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Relationship Between Liver Disease Severity and Coagulation Dysfunction: Insights from a Tertiary Care Study

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ABSTRACT

Background: Liver disease, which can range from acute failure to cirrhosis, disturbs coagulation by impairing procoagulant and anticoagulant factor synthesis, which is essential to bleeding or thrombosis. Conservative tests like PT and activated partial thromboplastin time (aPTT) have limits, while advanced approaches like TEG and ROTEM offer better assessment. Sympathetic, this relationship is critical for optimising diagnostic and therapeutic approaches in liver disease management.

Methods: This retrospective observational study, conducted at a tertiary care center, investigates the relationship between liver disease severity and coagulation dysfunction in 310 patients with chronic liver disease, cirrhosis, and hepatocellular carcinoma. The study assesses the association between liver disease progression and changes in coagulation parameters. The occurrence of coagulation disorders was evaluated, and the efficacy of viscoelastic testing methods in measuring coagulation dysfunction was analysed.

Results: Among 310 liver disease patients, 20% had normal coagulation, while 35% had a single disorder (n=109), 20% had two (n=62), and 25% had three or more (n=77). Treatment success was highest in patients with one disorder (96.5%), decreasing to 94.4% in those with two and 95.2% in those with three or more. Mortality increased with severity, reaching 25% in complex cases, indicating a strong association between multiple coagulation abnormalities and poor outcomes.

Conclusion: This study confirms a strong correlation between liver disease severity and coagulation dysfunction. The progression of liver disease increases the likelihood of multiple coagulation abnormalities, influencing both treatment outcomes and mortality

Key-words: Liver disease, Coagulation dysfunction, Cirrhosis, Hepatocellular carcinoma, Child-Pugh score, MELD score, Prothrombin time

INTRODUCTION

Liver disease includes a broad spectrum of circumstances, fluctuating from acute liver failure to chronic liver diseases such as cirrhosis and hepatocellular carcinoma. [1] The liver is essential in various physiological procedures, including metabolism, detoxification, and synthesising proteins necessary for coagulation. [2] Any impairment in liver function can profoundly affect haemostatic balance, prompting entities to either bleeding or thrombotic difficulties. [3]

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Coagulation is a compound physiological procedure concerning a delicate interaction between procoagulant, anticoagulant, and fibrinolytic pathways. The liver is the leading site of synthesis for maximum coagulation factors, including fibrinogen, prothrombin (factor II), and factors V, VII, IX, X, XI, and XII. [4] It is also responsible for producing key anticoagulant proteins such as protein C, protein S, and antithrombin. [5] The liver synthesises plasminogen, a vital enzyme involved in fibrinolysis. Any degree of hepatic dysfunction may disturb this balance, resulting in a coagulopathy that demonstrates either a tendency for extreme bleeding or an increased risk of thrombosis. [6]

Patients with chronic liver disease (CLD) frequently exhibit irregularities in standard coagulation tests such as prothrombin time (PT), aPTT, and international normalised ratio (INR). These tests have been used to

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evaluate bleeding risk in liver disease. [7] Still, emergent evidence proposes that they do not entirely reflect the complications of coagulation changes in hepatic impairment. As an alternative to a simple bleeding disorder, liver disease-associated coagulopathy is now recognised as a condition of rebalanced haemostasis, where both procoagulant and anticoagulant factors are reduced. This changed state increases the risk of impulsive bleeding in certain circumstances while also increasing the risk of thrombosis, predominantly in the portal and hepatic veins. [8]

The severity of liver disease is directly associated with the degree of coagulation dysfunction. In early-stage liver disease, minor alterations in coagulation parameters may be observed without important clinical significance. [9] However, as liver disease develops into cirrhosis and end-stage liver failure, the synthesis of coagulation factors declines considerably, and complications such as variceal haemorrhage and disseminated intravascular coagulation (DIC) become more predominant. [10] In addition, the presence of systemic inflammation and endothelial dysfunction exacerbates coagulation irregularities, generating a state of chronic low-grade intravascular coagulation that underwrites multi-organ dysfunction. [11]

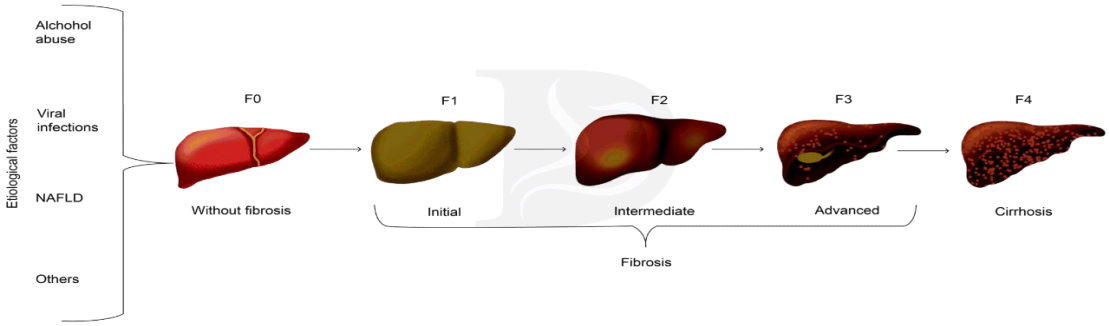

Fig. 1: Liver cirrhosis (Cirrhosis - Digestive and Liver Health Specialists)

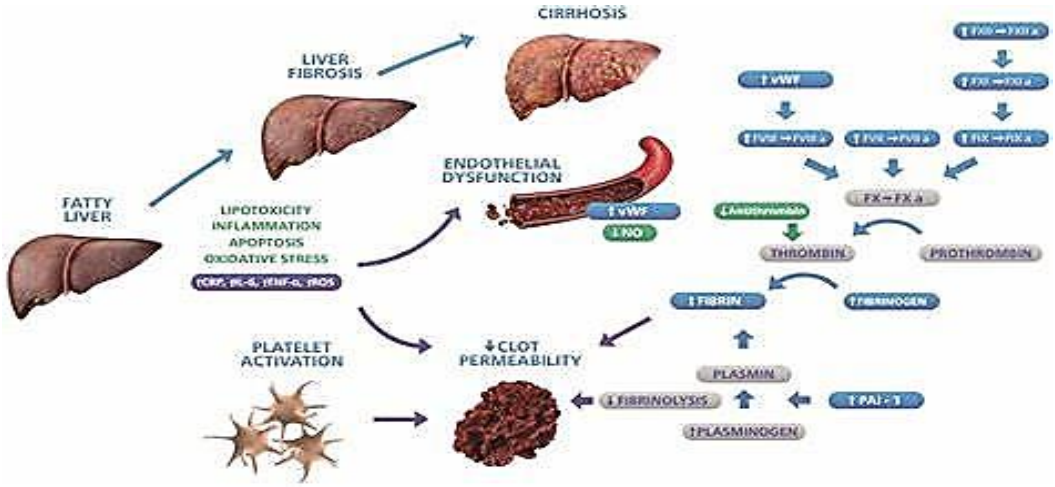

Fig. 2: Effect of liver

One of the most severe complications of liver disease-related coagulopathy is impulsive or procedure-related bleeding. Patients with cirrhosis, for example, frequently develop gastrointestinal varices due to portal hypertension, which poses a significant risk of life-threatening haemorrhage. [12] Also, aggressive measures such as liver biopsy, paracentesis, or surgery necessitate a careful pre-procedural evaluation of coagulation status to minimise the risk of extreme bleeding.

The discriminating risk of thrombosis in liver disease is often undervalued. [13] Portal vein thrombosis (PVT) is a well-recognised thrombotic difficulty of cirrhosis, and studies recommend that patients with advanced liver disease are also at increased risk for deep vein thrombosis (DVT) and pulmonary embolism (PE), despite having abnormal standard coagulation test results indicative of a bleeding predisposition. [14]

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Recent progressions in haemostasis research have emphasised the limitations of predictable coagulation tests in liver disease. Viscoelastic testing methods such as thromboelastographic (TEG) and rotational thromboelastometry (ROTEM) have appeared as superior tools for measuring global coagulation profiles in these patients. [15] Different PT and aPTT, which measure isolated features of the coagulation cascade, TEG and ROTEM, provide a dynamic assessment of clot formation, stabilisation, and lysis, offering a more comprehensive evaluation of bleeding and thrombotic risks. These tests have been established as predominantly valuable in controlling blood product transfusion approaches and anticoagulation therapy in patients with progressive liver disease. [16]

The administration of coagulation abnormalities in liver disease requires a nuanced approach. By tradition, fresh frozen plasma (FFP) and platelet transfusions have been used to correct coagulation abnormalities before invasive procedures. Still, their efficacy remains doubtful, and they may contribute to volume overwork and other problems. [17] The use of targeted therapies such as recombinant factor VIIa and prothrombin complex concentrates (PCCs) is under examination, and anticoagulation therapy for thrombotic complications remains controversial, requiring a cautious risk-benefit evaluation.

Sympathetic to the complicated relationship between liver disease severity and coagulation dysfunction is critical for optimising patient outcomes.[18] This study aims to explore the correlation between liver disease progression and haemostatic modifications using data from a tertiary care centre, and whether this understanding may assist in developing enhanced diagnostic and therapeutic approaches.

MATERIALS AND METHODS

Research Design- This retrospective observational study was conducted during the period of one year at a tertiary care center to evaluate the relationship between liver disease severity and coagulation dysfunction in 310 patients. Data were collected from medical records of patients with various stages of chronic liver disease, cirrhosis, and hepatocellular carcinoma.

The study aimed to assess the association between liver disease development and changes in coagulation parameters, including prothrombin time, activated partial thromboplastin time, international normalised ratio, fibrinogen levels, and platelet count. These parameters were evaluated based on the Child-Pugh classification and Model for End-Stage Liver Disease scores, which are extensively used to control liver disease severity.

Patients with recognised coagulation abnormalities were additionally categorised based on their risk of bleeding and thrombotic problems. The study also analysed the efficacy of viscoelastic testing methods, such as thromboelastographic and rotational thromboelastometry, in expansively measuring coagulation dysfunction in liver disease.

Inclusion Criteria

- Analysed with chronic liver diseases, cirrhosis, or hepatocellular carcinoma at the tertiary care center.
- The coagulation limitations, such as PT, aPTT, INR, fibrinogen, and platelet count, were known during diagnosis and follow-up.
- Age ≥ 18 years with a recognised diagnosis of liver disease through imaging, biopsy, or clinical evaluation.
- Accessible records of Child-Pugh or MELD scores to assess liver disease severity.
- Patients who experienced invasive procedures such as liver biopsy, paracentesis, or surgery and had pre-procedural coagulation evaluations.

Exclusion Criteria

- Patients with acute liver failure or temporary liver dysfunction unrelated to chronic liver disease.
- Patients getting anticoagulation therapy for non-liver-related circumstances (e.g., atrial fibrillation, deep vein thrombosis).
- Patients with genetic coagulation disorders (e.g., haemophilia, von Willebrand disease) that could confuse the study results.
- Incomplete medical records with missing coagulation data or liver function evaluations.
- Patients with active malignancies (excluding hepatocellular carcinoma) or those experiencing chemotherapy, which could affect coagulation status and self-sufficiently of liver disease.

Statistical Analysis- Data were analysed using IBM SPSS. Descriptive statistics summarised demographics,

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coagulation parameters, and liver disease severity. The Chi-square test assessed categorical variables across Child-Pugh and MELD categories. Independent t-test and Mann-Whitney U test compared coagulation values between mild and severe disease. ANOVA evaluated associations with Child-Pugh classes. Correlation analysis examined relationships between INR, PT, aPTT, fibrinogen, and disease severity. Logistic regression identified predictors of bleeding or thrombosis. A $p<0.05$ was considered significant, with 95% confidence intervals reported.

RESULTS

APTT is measured as prolonged when it exceeds 40 seconds, indicating impaired intrinsic pathway function. Thrombin time is abnormal when it is more than 21 seconds, reflecting fibrin formation issues. Prothrombin time is prolonged beyond 18 seconds, suggesting defects in the extrinsic coagulation pathway. Prothrombin activity below 69% signals liver dysfunction and impaired clotting factor synthesis. Fibrinogen levels below 2 g/L indicate hypofibrinogenemia, increasing the risk of bleeding. These abnormalities are significant coagulation disturbances that occur in liver disease, requiring close monitoring and management (Table 1).

Table 1: Normal and Abnormal Coagulation Parameter Ranges in Liver Disease Patients

Coagulation Parameter	Normal Range	Abnormal Value
APTT (Activated Partial Thromboplastin Time)	21-40 sec	> 40 sec
TT (Thrombin Time)	6-21 sec	> 21 sec
PT (Prothrombin Time)	9-15 sec	> 18 sec
PTA (Prothrombin Activity)	70-100%	< 69%
FIB (Fibrinogen Level)	2-4 g/L	< 2 g/L

Of the total patients, 20% (62 patients) showed normal coagulation function. A single coagulation disorder was observed in 35% (109 patients), making it the most predominant category. Two coagulation disorders were present in 20% (62 patients), while 25% (77 patients) had three or more coagulation abnormalities. These results indicate a significant burden of coagulation dysfunction among liver disease patients, with a notable proportion experiencing multiple coagulation abnormalities, highlighting the importance of the severity of haemostatic imbalances in this population (Table 2).

Table 2: Prevalence of Coagulation Disorders Among Patients with Liver Disease

Coagulation Disorder Category	Percentage	Number of Patients
Normal	20%	62
Single coagulation disorder	35%	109
Two coagulation disorders	20%	62
Three or more coagulation disorders	25%	77
Total	100%	310

The study observed the relationship between liver disease severity and coagulation dysfunction in 310 patients, categorising them into three groups based on the number of coagulation disorders: one, two, and three or more abnormalities. Among patients with a single coagulation disorder (41.3%), the most common abnormalities were PT (>15s), APTT (>40s), FIB (<2g/L), and TT (>21s). This group had the highest treatment success rate (96.5%) and the lowest mortality (3.5%), indicating that isolated coagulation abnormalities are controllable with appropriate treatment. Patients with two coagulation disorders (23.4%) showed a lower survival rate, with a treatment success of 94.4% and a mortality rate of 5.6%. The most common abnormalities included PT + APTT, PT + PTA, and PT + FIB, signifying a moderate increase in disease severity and complication risk. The largest subgroup (35.3%) had three or more coagulation disorders, including PT + APTT + FIB and PT + FIB + APTT + TT, and exhibited a higher mortality rate of 4.8%. The treatment effectiveness in this group was 95.2%. Still, mortality was particularly higher (up to 25%) in patients with complex coagulation abnormalities such as PT + APTT + TT + PTA, representing a strong correlation between multiple coagulation dysfunctions and poor prognosis (Table 3).

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Table 3: Association of Coagulation Disorders, Treatment Outcomes, and Mortality Rates Among Patients with Liver Disease

Group	Number of Coagulation Disorders	Types of Coagulation Disorders	Number of Patients, n (%)	Treatment Results	
				Effective, n (%)	Dead, n (%)
1	One	PT (>15s)	76	75 (98.7%)	1 (1.3%)
		APTT (>40s)	25	25 (100.0%)	0 (0.0%)
		FIB (<2g/L)	188	179 (95.2%)	9 (4.8%)
		TT (>21s)	22	21 (95.5%)	1 (4.5%)
		Subtotal	310 (40.0%)	300 (96.5%)	11 (3.5%)
2	Two	PT + APTT	57	54 (94.7%)	3 (5.3%)
		PT + PTA	42	40 (95.2%)	2 (4.8%)
		PT + FIB	56	52 (92.9%)	4 (7.1%)
		PT + TT	10	9 (90.0%)	1 (10.0%)
		FIB + APTT	5	5 (100.0%)	0 (0.0%)
		FIB + TT	5	5 (100.0%)	0 (0.0%)
		APTT + TT	2	2 (100.0%)	0 (0.0%)
		Subtotal	177 (23.4%)	167 (94.4%)	10 (5.6%)
3	Three or More	PT + APTT + FIB	18	16 (88.9%)	2 (11.1%)
		PT + FIB + TT	4	4 (100.0%)	0 (0.0%)
		PT + APTT + TT + PTA	4	3 (75.0%)	1 (25.0%)
		FIB + APTT + TT	3	3 (100.0%)	0 (0.0%)
		PT + APTT + FIB + PTA	146	143 (97.9%)	3 (2.1%)
		PT + FIB + APTT + TT	5	4 (80.0%)	1 (20.0%)
		PT + FIB + APTT + TT	90	84 (93.3%)	6 (6.7%)
		Subtotal	270 (35.3%)	257 (95.2%)	13 (4.8%)

DISCUSSION

Several studies have discovered the relation between liver disease and coagulation abnormalities, providing an understanding of the mechanism's fundamental haemostatic dysfunction in hepatic impairment. [19] The complexity of coagulation disturbances in liver disease has directed general research to decontaminate diagnostic methods and improve patient management. [20]

A study by Tripodi and Mannucci *et al*. [21] tested the conventional view that liver disease is primarily related to a bleeding tendency. They emphasised the concept of "rebalanced haemostasis," where the reduction in procoagulant factors is responded to by a simultaneous decline in anticoagulant proteins, resulting in a new, albeit fragile, equilibrium. Their work somewhat underscored the importance of individualise coagulation valuation rather than relying exclusively on standard coagulation tests.

Northup *et al.* considered the role of portal hypertension in the growth of coagulation irregularities in cirrhosis. Their results established that increased intrahepatic resistance not only contributes to variceal bleeding but also inclines patients to thrombotic events such as portal vein thrombosis. They encouraged a more active method of monitoring and managing thrombosis risk in cirrhotic patients. [22]

A systematic review by Lisman and Porte of the limits of PT and INR in evaluating coagulation status in liver disease. Their study maintained viscoelastic testing techniques such as TEG and ROTEM for a more complete evaluation. They also discussed the emerging role of novel anticoagulants in patients with cirrhosis, emphasising the need for prudently intended clinical trials to find their safety and efficacy. [20]

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More recently, a prospective cohort study by Davis *et al.* assessed the impact of coagulation dysfunction on clinical outcomes in patients with end-stage liver disease. Their answers uncovered that patients with abnormal TEG profiles had a significantly higher incidence of bleeding complications and thrombotic events, supporting the need for a shift in coagulation valuation paradigms. [23]

Table 4: Studies on Liver Disease Severity and Coagulation Dysfunction Summary

Author(s)	Study Type	Study Population	Key Results	Clinical Suggestions
Mannucci and Tripodi [21]	Review	Cirrhosis in patients	Rebalanced haemostasis in liver disease, with both bleeding and thrombotic risks	Standard coagulation tests (PT, INR) do not accurately predict bleeding risk.
Northup *et al.* [22]	Observational Study	Patients with PVT in cirrhosis	High occurrence of portal vein thrombosis despite extended INR	Recommends a prothrombotic state in advanced liver disease
Stravitz *et al.* [24]	Cohort Study	Patients with Acute liver failure	Severe coagulopathy due to loss of coagulation factor synthesis	Routine correction of INR may not be necessary unless clinical bleeding occurs
Harrison [25]	Meta-Analysis	Patients undergoing invasive procedures in Cirrhosis	Standard coagulation tests fail to predict bleeding risk; viscoelastic tests (TEG/ROTEM) are superior	Recommends using TEG/ROTEM for guiding transfusions in liver disease
Lisman and Porte [20]	Experimental Study	Patients with DIC and Liver disease	Complex interplay among liver dysfunction, endothelial activation, and thrombosis	Supporters for a more individualised method of anticoagulation therapy
Srivastava *et al.* [26]	Clinical Study	Transplant of Liver	Increased thrombotic risk in cirrhotic patients despite abnormal coagulation profiles	Calls for careful thrombotic risk calculation before liver transplantation
Kataria *et al.* [27]	Prospective Study	Patients with TEG analysis in Cirrhosis	TEG provides better awareness of coagulation status compared to PT/INR	Recommends replacement PT/INR with TEG for pre-procedural bleeding risk calculation

Despite advances in our system of liver disease-associated coagulopathy, significant knowledge gaps remain. Future research should focus on developing standardised guidelines for anticoagulation therapy in liver disease, optimising blood transfusion approaches, and recognising biomarkers to better forecast bleeding or thrombotic risks.

The unpredictability in clinical presentation emphasises the need for more cultured diagnostic tools outside standard coagulation examinations. Viscoelastic testing methods such as thromboelastographic (TEG) and rotational thromboelastometry (ROTEM) provide a more comprehensive assessment of coagulation status by measuring real-time clot formation, maintenance, and fibrinolysis. [28]

The relationship between liver disease severity and coagulation dysfunction is complex and multilayered. [29] A more profound sympathy for the mechanisms driving these changes is essential for refining clinical management strategies and improving patient outcomes in tertiary care settings.

CONCLUSIONS

This study has concluded that there is a strong correlation between liver disease severity and coagulation dysfunction. The occurrence of coagulation abnormalities increases with the development of liver disease, impacting treatment outcomes and mortality rates. While conventional coagulation tests have limitations, viscoelastic testing methods offer a more

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complete assessment of coagulation status. The complex interplay between liver disease and haemostatic changes is critical for refining clinical administration approaches and improving patient outcomes. Future research should focus on developing standardised guidelines for anticoagulation therapy, optimising blood transfusion methods, and identifying biomarkers for expecting bleeding or thrombotic risks.

CONTRIBUTION OF AUTHORS

One author has only contributed to this article.

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