

Relationship of Serum D-Dimer and Interleukin-6 Level in Various Stages of Liver Cirrhosis

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ABSTRACT

Background: Liver cirrhosis is a high burden disease with wide spectrum of etiology. It has significant morbidity and is an important cause of premature death. It requires multiple approach in treating cirrhosis and its complications. Hemostatic derangement and altered systemic inflammations in cirrhosis contribute to its pathophysiology and complications. Hyper fibrinolytic feature in hemostatic alteration often gets unnoticed which could be an important factor leading to coagulopathy and bleeding tendency. D-Dimer a fibrinolytic marker can be an asset to sought out this aspect in cirrhosis. It can also act as an individual marker with prognostic value for cirrhosis. Important role of cytokine interleukin-6 (IL-6) might prove to be a potential biomarker in evaluating inflammatory conditions and severity of cirrhosis.

Objective: To evaluate serum D-Dimer and IL-6 level in liver cirrhosis and determine its correlation with various stages of liver cirrhosis. **Methodology:** A cross-sectional study was carried out in the department of Biochemistry, Dhaka Medical College, Dhaka from July, 2023 to June, 2024 with a total forty-five diagnosed liver cirrhosis patients who were classified into group A, B, C according to severity based upon Child Pugh (CP) score. Serum D-Dimer and Interleukin-6 levels were evaluated by fluorescence immunoassay technique. Data was analyzed by Statistical Package for Social Science (SPSS) version 26.

Result: Mean $\pm$ SD age of study subject was 50.5 $\pm$ 12.8, majority were within 41-50 age group. Distribution of gender showed male predominance (86.7%). HBV infection was a prominent etiology of cirrhosis of the total study subjects with 47%. Serum D-Dimer and IL-6 level showed significant difference ($p < 0.001$, $p < 0.001$) among three CP groups. Median value for serum IL-6 were 3.20pg/ml, 5.80pg/ml, 31.0pg/ml for A, B, C CP groups respectively. Serum D-dimer showed similar rising fashion with increasing severity of cirrhosis with 1.25 mg/L, 2.45 mg/L, 10.0 mg/L for A, B, C CP groups. A significant positive correlation was found between disease severity of liver cirrhosis and D-dimer levels ($\rho = +.796$, $p < 0.001$) and IL-6 levels ($\rho = +0.737$, $p < 0.001$). D-dimer and IL-6 correlates with each other strongly and positively ($\rho = +0.702$, $p < 0.001$) in liver cirrhosis. Area Under the Receiver Operating Characteristic (AUCROC) curve analysis of D-Dimer has found cut off value for D-dimer 2.91mg/L,

3.95 mg/L and 4.50 mg/L and for IL-6 9.50 pg/ml, 12.45 pg/ml, 15.2 pg/ml for predicting severe stages of cirrhosis with (5-6), (7-9) and above 9 Child Pugh score respectively.

Conclusion: Serum D-dimer and IL-6 values are found significantly higher with increasing severe stages of liver cirrhosis. Serum D-dimer and IL-6 showed significant positive correlation with Child Pugh score.

Date of Submission: 16-09-2026

Date of Acceptance: 30-09-2026

I. INTRODUCTION

Liver cirrhosis is a chronic advanced stage of liver disease. It may lead to morbidity and mortality aforesaid (Zhou *et al.*, 2019). Irrespective of the etiology, cirrhosis leads to hepatic decompensation including ascites, hepatic encephalopathy, jaundice, variceal bleeding in its longer duration. It is one of a leading cause of death worldwide (Huang *et al.*, 2023).

The estimated prevalence of cirrhosis identified from autopsy studies ranges from 4.5% to 9.5% of the general population. This prevalence would project to hundreds of millions of patients affected with cirrhosis worldwide (Lim and Kim, 2008). According to the Global Burden of Disease (GBD) Study, the estimated number of people with compensated cirrhosis was 112 million worldwide, corresponding to an age-standardized global prevalence of compensated cirrhosis is 1.3% (Huang *et al.*, 2023).

In Bangladesh, a multicenter study conducted on 59,227 patients at tertiary level medical college hospitals reveals 13.2% presented with some sorts of liver problems. Among which 37% have been suffering from liver cirrhosis and its complications (Chowdhury *et al.*, 2022). From the distribution of liver disease it is acknowledged, cirrhosis of liver distribution is 37% in Dhaka, 38% in Barisal, 39% in Khulna, 69% in Rajshahi, 22.8% in Sylhet (Rahman *et al.*, 2014). It is considered as a major disease burden in Bangladesh with a prevalence of 2.6% (Islam and Khan, 1975).

Liver Cirrhosis is an advanced stage of liver fibrosis characterized by diffuse hepatic fibrosis and nodular formation (Gordon-Walker and Williams, 2023). Persistent and recurrent injury to hepatocyte due to any cause may lead to cirrhosis. Causes of cirrhosis includes wide range of infections, inflammation, metabolic or autoimmune diseases (Yi *et al.*, 2023). Histologically, it is a diffuse hepatic process characterized by advanced stage of liver fibrosis that is accompanied by distortion of the hepatic vasculature and the conversion of normal liver architecture into structurally abnormal nodules (Schuppan and Afdhal, 2008).

Liver is the site for synthesis of several proteins involved in enhancing and inhibiting coagulation and fibrinolysis. Chronic inflammatory condition of cirrhosis alters hemostatic regulation (Kujovich, 2015). The natural history of liver cirrhosis passes through a prolong course of asymptomatic stage to clinical consequences of liver failure, portal hypertension. These series of changes in cirrhosis follow characteristic features from preventable stages of compensation to decompensated stage with high mortality (Prystupa *et al.*, 2015). Among various complications there may develop a serious coagulopathy. Along with hypercoagulable state, an increased fibrinolytic state is responsible for premature removal of hemostatic plug in liver cirrhosis (Spadaro *et al.*, 2008). Liver function tests include standard laboratory tests in the evaluation of coagulopathy in liver disease. But patients with cirrhosis have a bleeding tendency that is often not evident from routine coagulation assays and do not properly assess the hemostatic derangement (Kujovich, 2015). In such patients, the incidence of hyperfibrinolysis varies from 19% to 95% and may contribute to serious bleeding complications (Spadaro *et al.*, 2008). For fibrinolysis, a process which have an impact upon the bleeding tendency in cirrhosis, D-Dimer can be an important tool for diagnosis of hyper fibrinolytic status in cirrhosis (Dhanunjaya, Anand and Anand, 2013).

D-Dimer is an end product of fibrin degradation, fibrin is degraded by plasmin. It is a stable and measurable parameter which reflects the enzymatic breakdown of the cross-linked fibrin. D-Dimer level rises with increased fibrinolysis in cirrhosis (Malaguarnera *et al.*, 2018). Serum levels of fragment D-dimer represent an accurate marker of fibrinolysis. It indicates activation of coagulation system and fibrinolysis as fibrinolysis is followed by coagulation (Zhou *et al.*, 2019). It is found higher in decompensated cirrhotic patients complicated with ascites, variceal bleeding, hepatic encephalopathy and jaundice than compensated patients (Dhanunjaya, Anand and Anand, 2013). An increase of D-Dimer is prevailed with advanced stages of Child Pugh group of cirrhosis and strong association with portal vein thrombosis (Li *et al.*, 2017). Therefore, D-dimer can be a prognostic factor to help in clinical evaluation of disease severity of cirrhosis to take earlier appropriate measure to delay the consequences.

Interleukin 6 (IL-6) is a pleiotropic cytokine. It contains a four-helix-bundle of 184 amino acids. It is synthesized by fibroblasts, monocytes, macrophages, T cells and endothelial cells (Schmidt-Arras and Rose-John, 2016). IL-6 plays various roles in exerting multiple functions in the body. It has regulatory biological activities as in immune regulation, hematopoiesis, inflammation, and oncogenesis (Rey and Effendi, 2021). In the liver, IL-6 acts as an important inducer of the acute phase response to defense against infection. It is conclusive for hepatocyte homeostasis and a potent hepatocyte mitogen. However, persistent activation of the IL-6 signaling pathway has been proved to be injurious to the liver (Schmidt-Arras and Rose-John, 2016). Changes of this inflammatory marker level in circulation can assess severity and predict prognosis of cirrhosis along with other systemic complications by coagulation dysfunction (Li *et al.*, 2021).

IL-6 mimics with hepatocyte stimulating factor 2. Under inflammatory conditions, it induces the liver to synthesize a group of acute phase proteins (Rey *et al.*, 2018). Acute phase proteins activate other inflammatory cascades leads to exaggerated inflammatory response involved in liver regeneration and metabolic function. A dramatic surge of IL-6 levels in liver vein following increased level of TNF alpha only after 2 hours of hepatectomy is cofounded by the evidence from experiments with parabiotic animals (Trautwein *et al.*, 1996). This cytokine plays roles in hepatic inflammation in many liver disorders, resulting in fibrosis and cirrhosis. Decompensated cirrhotic patients compared with compensated cirrhosis exhibit a greater exaggerated inflammatory response to bacterial products. This surge of inflammatory response is orchestrated by interferons and cytokines including IL-6 (Engelmann, Zhang and Claria, 2023). A high level of IL-6 is strongly associated with advanced stage of liver cirrhosis. It can predict probability of turning cirrhosis into carcinoma (Schmidt-Arras and Rose-John, 2016). IL-6 stimulates release of liver acute phase proteins CRP, fibrinogen. It might be a good predictor for turning compensated cirrhosis to more adverse stages and to even acute on chronic liver failure (Xiao *et al.*, 2022).

A high inflammatory condition in cirrhosis stimulates release of cytokine cascades. It causes generalized vasodilation and increases regional blood flow. Inhibitory effect of IL-6 on vascular smooth muscle contraction may give rise to portal hypertension in cirrhosis. It can predict an overall inflammatory status (Lee *et al.*, 1996).

IL-6 stimulates coagulation but no direct effect on fibrinolysis (Stouthard *et al.*, 1996). In a monocyte in vitro study, it is found that, fibrin degradation product D-Dimer induces the synthesis and release of IL-6 and plasminogen activator inhibitor associated with chronic inflammatory condition (Robson, Shephard and

Kirsch, 1994). This etiological complex regulation is evident in various stages of liver cirrhosis. Though how it is correlated with the severe progression of cirrhosis and link between IL-6 and D-Dimer demands further investigations.

IL-6 is an important marker of inflammatory status, good predictor of hypercoagulable state in cirrhosis (Li *et al.*, 2021). Increasing feature of D- Dimer level is found in cirrhosis, in GIT bleeding complications and ascites (Francis and Feinstein, 1984). D-Dimer, a fibrinolytic marker and IL-6, an inflammatory marker is used to predict and monitor many systemic and chronic inflammatory disease progression and its complications.

In conclusion, cirrhosis is linked to systemic inflammation, abnormal coagulation profile. In advance stages it complicates with hyperfibrinolysis. Altogether, D-Dimer and IL-6, these biomarkers can predict status of the disease condition and clinical events reliably in chronic course of liver cirrhosis with its various etiologies and complications in different stages.

These biomarkers thus can be helpful in early detection of severity, prognosis and monitor better of the disease which would be a valuable guide for physician for proper management of liver cirrhosis patients.

1.1 RATIONALE

Liver cirrhosis is a leading cause of mortality and morbidity and a major cause of death worldwide. In cirrhosis, patients show bleeding tendency that is often not clearly understood from routine coagulation tests. D-Dimer can be an excellent tool for evaluating hyper fibrinolytic status. It can be a potential biomarker for assessment of severity and predict prognosis of cirrhosis. IL-6 is an inflammatory mediator which has roles in hepatic inflammation resulting in fibrosis and cirrhosis. A high serum IL-6 in liver cirrhosis is evident of exaggerated inflammatory response where other inflammatory markers might be weak predictors. A very limited study on serum D-Dimer and IL-6 in cirrhotic patients are conducted in Bangladesh. The aim of the study was to further evaluate serum D-Dimer and IL-6 in liver cirrhosis in its various stages. It would be assets to predict prognosis, monitoring, assessment of disease severity in prolong course in assisting early and appropriate management plan for liver cirrhosis. Evaluation of D-dimer and IL-6 level might also reduce duration of hospital stay and contribute to increase life expectancy of the of liver cirrhosis patients.

1.2 RESEARCH QUESTION

Is there any relationship of serum D-Dimer and Interleukin-6 level in various stages of liver cirrhosis?

1.3 RESEARCH OBJECTIVES

General objective:

- To evaluate serum D-Dimer and Interleukin-6 level in liver cirrhosis and the relationship with various stages of liver cirrhosis.

Specific objectives:

- To estimate serum D-Dimer level in three stages of liver cirrhosis based upon Child Pugh Score.
- To estimate serum IL-6 level in three stages of Child Pugh Score in liver cirrhosis.
- To compare serum D-Dimer and IL-6 among cirrhosis severity groups.
- To assess correlation of serum D-Dimer and IL-6 with severity of liver cirrhosis.
- To determine correlation between serum D-Dimer and IL-6 in liver cirrhosis.

II. Literature Review

Liver Cirrhosis is an advanced, chronic, progressive disease of liver with wide spectrum of clinical presentation (Engelmann, Zhang and Claria, 2023). Liver is the main site of synthesis of several proteins that are involved in coagulation to fibrinolysis, inflammation and immune function. All of which are compromised and imbalanced in cirrhosis leads to complications, turning it in to decompensated stages (Dhanunjaya, Anand and Anand, 2013). Cirrhosis of liver is a consequence of prolong inflammatory conditions following persistent to recurrent injury to hepatocytes. Etiology of cirrhosis globally varies majorly from chronic viral hepatitis, prolonged excessive alcohol consumption to NAFLD. It is characterized histologically by diffuse hepatic fibrosis and nodular formation (Gordon-Walker and Williams, 2023).

Epidemiology of Liver Cirrhosis:

The epidemiology and the burden of cirrhosis are changing because of the contest between the etiology of cirrhosis and the early measures which are taken to prevent the poor outcomes. Rising prevalence of obesity, alcohol consumption are now a days contributing to chronic changes to liver (Lim and Kim, 2008). Improvement in the management of hepatitis B virus and hepatitis C virus infections are providing a reduction to global age standardized death rates. It is recognized as a progressing global disease burden, ranked as 10th

leading cause of death worldwide in 2001. According to the Global Burden of Disease (GBD) Study, the estimated number of compensated cirrhosis was 112 million worldwide. An age-standardized prevalence of compensated cirrhosis correspond to decompensated cirrhosis was 1.3%, 1395 case per 10, 000 population. Globally, hepatic viral infections remained still the leading cause. Published study by WHO between 1993 and 2021 disclosed 42% of HBV infection and 21% of HCV infection among cirrhosis individuals (Huang *et al.*, 2023). The autopsy identified estimated prevalence of cirrhosis ranges from 4.5% to 9.5% (Lim and Kim, 2008). A retrospective multicentered study conducted in Bangladesh included 59,227 patients. Among 13% of which were suffering from Chronic liver diseases. 37 to 69% of these CLD patients were suffering from cirrhosis associated complications including hepatic encephalopathy, variceal bleeding (Chowdhury *et al.*, 2022).

Cirrhosis of liver distribution revealed 37% in Dhaka, 38% in Barisal, 39% in Khulna, 69% in Rajshahi, 22.8% in Sylhet throughout Bangladesh (Rahman *et al.*, 2014). It is considered as a major disease burden with a prevalence of 2.6% liver cirrhosis in Bangladesh (Islam and Khan, 1975). Multiple etiological factors including metabolic syndrome recently has resulted in increasing incidence of cirrhosis in developed countries worldwide (Lim and Kim, 2008)

Liver Cirrhosis:

Liver Cirrhosis is a chronic, progressive condition that results in liver cell failure and portal hypertension. It can be defined as a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules (Anthony *et al.*, 1977)

Liver cirrhosis is an advanced stage of liver fibrosis characterized by diffuse hepatic fibrosis and nodular formation (Gordon-Walker and Williams, 2023). It is a diffuse hepatic process characterized by advanced stage of liver fibrosis that is accompanied by distortion of the hepatic vasculature and the conversion of normal liver architecture into structurally abnormal nodules. It is the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, which leads to portal hypertension and end stage liver disease (Schuppan and Afdhal, 2008).

Pathophysiology of Liver Cirrhosis:

The pathogenesis of liver cirrhosis is a complex process. It is the consequence of chronic liver injury. On exposure to inflammation multiple cells including Hepatic stellate cells, sinusoidal endothelial cells and Kupffer cells get activated. Activated cells transform into myofibroblast and start depositing collagens leads to fibrosis (Sharma and John, 2018). Repeated or continuous injury to the liver causes significant scarring leads to replacement of liver tissue by scar tissue. Scarring destroys normal architecture of liver cells, blood supply and bile drainage system. Function of the liver is severely compromised in cirrhosis. At the beginning of the disease cirrhosis might be asymptomatic and compensated. Advancement of the disease and continuous adverse etiological factors give rise to the complications and turn cirrhosis in to decompensated stages, leads to poor prognosis (Bengtsson, 2022). It involves the interaction of various immune cells and cytokines to work together resulting in homeostasis imbalance. This chronic pathological process caused by variety of liver diseases and results in constant liver injury (Yi *et al.*, 2023). Kupffer cells and hepatic cells of liver produce cytokines following injury. Cytokines activate stellate cells of liver in the space of Disse. Activated stellate cells are transformed into myofibroblast like cells, capable of producing collagen, pro-inflammatory cytokines and other mediators. This orchestrated mechanism promotes hepatocyte damage and tissue fibrosis. These histological damages evolve over years as progressive fibrosis with broad spectrum of hepatocellular loss. Ultimately it causes distortion of the normal liver architecture and disrupts hepatic vasculature, leads to portosystemic shunt. Most common complications of cirrhosis include ascites, variceal bleeding, hepatic encephalopathy, bacterial infections to hepatocellular carcinoma (Gordon-Walker and Williams, 2023). Cirrhosis is classified morphologically in to micronodular cirrhosis characterized by small nodule less than 3 mm, macronodular cirrhosis with larger nodules of various sizes greater than 3mm in diameter and mixed cirrhosis including features of both micro and macro nodules (Sharma and John, 2018).

Causes of cirrhosis:

The major causes of liver cirrhosis are viral hepatitis, alcoholic liver disease, non-alcoholic steatohepatitis. In addition, a wide variety of other factors including genetic factors, autoimmune diseases, cholestatic diseases, iron- copper load contribute to cirrhosis (Mishra *et al.*, 2020). More than 60% of cirrhotic cases are caused by Hepatitis B (HBV) and Hepatitis C (HCV) virus worldwide. Only a small number of cirrhotic patients are found to be infected with hepatitis D virus (HDV). Low immune function in pregnant women often plays role as a prerequisite for cirrhosis when infected with Hepatitis E virus (HEV). Alcohol related cirrhosis has been a significant cause of hospitalization in many developed countries. Development of hepatitis virus vaccines and effective antiviral therapy markedly reduced incidence and prevalence of end stage

liver cirrhosis. But now a days Non-alcoholic fatty liver disease (NAFLD) has sharply risen as a cause of cirrhosis in alarming rate. Sedentary life style, dietary changes, growing urbanization process led to develop NAFLD to be a rising cause of cirrhosis globally (Huang *et al.*, 2023). Cirrhosis is a dynamic diffuse pathological fibrosis with a transformation from normal liver tissue structure to abnormal nodular hyperplasia, turning cirrhosis from asymptomatic compensated stages to decompensated cirrhosis. However, prevention of cirrhotic process brings about the reversible liver fibrosis and the reversal of cirrhosis. That is the goal which prolongs life expectancy, delays complications and death in cirrhotic patient (Yi *et al.*, 2023).

D-Dimer:

The D-dimer is a by-product of the blood clotting and break-down process that can be measured via analysis of a blood sample. It is released when a blood clot begins to break down (Bounds and Kok, 2024). More specifically, D-dimer is a specific metabolite of cross-linked D domains of adjacent fibrin monomer formed by fibrinolytic enzyme (Bao *et al.*, 2017; Johnson, Schell and Rodgers, 2019).

D-Dimer molecules are produced by degradation of crosslinked fibrin during fibrinolysis. It requires active enzymes thrombin, factor XIIIa and plasmin. The process of D-Dimer generation starts with the thrombin formation in coagulation system which converts soluble fibrinogen to fibrin monomers. Following formation of fibrin polymers by fibrin monomers, fibrin is strengthened by other factors (factor XIIIa, thrombin) and crosslinks the D-domain of adjacent fibrin monomers. Plasmin digestion of the fibrin clots give rise to D-Dimer molecules (Balaceanu and Dina, 2024).

There are a variety of uses of D-Dimer under different pathologic conditions. Analysis of D-Dimer is critical for modern triage, deep vein thrombosis, pulmonary embolism, aortic dissection, disseminated intravascular coagulation, liver disease, aging (Johnson, Schell and Rodgers, 2019).

Interleukin- 6 (IL-6):

Interleukin 6 (IL-6) is a cytokine acts either as a proinflammatory cytokine or an anti-inflammatory cytokines under various circumstances (Zhang and An, 2007). It consists of 184 amino acids in a four helical form. It is a pleiotropic cytokine that exerts multiple functions in the body. This protein IL-6 is synthesized by fibroblasts, monocytes, macrophages, T cells and endothelial cells. IL-6 synthesis and secretion is induced during inflammatory conditions. IL-6 induces the broadest range of acute-phase proteins. In human IL-6 stimulates production of C-reactive protein, serum amyloid A, haptoglobin, fibrinogen, alfa-antitrypsin. IL-6 affects glycosylation of acute-phase proteins in human hepatoma cell lines by increasing N-glycosylation (Andus, Bauer and Gerok, 1991).

D-Dimer in liver cirrhosis:

As mentioned above, D- Dimer is a marker of fibrinolysis and fibrin turnover. It is a stable fibrin degradation product and an indicator of intravascular thrombosis. It is a soluble product results from systemic degradation of vascular thrombi through the fibrinolytic mechanism. This molecule exhibits unique properties as a biological marker of hemostatic abnormalities (Johnson, Schell and Rodgers, 2019). It is a specific metabolite of crosslinked fibrin formed by fibrinolytic enzyme. An increased concentration of D-Dimer level reflects fibrinolysis. D-Dimer also correlates with inflammatory parameters and ascertain inflammatory conditions in digestive and hepatobiliary diseases. At present D-Dimer has been widely used in diagnosis and evaluation of digestive diseases. It could be a potential biomarker for the diagnosis of portal hypertension and portal vein thrombosis in patient with cirrhosis. D-Dimer is marked gradually higher with advancement of cirrhosis which increases its utilization as a potential marker for monitoring severity of cirrhosis. From previous study, it is also found as a better predictor for poor prognosis and hospital death in liver cirrhosis (Bao *et al.*, 2017). Liver is the site of production of most proteins which are involved in the process of and inhibition of coagulation and fibrinolysis. A serious coagulopathy develops with the advancement of liver cirrhosis. This coagulopathy origins because of defective hepatic synthesis of clotting factors, secondary to portal hypertension. In patient with advanced cirrhosis hyper-fibrinolytic state contributes to bleeding tendency and it causes a premature removal of hemostatic plug (Spadaro *et al.*, 2008).

There is a combination of both defective coagulation and enhanced fibrinolysis in cirrhosis. Multifactorial coagulopathy in cirrhosis is accelerated by hyperfibrinolysis (El Gohary *et al.*, 2021). In short, hyperfibrinolysis in cirrhosis is assumed to be due to increased tissue plasminogen activator (tPA). tPA is bound to PAI-1 (Plasminogen Activator Inhibitor-1) and thus limits circulating tPA in healthy state. A decrease in synthesis of PAI-1 and decrease clearance of tPA by diseased liver causes the tPA-PAI-1 balance to be lost in cirrhosis. In addition, enhanced synthesis of tPA by activated endothelium in inflammatory condition rises tPA level in cirrhosis. tPA activates plasminogen to plasmin. Plasmin causes fibrin to breakdown which finally manifest as increased circulating D-Dimer level (Dhanunjaya, Anand and Anand, 2013). For hyperfibrinolysis in cirrhosis, D-Dimer is an accurate marker of fibrinolytic activity (Spadaro *et al.*, 2008)

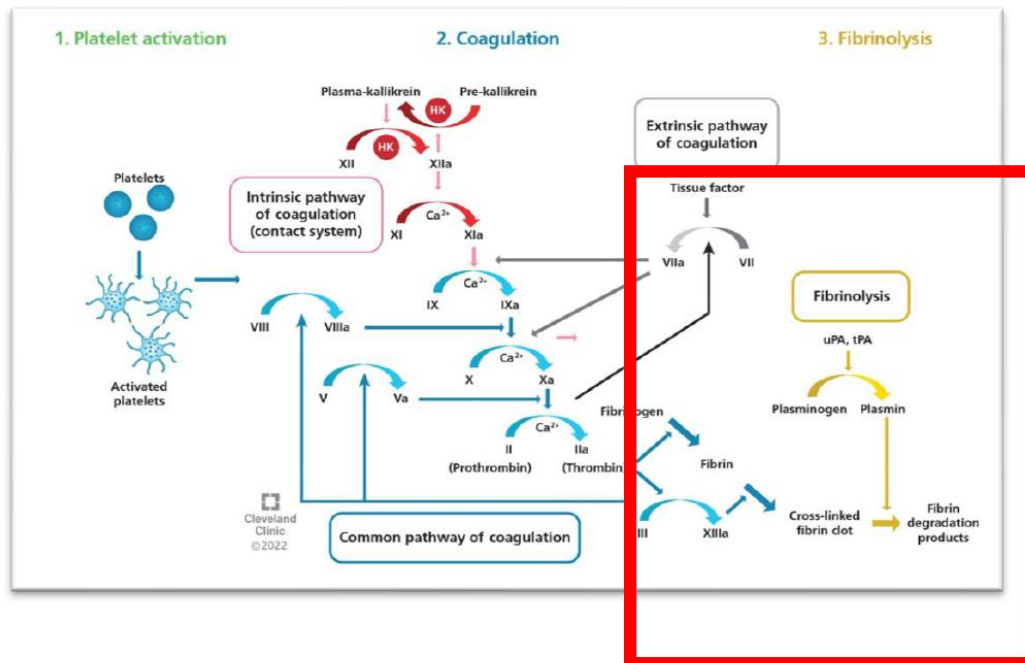


Figure: Common pathway of coagulation and fibrinolysis; Production of FDP (D-Dimer) (courtesy: Singh, Mucha and Lindenmeyer, 2022).

Ascites itself in cirrhosis contributes to rise of D-Dimer. A high D- Dimer concentration in cirrhosis decompensated by ascites suggests major role of ascites in the pathogenesis of hyper fibrinolytic state associated liver failure (Spadaro *et al.*, 2008). The elevated D-Dimer level in cirrhotic patient, more precisely decompensated with ascites is due to intraperitoneal activation of coagulation cascade along with systemic inflammation (Salgüero *et al.*, 2020).

Interleukin-6 (IL-6) in liver cirrhosis:

Inflammation which is a physiological response to injury but it is exaggerated with impaired resolution in cirrhosis (Engelmann, Zhang and Claria, 2023). Interleukin-6 (IL-6) is an inflammatory cytokine, a chemoattractant which plays a crucial role in hepatocyte homeostasis. It is a potent hepatocyte mitogen aids in regeneration of liver parenchyma cells and metabolic functions of liver (Schmidt-Arras and Rose-John, 2016). It has a direct effect on inducing hepatic acute phase response proteins including fibrinogen and CRP from liver during inflammation. Along with direct specific effect within the liver, it induces multiple systemic reaction in the body (Labenz *et al.*, 2019). On target cell IL-6 binds with interleukin-6 receptor (IL-6R). IL-6- IL-6R complex initiates a signaling pathway through a second receptor glycoprotein-130 (gp-130) and causes the activation of tyrosine kinase leads to autophosphorylation. This leads to activation of several intracellular signaling pathways. Initially, IL-6 plays a protective and regenerative role in liver. But persistent activation of IL-6 signaling pathway deteriorates liver functions and it may turn hepatocellular growth into liver tumor (Schmidt-Arras and Rose-John, 2016).

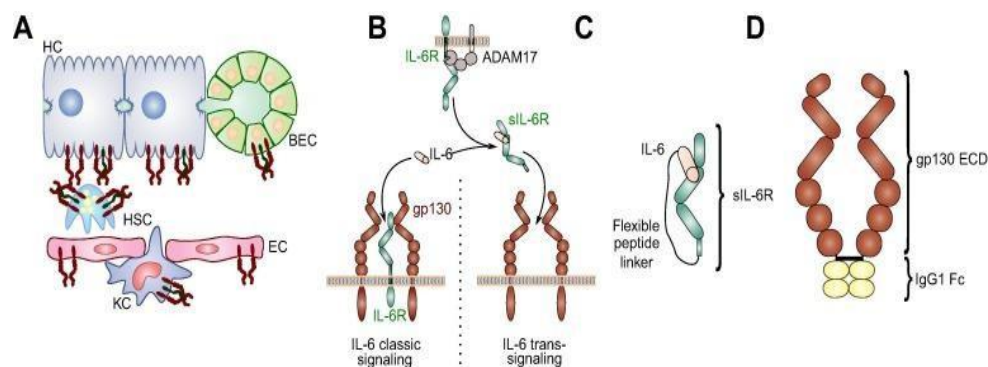


Figure: Expression of IL-6, IL-6R on different cell types of liver (Courtesy: Schmidt-Arras and Rose-John, 2016).

In various previous studies, systemic IL-6 concentrations are found elevated in liver cirrhosis. Impaired hepatic uptake of IL-6 in cirrhosis is considered as a contributing factor to high rise of serum IL-6 in cirrhosis. From the splanchnic organs IL-6 is transported to liver by portal vein. Direct correlation of porto-venous concentration of IL-6 with acute phase proteins confirms that it is a central indicator of hepatic acute phase proteins. In spite of having impaired acute phase response IL-6 is found markedly increased in cirrhotic patients (Wiest *et al.*, 2011). Patients with advanced cirrhosis are more prone to infections and in infective conditions exaggerated inflammatory response could be marked by elevated serum level of IL-6. Some studies have affirmed diagnostic value of IL-6 in deteriorated liver cirrhosis due to infection including serum bacterial peritonitis, acute on chronic liver failure, sepsis. It could be an early marker of inflammation and bacterial infection in cirrhosis (Lin *et al.*, 2015). IL-6 reacts faster to infectious stimuli.

IL-6 concentration is found higher in alcoholic liver cirrhosis (Prystupa *et al.*, 2015). High serum IL-6 level and higher IL-6 level in ascitic fluid of decompensated cirrhosis clearly indicates association of IL-6 with cirrhotic decompensation. It can be marker of prognosis in cirrhosis (Mayr *et al.*, 2020). Serum IL-6 level is found significantly higher in cirrhotic patient decompensated with hepatic encephalopathy. Without having evidence of active infection, the predictive performance of IL-6 is found superior to other established parameter including MELD score (Model for End Stage Liver Disease), covert hepatic encephalopathy status or CRP. In addition, serum IL-6 levels identify patients at high risk of developing overt hepatic encephalopathy, potentiality of survival among cirrhotic patients (Labenz *et al.*, 2019).

Child Pugh group and CP Score:

Child-Turcotte-Pugh criteria or Child Pugh criteria is a well-known method for assessing degree of liver damage in liver cirrhosis. CP score is calculated by using five factors (serum albumin, serum bilirubin, INR, ascites and hepatic encephalopathy) and patients are grouped in to Child Pugh class A, B, C accordingly (Salgüero *et al.*, 2020).

Prognosis of cirrhosis according to CP score:

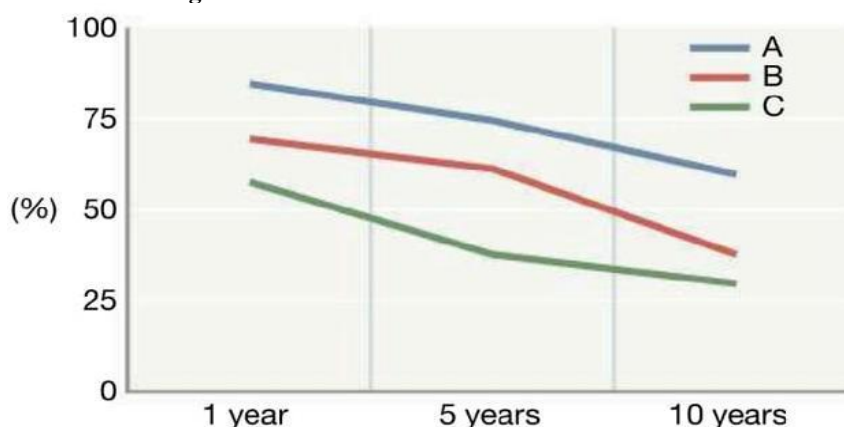


Figure: Survival in cirrhosis by CP score (Courtesy: Gordon-Walker and Williams, 2023)

Previous related study:

To evaluate biomarker linked to inflammation and coagulopathy in liver cirrhosis a cross-sectional study was done by Salgüero *et al.* (2020) among 97 cirrhosis patients. In the study, higher values of IL-6 and D-Dimer were found in all cirrhosis patients. Patients with Child-Pugh B cirrhosis (CTP 7-9) had higher values of D-Dimer and IL-6 than patients with Child-Pugh A cirrhosis (CTP<7). The values of these biomarkers were found significant to separate the study groups (Child-Pugh B vs Child Pugh A). The study found significant association between D-Dimer and the CTP score in all patients. It was concluded that, there were indications that higher levels of D-Dimer are found in patients with greater stage of cirrhosis. Besides systemic inflammation, the main reason for elevated D-Dimer in decompensated cirrhosis (mostly, with ascites) is systemic fibrinolysis due to intraperitoneal activation of coagulation cascades. Interleukin-6 was found independently associated with Child Pugh B cirrhosis with high accuracy. The severe cirrhosis may result from inflammatory syndrome, which increase the risk of acute-on chronic liver failure. Child Pugh C cirrhosis patients weren't included in the study.

A study on various stages of liver cirrhosis done by Dhanunjaya, Anand and Anand, (2013) conducted on 99 patients. Patients were classified into A, B, C group, according to Child Pugh Score in search for whether D-Dimer were abnormal in established diagnosis of liver disease. The study revealed significant higher value of D-Dimer in all three Child Pugh Group. The ANOVA test also showed gradual increase in D-Dimer value with

mean $\pm$ SD of 3.26 ($\pm$ 2.77) μ g FEU/ml in Child-Pugh A, 5.52 ($\pm$ 2.92) μ g FEU/ml in Child-Pugh B and 6.81($\pm$ 2.86) μ g FEU/ml in Child Pugh C. It was concluded significantly higher D-Dimer than normal, and the difference among three groups were found significant too. The study suggested D-Dimer as a valuable marker for hyper fibrinolytic status in cirrhosis patients which may further contribute to assess disease progression and bleeding tendency in liver cirrhosis.

With an aim to examine the correlation of D-Dimer levels with Child-Pugh scores to determine the predictive ability of D-Dimer for the in-hospital mortality of liver cirrhosis patients a retrospective study by Li *et al*, (2017) conducted between January 2011 and June 2014. In the study, D-Dimer tests were retrospectively analyzed. In total 703 cirrhotic patients were included in the study with an in-hospital mortality of 5.4%. The D-Dimer levels were correlated with Child Pugh score with correlation coefficient, .207; $P < 0.001$. The highest D-Dimer level was observed in the Child-Pugh C patients followed by Class B and Class A patients. Furthermore, significant differences were observed between three groups (C vs B, $P = .008$; B vs A, $P = 0.001$). The area under the Receiver Operating Characteristic Curve D-Dimer levels for predicting the in-hospital mortality rate for cirrhosis were found 0.729 ($P < 0.0001$) with a sensitivity of 86.84% and a specificity of 49.17%. The study revealed significant association of degree of liver dysfunction with D-Dimer levels and therefore concluded D-Dimer could be employed for the prognostic stratification of liver cirrhosis.

As growing evidence suggests cytokine's role in liver cirrhosis. To evaluate the association between serum IL-6 and severity of liver cirrhosis, a study conducted by Rey and Effendi-YS, (2021). A total 78 liver cirrhosis patients were enrolled with mean age 50.6 ± 11.4 . Among all cirrhosis patients 2.5%, 43.5% and 53.8% belonged to Child Pugh A, B, C groups respectively. The mean value of serum IL-6 was 24.5% which was highest among other cytokines in the study. A significantly higher IL-6 levels were found to be associated with severity of cirrhosis according to Child Pugh score. 38 patients were decompensated with Hepatic encephalopathy and 60 patients were decompensated with ascites. IL-6 showed high association in patient with hepatic encephalopathy.

In a bivariate correlations analysis of cardiac and proinflammatory markers, IL-6 was found correlated with indicators of disease severity in cirrhosis. Wiese *et al*. (2014) measured cytokine IL-6 in cirrhosis patients. The mean value of IL-6 was about 7.3, 7.6, 10.6 (pg/ml) in Child Pugh A, B and C groups respectively. IL-6 found significantly higher in patients decompensated with ascites (9.4pg/ml) than without ascites (8.0pg/ml). It concluded IL-6 as a marker associated with disease severity, degree of inflammation and survival of cirrhosis.

Liver cirrhosis with portal hypertension is associated with hyperdynamic circulation and it is characterized by generalized vasodilation and increased cardiac output. Lee *et al*. (1996) investigated whether IL-6 levels contribute to the pathogenesis of hyperdynamic circulation observed in cirrhotic patient. With the aim the study conducted in 58 consecutive patients. IL-6 level were found significantly higher in cirrhotic patients than healthy subjects. The study also found progressive increase of IL-6 concentration in relation to the severity of liver dysfunction. Liver dysfunction was graded by Child Pugh's classification. It was correlated with TNF-alpha and endotoxin to be found significant. From the study, IL-6 found to be an important biological marker increased with severity of cirrhosis which plays role in the hyperdynamic circulation in patients with cirrhosis.

III. Materials and Methods

3.1 Type of study: Cross-sectional observational study.

3.2 Place of study: Department of Biochemistry, Dhaka Medical College, Dhaka.

3.3 Study period: July 2023- June 2024

3.4 Study population:

45 diagnosed liver cirrhosis patients from the Department of Medicine, Department of Gastroenterology and Department of Hepatology of Dhaka Medical College Hospital, Dhaka.

3.5 Sample size calculation:

Sample size is calculated by GUILFORD and FRUCHER's formula:

$$n = \frac{z^2 pq}{d^2}$$

Here, n=sample size

z= 1.96 (at 95% confidence interval)

p= prevalence of liver cirrhosis in Bangladesh, 2.6% (Islam and Khan, 1975)

q= 1-p= 0.97

d= permissible error set at 5%= .05

$$n = \frac{(1.96)^2 \times .026 \times .97}{(.05)^2}$$

=38

Here, for convenience and proper study, a total 45 patients are considered.

3.6 Sample size: 45

Total sample size is grouped into A, B, C stages of liver cirrhosis based upon Child Pugh Score.

3.7 Sampling technique: Purposive Sampling.

3.8 Data collection technique: Data was collected by preformed datasheet.

3.9 Selection criteria:

Inclusion criteria:

- Age: 18 to 70 years.
- Diagnosed case of liver cirrhosis.
- Gender: Both male and female.

Exclusion criteria:

1. Patient with hepatoma, sepsis, deep vein thrombosis.
2. Patient with other systemic disease including cardiac failure, CKD.
3. Patient receiving hematinic, blood transfusion within one month.
4. History of malignancy.

3.10 Study Variables:

Independent variable:

Age Gender CP Score

Dependent variable:

Serum D-Dimer level Serum Interleukin-6 level

3.11 OPERATIONAL DEFINITIONS

Liver Cirrhosis:

Cirrhosis is defined histologically as a diffuse hepatic process characterized by advanced stage of liver fibrosis that is accompanied by distortion of the hepatic vasculature and the conversion of normal liver architecture into structurally abnormal nodules. It leads to shunting of the portal and arterial blood supply directly in to the hepatic outflow (central veins), compromising exchange between hepatic sinusoids and the adjacent liver parenchyma (Schuppan and Afdhal, 2008).

Liver cirrhosis was diagnosed by a combination of imaging (this included ultrasound, CT scan, MRI and transient elastography), clinical signs and examinations and a few patients were diagnosed by histopathological study in the Department of Medicine, Department Gastroenterology and Department of Hepatology, DMCH.

Child Pugh Score:

The Child-Pugh score is an internationally accepted system for grading the severity of cirrhosis and predictor of prognosis. It includes five measures including serum bilirubin, serum albumin, INR, presence of ascites and hepatic encephalopathy (Dhanunjaya, Anand and Anand, 2013).

Child-Pugh Measure	1 point	2 points	3 points
Serum total bilirubin (mg/dl)	<2	2-3	>3
Serum albumin (gm/dl)	>3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.20	>2.20
Ascites	None	Mild	Marked
Hepatic encephalopathy	None	Mild	Marked
Adding the individual score	5-6 =Child's A,	7-9=Child's B	>9=Child's C

(Dhanunjaya, Anand and Anand, 2013).

D-Dimer:

The normal reference value of D-Dimer is considered ≤ 500 ng/mL converted to ≤ 0.5 mg/L (Jenks, 2023).

IL-6:

The normal reference value of IL-6 is considered ≤ 10 pg/mL (Song and Kellum, 2005).

3.12 Study procedure:

This cross-sectional study was carried out in the Department of Biochemistry, Dhaka Medical College, Dhaka from January, 2024 to June, 2024. In this study forty-five (45) diagnosed liver cirrhosis patient were selected from the Department of Medicine, Department of Gastroenterology and Department of Hepatology by purposive sampling technique. After meeting the inclusion and exclusion criteria, patients with liver cirrhosis were enrolled for the study. Purpose of the study were explained in details to each subject. Written informed consent was taken from each subject. Data was collected in a pre-designed data collection sheet including particulars of the patient, relevant history and investigations. Patients were classified into Child-Pugh A, B, C on the basis of Child Pugh score using serum albumin, serum bilirubin, INR value and presence or absence of ascites and hepatic encephalopathy. Serum D-Dimer and Interleukin-6 levels were obtained from each sample.

Collection and preservation of blood sample:

With all aseptic precaution 5 ml of venous blood sample was collected from each study subject in a disposable plastic syringe. Then the blood was immediately transferred to a dry cleaned red capped test tube with a gently pushed to avoid hemolysis. Each test tube was labeled and coded for identification and was allowed to clot by keeping the tubes upright position for 20 minutes. Clear serum was separated by centrifuging at 3000 rpm for 10 minutes and taken in to a sterile Eppendorf tube after proper labeling. The separated serum was used for biochemical assay or was stored at -20°C if the analysis was delayed.

Laboratory Procedure: (Appendix-VIII)

All tests were performed in the laboratory of Department of Biochemistry, Dhaka Medical College, Dhaka. Method: Fluorescence immunoassay technology, especially the sandwich immunodetection method for both D-Dimer and Interleukin-6.

3.13 Statistical Analysis:

After meticulous checking and rechecking all data were compiled in a predesigned data collection sheet. Data was expressed as mean $\pm$ SD, median and range. For analysis, Statistical Package for Social Science (SPSS) 26th version was used. Categorical variable was analyzed by using Chi-square and continuous variables by ANOVA and Kruskal Wallis test. Post hoc (Bonferroni) test was performed for significant result. Correlation test among variables was done by Spearman correlation coefficient test. AUC ROC was used to determine sensitivity, specificity and cut off value. p value $< .05$ was considered as statistically significant.

3.14 Ethical Consideration

1. The study did not seem to pose any potential risk, except minor puncture site injury during taking blood for biochemical investigation. As strict aseptic procedure was adopted to avoid the risk, the study was justified.
2. For protecting anonymity, the name and the address were recorded on a separate sheet and specific code was assigned for each patient which was followed in each and every step of the procedure.
3. The nature, procedure, purpose, risk and benefits of the study were explained in detail to the study subjects followed by taking informed written consent from them.
4. Interests of the study subjects were not compromised to safe guard their rights and health.
5. The study used blood to carry out investigations. The study did not involve the testing of new drugs, placebo or use of organs. For obtaining blood, consent was taken from the subjects or their guardians involved.
6. Ethical clearance for the study was taken from the ethical review committee, Dhaka Medical College (Appendix-I)

IV. Result

A total 45 patients with liver cirrhosis fulfilling the selection criteria had taken part in the study. Age, gender, etiology history was collected. Categorical variables were expressed as frequency, percentage and continuous variables were expressed as mean, median, IQR and range. Categorical variables were assessed by using Chi-square test, comparison of intra-groups according to the CP score was done by ANOVA test and Kruskal Wallis test as appropriate. Post hoc (Bonferroni) test was performed for significant result. Correlation of the variables were analyzed using spearman correlation test. The AUC-ROC analysis was also performed which determined best cut off value for predicting severe stages of cirrhosis. The results were presented in tables and figures. Statistical analysis was performed by using the Statistical Package for the Social Science (SPSS) version 26.0 and was expressed as p value ($p < 0.05$ value considered as a level of significance).

Table-I: Distribution of age of the study subjects (N=45)

Age group (years)	Frequency (f)	Percentage (%)
20-30	5	11.1
31-40	7	15.6
41-50	12	26.7
51-60	11	24.4
61-70	10	22.2
Total	45	100.0
Mean $\pm$ SD	50.5 $\pm$ 12.8	
Range (min-max)	(25-70) years	

Table-I shows the age distribution of the study subjects. The majority of patients (26.7%) were in the 41-50 age group. The mean age of the patients was 50.5 $\pm$ 12.8 years, and the age range spanned from 25 to 70 years.

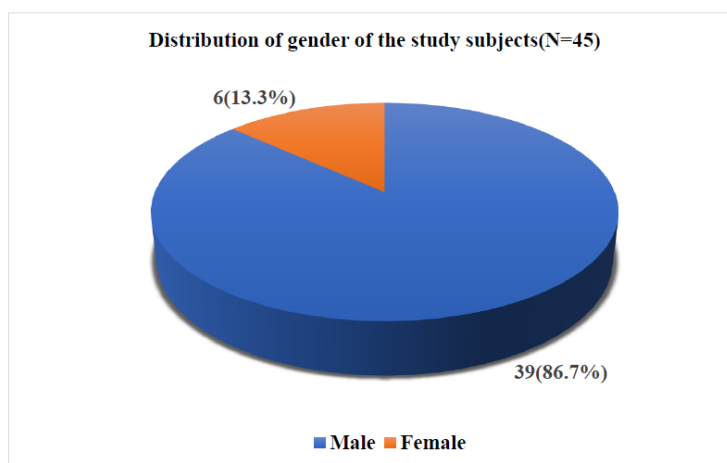


Figure-1: Pie diagram showing the distribution of gender of the study subjects

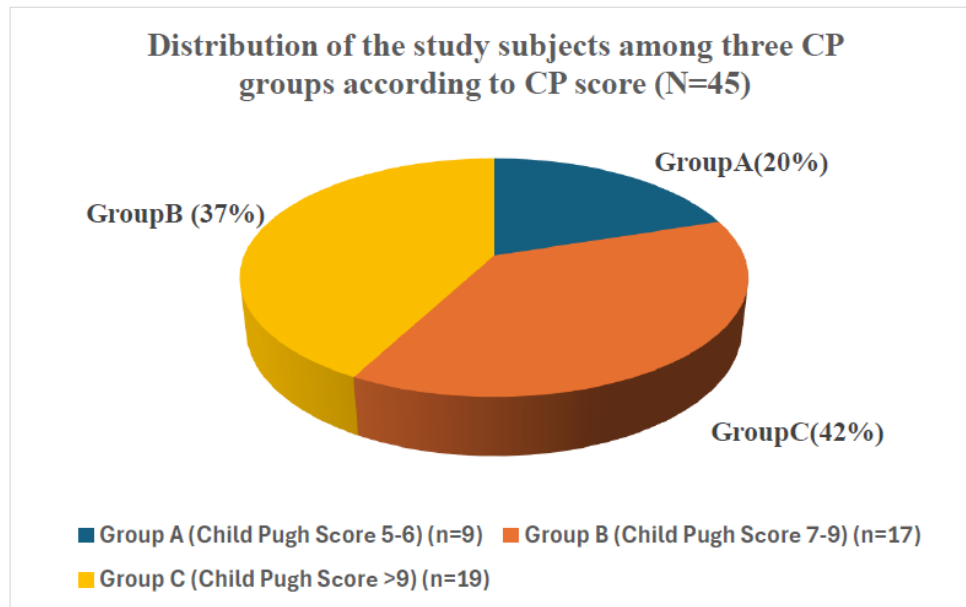


Figure-2: Pie diagram showing the distribution of the study subjects among three CP groups according to CP score (N=45)

Table- II: Association of pathophysiology among three groups (N=45)

Pathophysiology	Group by Child Pugh Score						p-value	
	Group A		Group B		Group C			Total f (%)
	(n=9)		(n=17)		(n=19)			
	n	%	n	%	n	%		
HBV	2	22	9	53	10	53	21(47)	
NAFLD	3	34	4	23	5	26	12(27)	
Cryptogenic	1	11	2	12	3	16	6(13)	
HCV	1	11	2	12	1	5	4(9)	
Wilson's disease,	1	11	0	00	0	00	1(2)	
Primary biliary cirrhosis	1	11	0	00	0	00	1(2)	
Total	9	100	17	100	19	100	45(100)	

Data were expressed as frequency (%)

p-value is obtained by Chi-square test

Table-II displays the distribution of pathophysiology among liver cirrhosis patients categorized by Child Pugh Score groups. No significant difference of pathophysiology among three groups was found ($p = 0.415$).

Table-III: Comparison of S. bilirubin, S. albumin and INR for CP score among three CP groups (N=45)

Parameters for CP score	Group by Child Pugh Score			p-value
	Group A	Group B	Group C	
	(n=9)	(n=17)	(n=19)	
S. Bilirubin(mg/dl)				
Mean±SD	1.17±0.44	1.57±1.29	7.44±8.92	0.041*
Median	1.20	1.0	2.3	
Range (min)	(0.7–1.9)	(0.6–5.4)	(0.5–25)	
S. Albumin (gm/dl)				
Mean±SD	3.90±0.47	3.12±0.75	2.59±0.82	<0.001*
Range (min)	(3.2–4.4)	(2–5)	(1.05–5.2)	
INR				
Mean±SD	1.16±0.14	1.30±0.29	1.67±0.59	0.007*
Range (min)	(1–1.41)	(1–2.14)	(0–2.8)	
Parameters for CP score	Post Hock (Bonferroni test)			
	Group A vs	Group A vs	Group B vs	
	Group B	Group C	Group C	
S. Bilirubin(mg/dl)	1.000	0.036*	0.014*	
S. Albumin (gm/dl)	0.044*	<0.001*	0.112	
INR	1.000	0.016*	0.043*	

p-value is obtained by ANOVA test, Kruskal Wallis test and Post Hoc Bonferroni test, $p < 0.05$ considered as a level of significance

Table-III illustrates significant biochemical and coagulation changes for CP score across different severity groups of liver cirrhosis, categorized by Child Pugh Score among 45 patients.

Table-IV: Association of clinical parameters for CP score among three CP groups (N=45)

Clinical parameters for CP score		Group by Child Pugh Core			p-value
		Group A	Group B	Group C	
		(n=9)	(n=17)	(n=19)	
Ascites					
	No ascites	8(88.9%)	5(29.4%)	1(5.3%)	<0.001*
	Mild ascites	1(11.1%)	9(52.9%)	3(15.8%)	
	Marked ascites	0(0.0%)	3(17.6%)	15(78.9%)	
Hepatic encephalopathy					
	No HE	9(100.0%)	8(47.1%)	4(21.1%)	<0.001*
	Mild HE	0(0.0%)	9(52.9%)	11(57.9%)	
	Marked HE	0(0.0%)	0(0.0%)	4(21.1%)	

p-value is obtained by Chi-square test, $p < 0.05$ considered as a level of significance

Table-IV illustrates significant changes of clinical parameters from absence of ascites and hepatic encephalopathy to mild to marked presence of the parameters across different severity groups of liver cirrhosis, categorized by Child Pugh Score among 45 patients.

Table-V: Comparison of serum IL-6 among three groups (N=45)

S. IL-6 (pg/ml)	Group by Child Pugh Score			p-value
	Group A	Group B	Group C	
	(n=9)	(n=17)	(n=19)	
Median	3.20	5.80	31.0	<0.001
Range (min-max)	(3–24.4)	(3.0–72.6)	(6.20-206.8)	
IQR	3.1-15.7	3.9-9.90	22.9-64.0	
Post Hoc (Bonferroni)				
Group A vs Group B				1.000
Group A vs Group C				0.005*
Group B vs Group C				0.002*
Data were expressed as median, IQR and range				
p-value is obtained by Kruskal Walis test and Post Hoc Bonferroni test				

Table-V presents the comparison of serum IL-6 levels among liver cirrhosis patients categorized by Child Pugh Score groups. The Median IL-6 levels are found significantly higher from 3.20 pg/ml in Group A, 5.80 pg/ml in Group B to 31.0 pg/ml in Group C ($p < 0.001$). The difference among Group A vs Group C and Group B vs Group C was also found statistically significant using Post Hoc Bonferroni test. The mean serum IL-6 level was 8.71 ± 8.93 pg/ml, 12.75 ± 18.02 pg/ml, 54.02 ± 47.6 pg/ml in Group A, B, C respectively.

Table- VI: Association of high serum IL-6 among three groups (N=45)

Serum IL-6	Group by Child Pugh Score						p-value
	Group A		Group B		Group C		
	(n=9)		(n=17)		(n=19)		
	n	%	n	%	n	%	
High (>10pg/ml)	2	22.2%	3	17.6%	18	94.7%	<0.001
Normal(≤10pg/ml)	7	77.8%	14	82.4%	1	5.3%	
Total	9	100.0%	17	100.0%	19	100.0%	
Data were expressed as frequency (%)							
p-value is obtained by Chi-square test, result is significant							

Table-VI shows the association of high serum IL-6 levels (>10 pg/ml) among liver cirrhosis patients categorized by Child Pugh Score groups (Group A: 5-6, Group B: 7-9, Group C: >9) in 45 patients.

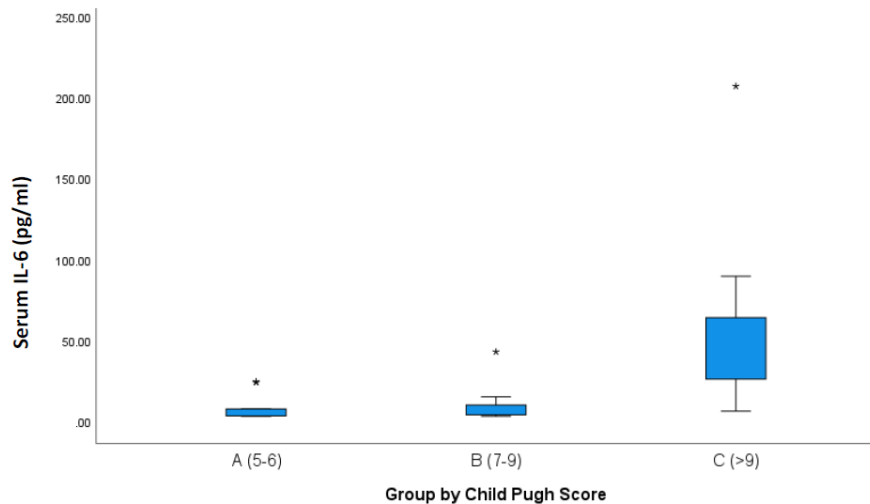


Figure-3: Box plot showing the serum IL-6 level according to Child Pugh Score

Table-VII: Comparison of serum D-dimer (mg/L) among three groups (N=45)

S. D-dimer (mg/L)	Group by Child Pugh Score			p-value
	Group A (n=9)	Group B (n=17)	Group C (n=19)	
Median	1.25	2.45	10.0	
Range (min-max)	(0.85–4.34)	(0.86–8.92)	(2.52–10.0)	<0.001
IQR	1-2.91	1.58-6.84	6.25-10.0	
Post Hoc (Bonferroni)				
Group A vs Group B				0.188
Group A vs Group C				<0.001*
Group B vs Group C				<0.001*

Data were expressed as median, IQR and range
p-value is obtained by Kruskal Wallis test and Post Hoc Bonferroni test

Table-VII presents the comparison of serum D-dimer levels among liver cirrhosis patients categorized by Child Pugh Score groups in 45 patients. The median D-dimer levels values were 1.25 mg/L in Group A, 2.45 mg/L in Group B, and 10.0 mg/L in Group C. The difference among Group A vs Group C and Group B vs Group C was also found statistically significant using Post Hoc Bonferroni test. The mean serum D-dimer level was 1.93 ± 1.21 mg/L, 3.87 ± 2.86 mg/L, and 8.57 ± 2.50 mg/L in Group A, B, C respectively.

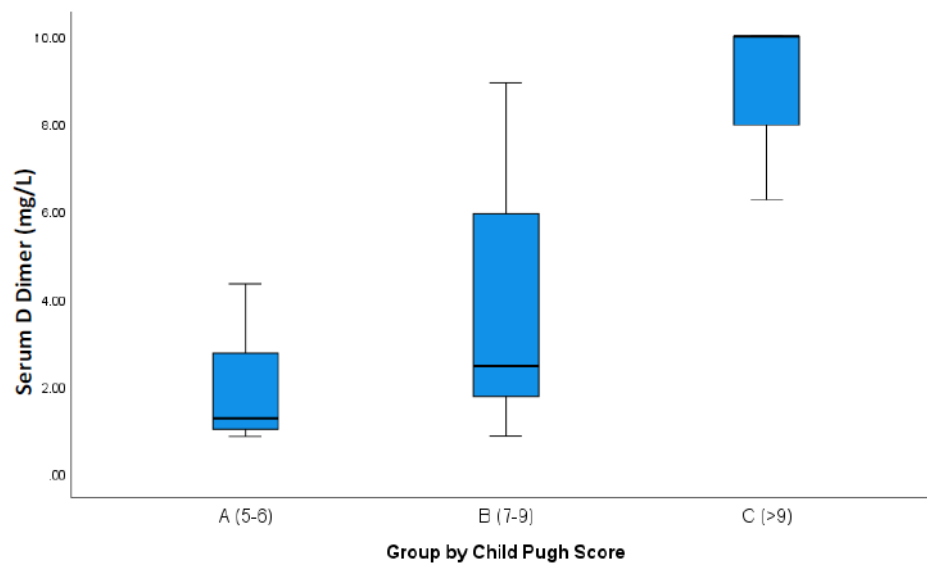


Figure-4: Box plot showing the serum D-dimer level according to Child Pugh Score

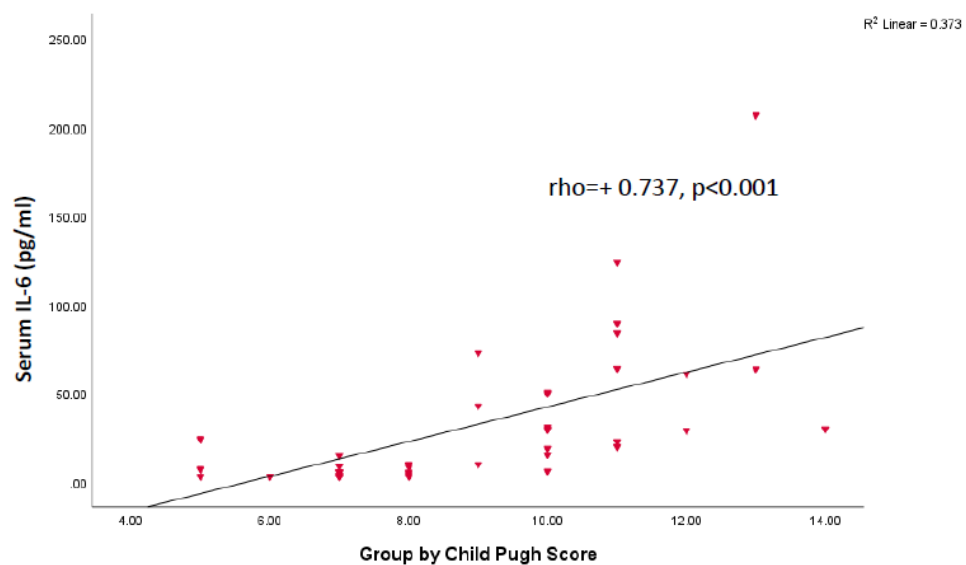


Figure-5: Correlation of disease severity of liver cirrhosis with serum IL-6

Figure-5 the scatter diagram shows a strong positive correlation between disease severity of liver cirrhosis with serum IL-6 of liver cirrhosis patients ($\rho=+0.737$, $p<0.001$).

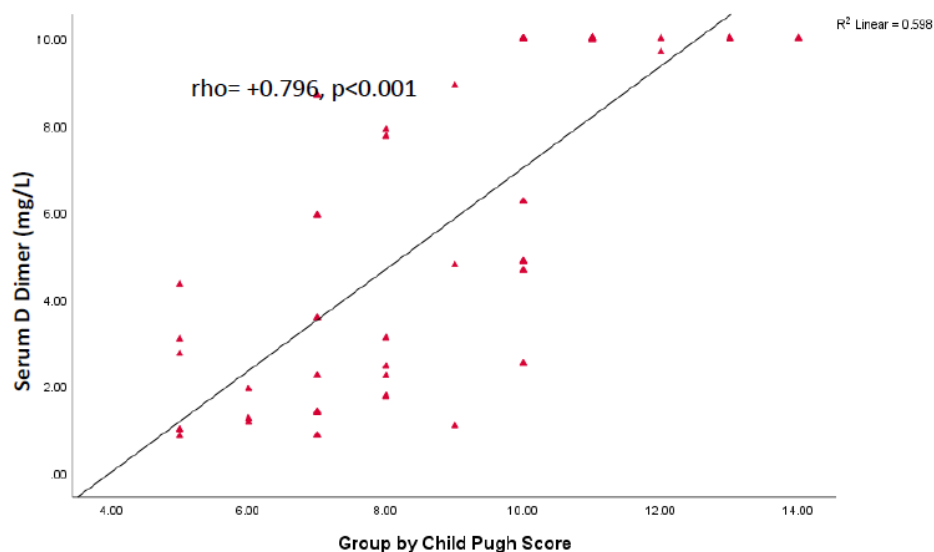


Figure-6: Correlation of disease severity of liver cirrhosis with serum D-dimer

Figure-6 the scatter diagram illustrates a strong positive correlation between disease severity of liver cirrhosis and serum D-dimer levels ($\rho=+0.796$, $p<0.001$).

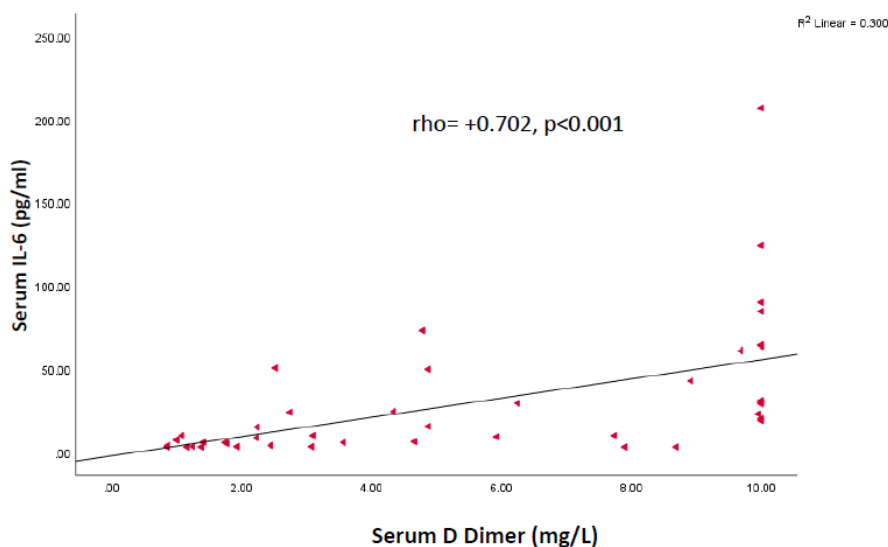


Figure-7: Correlation of serum D-dimer with serum IL-6

Figure-7 shows a strong positive correlation between serum D-dimer levels and serum IL-6 levels in patients with liver cirrhosis. The correlation coefficient (ρ) of $+0.702$, p -value <0.001 .

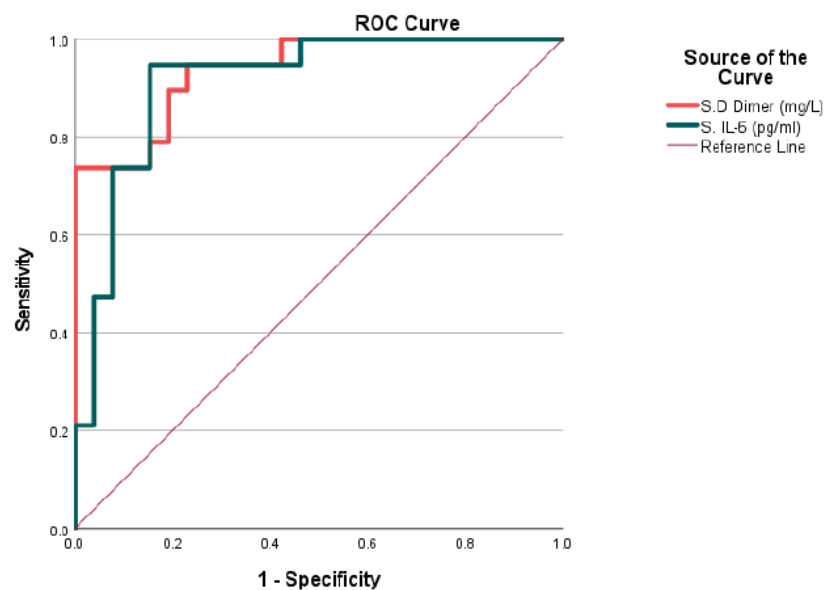
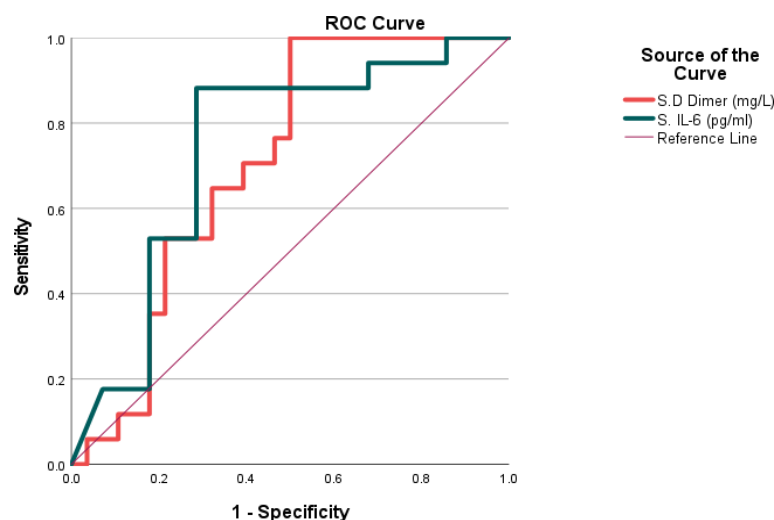


Figure-8: ROC Analysis of Serum D-dimer and IL-6 Levels for Predicting Severe Liver Cirrhosis (Child Pugh Score >9)

Test Result Variable(s)	Area Under the Curve				Sensitivity	Specificity	p-value	95%CI	
	AUC	SE	Cut off value					Lower	Upper
S.D dimer (mg/L)	.937	.034	4.50		94.7%	76.9%	.000	.871	1.00
S. IL-6 (pg/ml)	.913	.044	15.2		94.7%	84.6%	.000	.827	.999

Figure-8 shows the ROC (Receiver Operating Characteristic) analysis performed to determine the best cut-off values for serum D-dimer and serum IL-6 in predicting a Child Pugh Score greater than 9 in liver cirrhosis patients. The optimal cut-off value for serum D-dimer is 4.50 mg/L, sensitivity 94.7% and specificity 76.9%, a p-value of 0.000. The best cut-off value for serum IL-6 is 15.2 pg/ml, sensitivity 94.7% and specificity of 84.6%, with a p-value of 0.000.

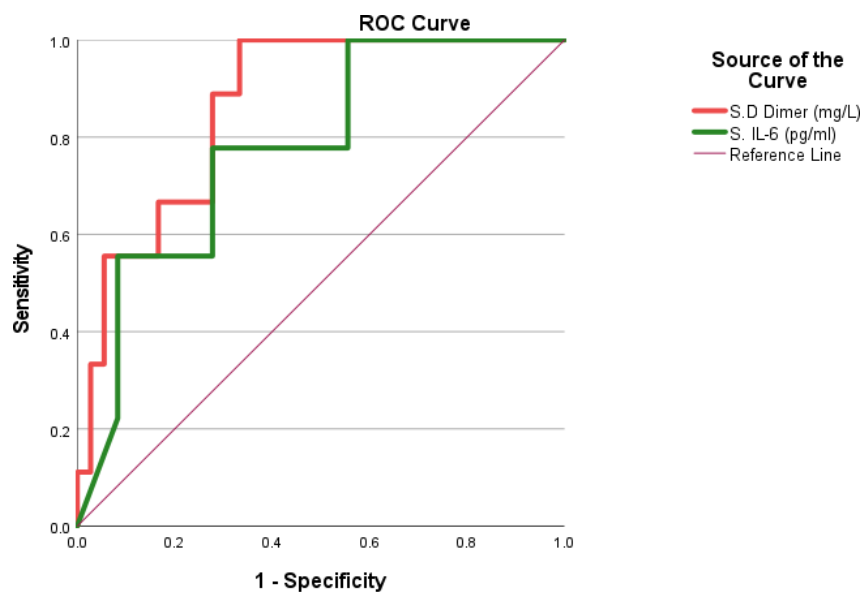


Diagonal segments are produced by ties.

Figure-9: ROC Analysis of Serum D-dimer and IL-6 Levels for Predicting Severe Liver Cirrhosis (Child Pugh Score 7-9)

Area Under the Curve								
Test Result	AUC	SE	Cut off	Sensitivity	Specificity	p-value	95%CI	
Variable(s)			value				Lower	Upper
S.D dimer (mg/L)	.706	.077	3.95	64.7%	67.9%	.002	.556	.856
S. IL-6 (pg/ml)	.739	.077	12.45	82.4%	71.4%	.008	.588	.891

Figure-9 shows the ROC (Receiver Operating Characteristic) analysis performed to determine the best cut-off values for serum D-dimer and serum IL-6 in predicting a Child Pugh Score 7-9 in liver cirrhosis patients. The optimal cut-off value for serum D-dimer is 3.95 mg/L, sensitivity 64.7% and specificity 67.9%, a p-value of 0.002. The best cut-off value for serum IL-6 is 12.45 pg/ml, sensitivity 82.4% and specificity of 71.4%, with a p-value of 0.008.



Diagonal segments are produced by ties.

Figure-10: ROC Analysis of Serum D-dimer and IL-6 Levels for Predicting Severe Liver Cirrhosis (Child Pugh Score 5-6)

Area Under the Curve								
Test Result	AUC	SE	Cut off	Sensitivity	Specificity	p-value	95%CI	
Variable(s)			value				Lower	Upper
S.D dimer (mg/L)	.706	.077	3.95	64.7%	67.9%	.002	.556	.856
S. IL-6 (pg/ml)	.739	.077	12.45	82.4%	71.4%	.008	.588	.891

Figure-10 shows the ROC (Receiver Operating Characteristic) analysis performed to determine the best cut-off values for serum D-dimer and serum IL-6 in predicting a Child Pugh Score 5-6 in liver cirrhosis patients. The optimal cut-off value for serum D-dimer is 2.91 mg/L, sensitivity 77.8% and specificity 72.2%, a p-value of 0.001. The best cut-off value for serum IL-6 is 9.50 pg/ml, sensitivity 77.8% and specificity of 66.7%, with a p-value of 0.011.

V. Discussion

This present study was conducted to evaluate the status of fibrinolytic and coagulopathy marker D-Dimer and inflammatory marker IL-6 and their relationship in various stages of liver cirrhosis. Their potential role as a predictor for the disease severity was analyzed where stages of severity of liver cirrhosis was evaluated

by Child Pugh score. For this purpose, total 45 diagnosed liver cirrhosis patients who were admitted in Department of Medicine, Department of Gastroenterology and Department of Hepatology of Dhaka Medical College, Dhaka were selected. Serum D-Dimer and IL-6 level in Child Pugh A, B, C group was estimated and compared among three cirrhotic groups. Their values were correlated with CP score. Their relation between each other in cirrhosis was also assessed. Liver cirrhosis related demographic variable and etiology were also observed. Clinical significance of the tests was assessed.

In this study, 26.7% of the study subjects are found to be within 41-50 age group which is the majority among all age group. Mean $\pm$ SD of age was 50.5 $\pm$ 12.8 years and the range of age spanned from 25 to 70 years. Researcher Zhou *et al.* (2019) found

52.8 $\pm$ 11.7 years as mean age for cirrhosis. Most of the patients of liver cirrhosis are found belonged to over fifth decade of age probably because of the requirement of time for cirrhotic change in liver as it is a chronic disease. A study by Georgieva, Xenodochidis and Krasteva, (2023) mentioned reducing regenerating capacity of liver and susceptibility to chronic disease with increasing age were suggestive of more severe cirrhosis.

86.7% of total subjects were found male in this study. The male to female ratio was

6.5:1. Several studies on liver cirrhosis found majority of the patients are male. Rubin, Sundaram and Lai, (2020) stated spontaneous hepatic clearance of hepatitis C and female sex hormone acting as a protective factor for less fibrosis progression are favorable causes for liver cirrhosis occurring less in women.

The distribution of patients according to Child Pugh criteria was not evenly distributed among three groups. Among total 45 liver cirrhosis patients 9 (20%), 17

(37%) and 19 (42%) patients were in Group A (5-6), B (7-9), C (>9) respectively. In a referral hospital like Dhaka Medical College Child Pugh class B and C patients were mostly found admitted for treatment during data collection. The biochemical parameters for CP score among three CP groups showed significant differences. The differences between groups A vs C and B vs C for S. bilirubin, group A vs B and group A vs C for S. albumin and group A vs C and B vs C for INR were also found significant. Clinical parameters for CP score showed significant changes from absence of ascites and hepatic encephalopathy to mild to marked presence of the parameters across different severity groups of liver cirrhosis. Cirrhotic patients with CP group A are often asymptomatic without any complications.

The etiology of cirrhosis showed predominance of hepatitis B virus. Other etiologies included HCV infection, Nonalcoholic Fatty Liver disease, Primary biliary cirrhosis Wilson's disease to cryptogenic. This finding is in support as study of Huang *et al.* (2023) mentioned HBV infection, HCV infection, NAFLD are major causes of cirrhosis globally. Alcoholic liver disease is also a common cause worldwide (Sharma and John, 2018). But not very common in Bangladesh as study by Rahman *et al.* (2014), it was reflected in this study as no patient was found with that etiology.

Comparison of serum D-Dimer levels among three CP groups were statistically significant ($p < 0.001$). The median D-dimer levels were 1.25 (range 0.85-4.34) mg/L,

2.45 (0.86-8.92) mg/L, 10.0 (range 2.52-10.0) mg/L for A, B, C group respectively. The result has clearly shown that, patients with cirrhosis have an evident hyper fibrinolytic feature. The difference among Group A vs Group C and Group B vs Group C was also found statistically significant using Post Hoc Bonferroni test. The result is consistent with Dhanunjaya, Anand and Anand, (2013) who found increased D-Dimer in 63% of patients with liver cirrhosis with significant difference among three groups.

In this study 100% of patients are found with high D-Dimer value. High D-Dimer value was found from a very early stage of Child-Pugh group. It indicates incidence of significant fibrinolysis from very early stage of cirrhosis. It suggests D-Dimer to be an asset in assessing cirrhotic change long before the development of decompensating complications.

Serum D-Dimer value showed significant strong positive correlations ($\rho = +0.796$, $p < 0.001$) and gradual increase with increasing Child-Pugh score. Cirrhosis patients with Child Pugh class C group had higher D-Dimer value than group B, which has declined more in group A. The AUC-ROC analysis was also performed which determined best cut off values of D-Dimer 2.91 mg/L, 3.95 mg/L and 4.50mg/L for predicting severe stages of cirrhosis with 5-6, 7-9 and above 9 Child Pugh score respectively.

This gradual increase of D-Dimer level according to severity is also coherent with studies by Li *et al.* (2017) and Salgüero *et al.* (2020). D-Dimer showed positive correlation with CP score in both studies. Li *et al.* (2017) found D-Dimer to be a good predictor for predicting the in-hospital mortality in liver cirrhosis. The calculated cut off value was 0.28 μ g/ml by AUCROC for predicting in hospital mortality rate of liver cirrhosis. A current study by Volkanovska *et al.* (2023) also demonstrated significant strong positive correlation between D-dimer level and CP scores ($r = 0.74$, $p = 0.0001$).

D-dimer is a sensitive marker of coagulation and fibrinolysis. Higher levels of D-Dimer can be pointed out in liver cirrhosis. The main reason for elevated D-Dimer levels in cirrhosis is hyperfibrinolysis because of intraperitoneal activation of coagulation cascade and systemic inflammation. Spadaro *et al.* (2008) proposed,

when cirrhosis is complicated with ascites, ascitic fluid itself contributes to fibrinolysis by exchanging coagulation and fibrinolytic protein between circulatory fluid and ascitic fluid. Decreased clearance of tissue plasminogen activator (tPA) and decreased synthesis of plasminogen activator inhibitor (PAI-1) increases plasmin activity which causes hyperfibrinolysis. That might contribute to increased bleeding risk too in liver cirrhosis patients.

In this study, biomarker IL-6 is evaluated in liver cirrhosis. It can be validated from this study that IL-6 might be a suitable inflammatory marker for cirrhotic inflammation. Serum IL-6 is found significantly increasing from Child Pugh group A to C with p value < 0.001 . The median IL-6 levels were 3.20 (range 3-24.4) pg/ml in group A, 5.80 (3.0-72.6) pg/ml in group B and 31.0 (6.20-206.6) in group C. The difference among groups were significant ($p < 0.001$). The difference among Group A vs Group C and Group B vs Group C was also found statistically significant using Post Hoc Bonferroni test. It showed significant association with increasing severity of cirrhosis ($p < 0.001$).

The result of this study is in agreement with Rey and Effendi-YS, (2021) who found serum IL-6 to be associated with more severe liver cirrhosis. Total patients of the study were classified accord to Child Pugh group. IL-6 level were found higher in class C patients than combined A and B group. Along with IL-6, some other cytokines were also studied but only IL-6 was found significantly associated with severity of liver cirrhosis.

In this study, IL-6 showed significant strong positive correlation with Child Pugh score with $\rho = 0.737$, $p < 0.001$). The AUCROC analysis was also performed for diagnosis of severity of Child Pugh cirrhosis. The best cut off value for serum IL-6 was 9.50 pg/ml, 12.45 pg/ml, 15.2 pg/ml for predicting severe stages of cirrhosis with 5-6, 7-9 and above 9 Child Pugh score respectively.

Wiese *et al.* (2014) and Salguero *et al.* (2020) also found higher value of IL-6 were related to liver cirrhosis severity (according to CP score). Salguero *et al.*, (2020) found only IL-6 among other cytokines, had the potential in separating patients with Child-Pugh B cirrhosis accurately. IL-6 was independently associated with Child Pugh B cirrhosis. That study couldn't include any patients of Child- Pugh C group. Labenz *et al.* (2019) identified raised serum IL-6 in patient with liver cirrhosis at high risk for overt hepatic encephalopathy. Mariadi *et al.* (2020) found significant moderate correlation of IL-6 with CP score with $r = 0.51$; $p < 0.001$.

Prystupa *et al.* (2015) found significant higher value of IL-6 in group B and C in alcoholic cirrhosis patients. Rey and Effeny-YS, (2021) suggested upregulation of IL-6 along with other regulatory cascade promote hepatic stellate cell activation, causing liver fibrosis and cirrhosis. This condition is termed as inflammation-fibrosis axis. Host immune response and inflammatory cytokine production together are responsible for liver injury in different etiology of cirrhosis. IL-6 could be a valuable inflammatory marker in liver cirrhosis. Though Rey *et al.* (2018) in a different study found no significant difference value of IL-6 among Child Pugh A, B, C group.

Despite having many limitations and small sample size this study found relevant findings of strong relation of serum D-Dimer and IL-6 with various severe stages of cirrhosis. However, in a different study design with larger sample size these finding could be evaluated more precisely.

VI. Conclusion, Limitation and Recommendation

6.1 Conclusion

In this study, the majority of the subjects belonged to 41 to 50 age group. 86.7% of all subjects were found to be male. HBV infection was a prominent etiology of cirrhosis of the total study subjects with 47% and it was also a major etiology in CP group B and C. Serum D-dimer and IL-6 values are found significantly higher with increasing severe stages of liver cirrhosis. D-dimer and IL-6 showed significant positive correlation with Child Pugh score.

6.2 Limitation

- All samples were collected from single tertiary center; therefore, it may not reflect the entire population.
- Sample size could not be evenly distributed among three CP groups.
- Time constraints.

6.3 Recommendations

- This study was conducted in a cross-sectional study design, no intervention or follow up could be done. Further prospective cohort study or experimental study should be carried out to establish a better relationship of serum D-Dimer and IL-6 among different stages of liver cirrhosis.

- More study with larger sample size should be conducted for precise result for assessing the role of serum D-Dimer and IL-6 in various stages of cirrhosis for better predictive value for prognosis.

ACKNOWLEDGEMENTS

In the name of almighty Allah, most gracious, most merciful, I would like to express my heartiest gratitude to my respected teacher and supervisor Prof. Dr. Monzarin Mahal, Professor, Department of Biochemistry, Dhaka Medical College, Dhaka, whose keen supervision, scholastic guidance, constructive criticism, suggestions and kind co-operation has made this study a successful one. Without her guidance it would have been impossible for me to carry out this thesis and which may not come to light. She deserves more than I can express, and I consider myself very fortunate to have her as my supervisor.

I am highly grateful to Prof. Dr. Khadija Akther Jhuma, Professor & Head, Department of Biochemistry, Dhaka Medical College for her inspiration, sincere guidance and help to carry out the procedures throughout the course.

I am grateful and convey my gratitude and respect to Prof. Dr. Md. Asadul Kabir, Professor and Head, Department of Medicine, Prof. Dr. Hafeza Aftab, Professor and Head, Department of Gastroenterology, Prof. Dr. Faroque Ahmed, Professor and Head, Department of Hepatology, Dhaka Medical College, Dhaka for their kind co-operation.

With due respect, I would like to express my special thanks to Prof. Dr. Segupta Kishwara, Head, Department of Anatomy, Ex-Chairman, Ethical Review Committee (ERC) and Prof. Dr. Debesh Chandra Talukdar, vice principal, Chairman, Ethical Review Committee (ERC), Dhaka Medical College, Dhaka.

I would like to thank Dr. Shahnoor Sharmin, Associate Professor, Medicine, Dhaka Medical College, Dhaka for her valuable review.

I am grateful and I convey my respect to Prof. Dr. Neelufar Chowdhury, Professor, Prof. Dr. Afia Shahnaj, Professor, Dr. Mehbooba Akhter, Associate Professor, Dr. Nafisa Sultana Khanom, Associate Professor, Dr. Urmee Rahman Nipa, Assistant Professor, Dr. Bidoura Sharmin, Assistant Professor and all other teachers of the Department of Biochemistry, Dhaka Medical College, Dhaka.

I want to give my special thanks to Hafizur Rahman, Biochemist, Department of Biochemistry for their help in performing the laboratory test. I am also thankful to all the staff of the Department of Biochemistry.

I also extend my gratitude to all my course mates who have always helped me, gave me valuable suggestions, and encouraged me during this study period. I pray for their well-being.

I will remain grateful to all the patients who have participated in this study. I pray for their good health.

I would like to thank all the doctors, nurses and staffs of respected Department of Medicine, Gastroenterology and Hepatology for their kind contribution.

Finally, I am grateful to my family members for their utmost patience, unimaginable support and sacrifice during the completion of the thesis.

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