.001
31-40 Years	14 (23.7%)	45 (76.3%)	59 (100%)	
41-50 Years	27 (23.7%)	87 (76.3%)	114 (100%)	
51-60 Years	9 (25.0%)	27 (75.0%)	36 (100%)	
Total	74 (30.8%)	166 (69.2%)	240 (100%)	
Gender				
Male	34 (26.8%)	93 (73.2%)	127 (100%)	0.001
Female	40 (35.4%)	73 (64.6%)	113 (100%)	
Total	74 (30.8%)	166 (69.2%)	240 (100%)	

Ninety patients (37.5%) had normal PT, lasting less than 15 seconds (mean + SD = 11.28 ± 2.02 sec), while 121 patients (50.4%) had prolonged PT (mean + SD = 22.94 ± 5.93 sec). Table 3 indicated a statistically significant difference of PT in cirrhosis of the liver (p value <0.05). In this study, 105 (43.75%) patients had normal APTTs, meaning they took less than 40 seconds (mean + SD = 34.12 ± 2.32 sec), while 135 (56.25%) patients had prolonged APTTs (mean + SD = 46.42 ± 5.58sec).

Table 2: Stratification of Coagulopathies According to Diabetes Mellitus, Smoking Status and Hypertension (n=240)

Diabetes Mellitus	Coagulopathies N (%)		Total N (%)	p-Value
	Yes	No		
Yes	34 (53.1%)	30 (46.9%)	64 (100%)	0.023
No	40 (22.7%)	136 (77.3%)	176 (100%)	
Total	74 (30.8%)	166 (69.2%)	240 (100%)	
Smoking Status				
Yes	34 (37.0%)	58 (63.0%)	92 (100%)	0.034
No	40 (27.0%)	108 (73.0%)	148 (100%)	
Total	74 (30.8%)	166 (69.2%)	240 (100%)	
Hypertension				
Yes	34 (43.6%)	44 (56.4%)	78 (100%)	0.001
No	40 (24.7%)	122 (75.3%)	162 (100%)	
Total	74 (30.8%)	166 (69.2%)	240 (100%)	

Table 3 presented a statistical analysis demonstrating the significant increase of APTT in liver cirrhosis (p-value <0.05).

Table 3: Partial Thromboplastin Time in Cirrhotic Patients

Partial Thromboplastin Time	N (%)
Normal (30-40 Seconds)	105 (43.75%)
Prolonged	135 (56.25%)
Total	240 (100%)

P-Value < 0.05 (Significant)

DISCUSSION

The results of this study show that a hypercoagulable state does exist in liver cirrhosis confirming the findings of Wan J *et al.*, who demonstrated that the ratio between the thrombin generation with and without TM was able to indicate a condition which represents a resistance to the natural anticoagulant activity of TM. This was an endothelial receptor for thrombin dedicated to the conversion of Protein C to its activated form [12, 14]. Some mechanisms were involved in the pathogenesis of the hypercoagulable state in liver cirrhosis such as an increased level of von Will brand factor, a decreased level of natural anticoagulants and elevated levels of intravascular tissue factor [15]. Again, the concomitant and opposite behavior of Protein C (decreased), and factor VIII (increased) can further explain why cirrhotic patients present such a complex hemostatic abnormality. All these biochemical pathological conditions can lead to a higher risk for venous thromboembolism [16]. Table 3 indicates a statistically significant difference of PT In this study, the mean prothrombin time was 18.36 ± 6.9 seconds. In 121 (50.4%) patients, PT was prolonged (mean + SD = 22.94 ± 5.93 sec) while in 90 (37.5%) patients had normal PT which was less than 15 seconds (mean + SD = 11.28 ± 2.02 sec). This finding concur with those of Vecerzan L *et al.*, cirrhotic patients had a higher prothrombin time (beta = 0.908, P = 0.004) [17]. Prolonged prothrombin times have also been documented in cirrhotic patients by other research. Bohania N et al., in 2022 reported prolonged PT, aPTT, was noted in 27 (35%) and 27 (35%), respectively and a most common cause of prolonged PT and aPTT was liver disease in 11 (14%) in this study, a progressive delay in prothrombin time associated with altered APTT was not significantly noted in the patients with liver cirrhosis [18]. In this study, the mean activated partial thromboplastin time was 38.05 ± 6.23 seconds. In 135 (56.25%) patients, APTT was prolonged (mean + SD = 46.42 ± 5.58sec). 105 (43.75%) patients had normal PT which was less than 15 seconds (mean + SD = 34.12 ± 2.32 sec). Patients with chronic and acute liver disease may acquire complex disorders of their hemostatic system. Although alterations in routine diagnostic tests of hemostasis (thrombocytopenia and PT/APTT prolongation) were suggestive for a bleeding tendency, patients with liver disease were in hemostatic balance due to the simultaneous decline of pro- and anticoagulant drivers. No study to date favors this finding which can be due to the small sample size of this study or single setting study location. In contrast, Liliana Vecerzan L *et al.*, in 2021 Parameters of classical coagulation tests (APTT, PT) were significantly higher in cirrhotic than in hepatitis patients [19]. Another study reported Severity of liver dysfunction showed a significant association (p<0.05) with prolongation of Prothrombin Time (PT), activated partial thromboplastin time (aPTT) [17, 20]. Deficits or anomalies in factors 'VII, IX, XI, XII, X, V', 'II (prothrombin)',

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and 'I (fibrinogen)' cause an extension of the 'APTT in cirrhosis'. The fact that the aforementioned work was consistent with earlier research workers' findings was quite intriguing. In liver illnesses, 'prothrombin time' was frequently elevated because the liver cannot produce enough 'clotting factors', particularly those that were part of the extrinsic pathway. 'Factor VII has the biggest impact on the prothrombin time among factors II, V, VII, and X since it was the pathway's rate-limiting factor'. The prognosis was poor for factor VII fall, which has the 'shortest half-life' (6 hours). Because the liver also produces fibrin stabilizing factors, 'factors IX, XI, and XII', and when liver function declines, the APTT may become abnormal [20]. This study's findings regarding the lengthening of PT and APTT point to the possibility that anomaly results from the liver cirrhosis patients' growing liver damage. However, it has been found that the clot formation of patients with liver cirrhosis was weak when measured by means of the Clot Waveform Analysis (CWA) which showed hidden parameters of both PT ratio and a PTT ratio, i.e., the 1st and 2nd derivatives. A significant association between the PT ratio and the clot waveform analysis with both the hemorrhagic score and the history positive for bleeding in the cirrhotic patients has been also described [16].

CONCLUSIONS

Patients with cirrhosis of the liver had considerably higher and prolonged PT values. Patients with cirrhosis also exhibited raised and prolonged APTT values.

Authors Contribution

Conceptualization: SR
Methodology: AR, GM
Formal analysis: TA, AR, GM
Writing, review and editing: SK, MUH, TA, SR

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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REFERENCES

[1] Tanwar S, Rhodes F, Srivastava A, Trembling PM, Rosenberg WM. Inflammation and fibrosis in chronic liver diseases including non-alcoholic fatty liver disease and hepatitis C. World Journal of Gastroenterology. 2020 Jan; 26(2): 109. doi: 10.3748/wjg.v26.i2.109.

[2] Zermatten MG, Fraga M, Moradpour D, Bertaggia Calderara D, Aliotta A *et al.* Hemostatic alterations in patients with cirrhosis: from primary hemostasis to fibrinolysis. Hepatology. 2020 Jun; 71(6): 2135-48. doi: 10.1002/hep.31201.

[3] GinËs P, Krag A, Abraldes JG. Solǂ E, Fabrellas N, Kamath PS. Liver Cirrhosis. Lancet. 2021 Oct; 398(10308): 1359-76. doi: 10.1016/S01406736(21)01374-X.

[4] Sepanlou SG, Safiri S, Bisignano C, Ikuta KS, Merat S, Saberifiroozi M *et al.* The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet Gastroenterology & Hepatology. 2020 Mar; 5(3): 245-66. doi: 10.1016/S2468-1253(19)30349-8.

[5] Huang DQ, Terrault NA, Tacke F, Gluud LL, Arrese M, Bugianesi E *et al.* Global epidemiology of cirrhosis-aetiology, trends and predictions. Nature Reviews Gastroenterology & Hepatology. 2023 Jun; 20(6): 388-98. doi: 10.1038/s41575-023-00759-2.

[6] Islam R, Kundu S, Jha SB, Rivera AP, Monar GV, Islam H, Puttagunta SM, Sange I. Cirrhosis and coagulopathy: mechanisms of hemostasis changes in liver failure and their management. Cureus. 2022 Apr;14(4). doi: 10.7759/cureus.23785.

[7] Kim A, Niu B, Woreta T, Chen PH. Clinical considerations of coagulopathy in acute liver failure. Journal of Clinical and Translational Hepatology. 2020 Dec 12;8(4):407. doi:10.14218/JCTH.2020.00058.

[8] Gracia-Sancho J, Caparrós E, Fernández-Iglesias A, Francés R. Role of liver sinusoidal endothelial cells in liver diseases. Nature reviews Gastroenterology & Hepatology. 2021 Jun; 18(6): 411-31.doi:10.1038/s41575-020-00411-3.

[9] Ren W, Zhang J, Chen Y, Wen M, Su Y, Zhao Y *et al.* Evaluation of coagulation, fibrinolysis and endothelial biomarkers in cirrhotic patients with or without portal venous thrombosis. Clinical and Applied Thrombosis/Hemostasis. 2020 Dec; 26: 1076029620982666. doi: 10.1177/1076029620982666.

[10] La Mura V, Bitto N, Tripodi A. Rational hemostatic management in cirrhosis: from old paradigms to new clinical challenges. Expert Review of Hematology. 2022 Dec; 15(12): 1031-44. doi:10.1080/17474086.2022.2144217.

[11] Chen H, Liu L, Qi X, He C, Wu F, Fan D et al. Efficacy and safety of anticoagulation in more advanced portal vein thrombosis in patients with liver cirrhosis. European Journal of Gastroenterology & Hepatology. 2016 Jan; 28(1): 82-9.doi:10.1097/MEG.0000000000000482.

[12] Wan J, Konings J, de Laat B, Hackeng TM, Roest M. Added value of blood cells in thrombin generation

DOI: https://doi.org/10.54393/pjhs.v5i10.1726

testing. Thrombosis and Haemostasis. 2021 Dec; 121(12): 1574-87. doi: 10.1055/a-1450-8300.

[13] Gish RG, Regenstein FG, Flamm SL, Stravitz RT, Brothers JM. Guidance for coagulation management in patients with acute or chronic liver failure. Gastroenterol. Hepatol. 2021 Jan; 17: 3-26.

[14] Ruberto MF, Piras MS, Sorbello O, Civolani A, Usai P, Fanni D *et al.* Chronic intravascular coagulation in liver cirrhosis predicts a high hemorrhagic risk. European Review for Medical & Pharmacological Sciences. 2021 Sep; 25(17): 5518-5524. doi: 10.26355/eurrev_202109_26663.

[15] Zhong HJ, Xiao P, Lin D, Zhou HM, He XX. Cirrhosis in Wilson disease is characterized by impaired hepatic synthesis, leukopenia and thrombocytopenia. International Journal of Medical Sciences. 2020 May; 17(10): 1345. doi: 10.7150/ijms.44338.

[16] Hazim AZ, Ruan GJ, Khodadadi RB, Slusser JP, Marshall AL, Pruthi RK. A single-institution retrospective study of causes of prolonged prothrombin time and activated partial thromboplastin time in the outpatient setting. International Journal of Laboratory Hematology. 2022 Feb; 44(1): 209-15. doi: 10.1111/ijlh.13727.

[17] Vecerzan L, Olteanu A, Maniu I, Boicean A, Cipăian CR, Dura H *et al.* Thrombin generation in chronic liver diseases-a pilot study. InHealthcare 2021 May; 9(5): 550. doi: 10.3390/healthcare9050550.

[18] Bohania N, Agrawal A, Prakash A, Nangia A, Kumar A. Coagulation profile and its correlation with severity of liver dysfunction and gastrointestinal bleed in alcoholic liver disease patients. Journal Association Physicians India. 2021 Jun; 69(6): 11-2.

[19] Bulut Y, Sapru A, Roach GD. Hemostatic balance in pediatric acute liver failure: epidemiology of bleeding and thrombosis, physiology, and current strategies. Frontiers in Pediatrics. 2020 Dec; 8: 618119. doi: 10.3389/fped.2020.618119.

[20] Sadamatsu K, Kugai T, Eto Y, Muta M, Maeda T, Ishimatsu T, et al. Manual compression hemostasis using a hemostatic pad for the distal radial artery approach. Cardiovascular Revascularization Medicine. 2024 May. doi: 10.1016/j.carrev.2024.05.028.