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Original Research Article

# Comparision of coagulation profile trends in case of liver cirrhosis with HCC versus cirrhosis without HCC: Analysis of 150 cases in a tertiary health care

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ABSTRACT

**Context:** The physiology of haemostasis and blood coagulation is intimately linked to the hepatic function. Liver disorders can be associated with deranged coagulation profile, thrombocytopenia, and dysfibrinogenemia. In hepatocellular injury, both quantitative and qualitative abnormalities in coagulation factors are often seen. Hepatocellular carcinoma (HCC), peculiar as both cancer and liver cirrhosis to dismay the haemostatic balance towards a prothrombotic state.

**Aims:** Our study aims to assess the hemostatic changes and the comparision of coagulation profile trends that occur in cases of liver cirrhosis with HCC versus cirrhosis without HCC

**Materials and Methods**: The present study is the hospital based cross-sectional study in a tertiary care centre, New Delhi. A maximum 150 cases of liver cirrhosis with and without hepatocellular carcinoma (HCC) studied from Dec 2017 to Nov 2019 and analysed for parameters related to coagulation i.e. prothrombin time (PT/INR), fibrinogen level and platelet count 1 day prior to the liver transplant. Statistical analysis used: Statistical analysis was done using SPSS 20.0. Comparisons between groups frequencies were made using Chi-square test. P< 0.05 was considered as significant.

**Result**: Prothrombin time was found to be increased in all the cirrhotic patients (both with and without HCC). Decrease in the level of fibrinogen was observed in 90 % cases of cirrhosis with HCC and 80% of cases of cirrhosis without HCC. Platelet count were almost in normal range among majority of the cirrhosis cases both with and without HCC (86.0% and 75.0% respectively).No significant difference was observed in prothrombin time, fibrinogen level and platelet count among the cases with and without hepatocellular carcinoma (p>0.05).

**Conclusion**: All the cases showed haemostatic abnormalities in the form of hypofibrinogenemia and increase PT/INR.

**KeyMessages:** There is no significant difference in the coagulation profile in cases of cirrhosis with HCC in comparison to cases of cirrhosis without HCC.



## 1. Introduction

The liver plays several key roles in blood coagulation, being involved in both primary and secondary haemostasis.[1] The haemostatic system is a delicate balance between prothrombotic and antithrombotic processes, aiming to prevent excessive blood loss from injured vessels and to prevent spontaneous thrombosis. Liver failure is accompanied by multiple changes in the haemostatic system, because of reduced plasma levels of procoagulant and anticoagulant clotting factors synthesized by hepatocytes and sinusoidal cells.[2] Severe coagulopathy of liver disease is more frequently seen in acute liver failure, but still remains important complication of liver cirrhosis

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and hepatic malignancies. A mild to moderately reduced platelet count is frequently present in patients with acute or chronic liver diseases. An important cause for thrombocytopenia in chronic liver disease is an increased platelet sequestration in the spleen as a result of congestive splenomegaly, which is related to portal hypertension.[3] Prothrombin time (PT), which is used to measure the coagulation factors of the "extrinsic pathway", is the most frequently used coagulation test in routine laboratories. International normalized ratio (INR), which was introduced to overcome the problem of marked variation in PT results among laboratories, has been used to standardize PT value in liver diseases and been included in some prognostic models of HCC and liver cirrhosis, such as Child-Turcotte-Pugh (CTP) score and the model for end stage liver disease (MELD).[4] Fibrinogen is an an important coagulation factor, An essential glycoprotein that is converted into a fibrin clot by the coagulation cascade. Measurement of this level can indicate whether substrate is present to allow for clot formation, because its absence would increase bleeding risk. Decreased levels of fibrinogen have been noted in almost 40% of patients with cirrhosis.[5] In situations such as tissue injury, infection, and inflammation, fibrinogen concentrations are rapidly elevated.[6] Recently, emerging evidence has associated the elevation of fibrinogen level with tumour progression in several malignancies, such as breast cancer.[7] gallbladder cancer,[8] gastric cancer,[9] colorectal cancer,[10] and lung cancer.[11] Few studies have also reported that patients with HCC and elevated pre treatment plasma fibrinogen levels have poor outcomes.[12] Patients with cirrhosis often experience mucosa associated bleeding, which can be seen in hyper fibrinolytic states, Estimation of plasma fibrinogen levels helps in preventing bleeding tendencies. Raised fibrinogen levels have been associated with tumor. progression in several malignancies. In present scenario, it is the scientific need to investigate the markers for predicting severity and outcome of HCC, more so to explore more simple and accurate prognostic factors from the clinical routine investigations. The pathological conditions that includes inflammation, thrombosis, and tissue injury lead to the activation of coagulation factors and fibrinolysis. These markers have the potential to serve as predictors of disease and disease severity. Moreover, there are conflicting findings on the trend of coagulation profile in HCC patients compared to that in cirrhotic groups. Therefore, the recent debate on the presence of a major hemostatic defect in patients with liver disease seems justified. Our aim is to analyse and compare the coagulation profile trends in case of liver cirrhosis with HCC versus cirrhosis without HCC.

## 2. Materials and Methods

The present study is the hospital based cross-sectional study in a tertiary care centre, New Delhi. A maximum 150 cases of liver cirrhosis with and without hepatocellular carcinoma (HCC) studied from Dec 2017 to Nov 2019 and analysed for parameters related to coagulation i.e. prothrombin time (PT/INR), fibrinogen level and platelet count 1 day prior to the liver transplant. HCC diagnosis was based on the histological findings of needle biopsy/surgery or typical radiological features shown by at least two image examinations including ultrasound (US), contrast-enhanced dynamic computed tomography (CT) and magnetic resonance imaging (MRI) and hepatic angiography or by a single positive imaging with a serum alpha fetoprotein level > 400 ng/Ml.

Study Procedure: For coagulation studies blood was collected in blue top (containing 3.2% sodium citrate) vacutainers in a ratio of 9 volume blood to 1 volume of anticoagulant. Platelet Poor Plasma (PPP) was made by centrifugation at 2000 g for 10 minutes. Coagulation tests were done immediately or PPP were stored in cuvettes at temperature of -20 to -40 degree Celsius for later dates. Almost 2 ml blood was collected in EDTA vial for platelet count by Beckman Coulter Haematology Fully Automated Autoanalyser LH750.

### *2.1. Statistical analysis*

Statistical analysis was done using SPSS 20.0. Comparisons between groups frequencies and groups means were made using Chi-square test and Student's t-test, respectively. P< 0.05 was considered as significant.

## 3. Results

The present study has total 150 cases (n=150). The mean age of patients was 56.4 ± 11.0 years and out of all patients 128 (85.3 %) patients were male. Prothrombin time was found to be increased in all the cirrhotic patients (both with and without HCC). (Table 1) Mean PT was found to be 21.98±5.05. Decrease in the level of fibrinogen was observed in almost 90 % cases of cirrhosis with HCC and 80% of cases of cirrhosis without HCC. Mean Fibrinogen level was 198.50±104.05. 80 cases without HCC and 45 cases with HCC showed lower fibrinogen value. (Table 2) Platelet count was almost in normal range among majority of the cirrhosis cases both with and without HCC (86.0% and 75.0% respectively). (Table 3) Mean platelet count was 292130±72824/ $mm^3$ No significant difference was observed in prothrombin time, fibrinogen level and platelet count among the cases with or without hepatocellular carcinoma (p>0.05).

## 4. Discussion

Cancer cells can activate blood coagulation through the expression of procoagulant molecules such as tissue factors and cancer procoagulant which consequently activate serine proteases factor VIIa, factor Xa and thrombin.[13,14]

**Table 1:** Association between prothrombin time in patients with cirrhosis and hepatocellular carcinoma

| Cases | Prothrombin time | | p value |
|---|---|---|---|
| | Increased (n = 150) | Normal (n = 0) | |
| With HCC (n = 50) | 50(100%) | 0(0.0%) | 1.0(NS) |
| Without HCC (n = 100) | 100(100%) | 0(0.0%) | |

**Table 2:** Association between fibrinogen levels in patients with cirrhosis and hepatocellular carcinoma

| Cases | Fibrinogen levels | | p value |
|---|---|---|---|
| | Normal (n = 25) | Low (n = 125) | |
| With HCC (n = 50) | 5(10.0) | 45(90.0) | 0.18(NS) |
| Without HCC (n = 100) | 20(20.0) | 80(80.0) | |

**Table 3:** Association between platelet count in patients with cirrhosis and hepatocellular carcinoma

| Cases | Platelet count | | | p value |
|---|---|---|---|---|
| | Increased (n = 5) | Normal (n = 118) | Decreased (n = 27) | |
| With HCC (n = 50) | 0(0.0) | 43(86.0) | 7(14.0) | 0.15(NS) |
| Without HCC (n = 100) | 5(5.0) | 75(75.0) | 20(20.0) | |

However, HCC patients with impaired liver function have a more complex hemostatic disturbance, especially those with liver cirrhosis.[15,16] In hepatocellular disease, abnormalities of coagulation factors are quite common. Patients with cirrhosis are believed to develop thrombotic complications more frequently than non-cirrhotic patients[17] In the studies by Hwang et al.[18] and Carr et al.[19] the proportion of increased platelet count > 400×109 was reported in 2.7% and 9% of the cases respectively . Afdhal N et al., found that thrombocytopenia (platelet counts <150,000/dL) was a common complication in patients with CLD and reported in as many as 76% of cirrhotic patients[20] Various factors can lead to thrombocytopenia like splenic platelet sequestration, bone marrow suppression by chronic hepatitis C infection and antiviral treatment with interferon-based therapy.[20] Reduced level or activity of the thrombopoietin (TPO) may also play a intervening role.[20] However our study showed normal platelet count in 43 cirrhosis patient with HCC (86.0 %) and 75% cirrhotic patient without HCC. Though few studies have shown that patients with HCC alike any other malignancy are peculiar to perturb the haemostatic balance towards a hypercoagulable state. According to a very recent review by Zanetto A. et al[21] cirrhotic patients with hepatocellular carcinoma may exhibit hypercoagulability, with its main determinant being the increased fibrinogen concentration/polymerization and thrombocytosis related to cancer. But our study showed that there is no significant difference in the coagulation trends in cases of cirrhosis with HCC in comparison to cases of cirrhosis without HCC.

Hessien et al[22] indicated lower levels of fibrinogen in HCC patients compared to that in cirrhotic patients. Several studies reported that HCC patients showed higher levels of pre-treatment plasma fibrinogen compared to healthy controls or cirrhotic patients.[23,24] However, Our findings of serum fibrinogen level were in line with similar study done by Basili et al[25] and Liu et al[26] who found no significant difference in the plasma fibrinogen levels between HCC and control or cirrhotic groups,

Findings of PT and aPTT in our study are in concordance with study done by Saray A et al., and Saja MF et al., and confirmed that prolongation of conventional coagulation screening tests appears in advanced liver disease and are not sensitive markers of liver damage.[27,28] Furthermore, recent studies have shown that these global tests are not predictive of bleeding in patients with hepato cellular carcinoma however PT has kept its place as one of the parameters of common prognostic indices in advanced liver disease.[29]

## 5. Conclusions

In cirrhosis patient's severe derangement in both anti and procoagulant factors occurs similarly In hepatocellular disease, abnormalities of coagulation factors are quite common. Though few studies have shown that patients with HCC alike any other malignancy are peculiar to perturb the haemostatic balance towards a hypercoagulable state, but our study showed that there is no significant difference in the coagulation trends in cases of cirrhosis with HCC in comparison to cases of cirrhosis without HCC. All the cases showed haemostatic abnormalities in the form of hypofibrinogenemia and increase PT/INR.

## 6. Conflict of Interest

None.

## 7. Source of Funding

None.

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