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Assessment of coagulation abnormalities associated with liver diseases

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Abstract

Coagulation abnormalities in patients with liver diseases occur frequently. The disorders include, changes in procoagulant factors, natural anticoagulant factors, fibrinolytic, antifibrinolytic, inhibitors of coagulation factors, endothelial dysfunction, thrombocytopenia and thrombocytopathy disturbing the normal hemostatic balance, results in different clinical conditions from abnormal bleeding to thrombosis. This study was aimed to assess the coagulation abnormalities associated with liver diseases. Routine coagulation tests such as *Prothrombin Time*, *Activated Partial Thromboplastin Time* and Platelet count were carried out for all patients. Data and samples of 278 patients admitted in Gastroenterology Ward of Hayatabad Medical Complex Peshawar (excluding patients with congenital coagulation disorders). Patients with prolonged PT= 91.7%, (mean value 28.6 ± 15.1 sec), with cumulative percentage of patients with International Normalized Ratio=3 was 78%, prolonged APTT= 88%, with (mean value = 50.6 ± 19 sec), Prolonged PT and APTT both= 84.9%, low platelet count= 59%. No significant difference was found between male and female patients regarding coagulation disorder. Patients with gastrointestinal bleeding were 13%.The study concluded that most of the patients were at risk for abnormal bleeding or thrombo-embolism. These patients would need prophylaxis before going through surgery and would need special care after any trauma or injury.

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Introduction

The physiological mechanism of blood coagulation is associated with the liver function. Most of the clotting factors are synthesized and controlled by liver parenchymal cells except von Willebrand factor and the two important activators of the fibrinolytic system, tissue plasminogen activator (t-P A) and urokinase-type plasminogen activator (u-PA). The liver not only synthesizes the coagulation proteins but also regulated the phenomena of coagulation. It helps in the clearance of the fibrinolytic factor, products of the fibrinogen to fibrin conversion by its reticuloendothelial system. As liver has a vital role in regulating blood coagulation therefore any abnormality in its function will lead to impaired hemostasis. Liver disorders can result in the deficient synthesis of coagulation proteins, synthesis of abnormal clotting factors or impaired clearance of the activators fibrinolytic factors.

Blood coagulation and fibrinolysis works as a defense mechanism for vasculature. They maintain the integrity of the vascular system with a primary function to prevent loss of blood and prevent unwanted thrombosis (Ziedins *et al.,* 2009). After injury or surgery, the balance of hemostasis shifts toward a net Procoagulant activity to promote clot formation and to stop bleeding. Once the control over abnormal bleeding is achieved, the balance then shifts toward a net anticoagulant activity to limit the clot to the site of injury only. It is important to understand the coagulation phenomena as it helps in choosing treatment. Hemostasis can be considered as control of bleeding within the finely tuned balance of Procoagulant, anticoagulant, Fibrinolytic, and antifibrinolytic activities (Adams GL *et al.,* 2007).

The hemostatic network consists of the Blood vessels, Platelets, Procoagulant factors, Natural anticoagulant factors, Fibrinolytic factors and their inhibitors, Antifibrinolytic factors. When there is no injury or any pathology in the normal circulation, endothelium play a major role in keeping the patency and integrity of vasculature and have anticoagulant activity to prevent any unwanted coagulation in the normal circulation. Endothelial cells express protein C receptors, tissue factor pathway inhibitor (TFPI), tissue plasminogen activator (tPA), thrombomodulin, heparin, Prostacycline and nitric oxide (NO) to prevent clot formation. But after vascular injury, endothelial cells express tissue factor (TF), and secrete plasminogen activator inhibitor (PAI), von Willebrand factor and protease activated receptors, all of which are procoagulant. Different gene expression in response to change in the microenvironment keeps the hemostatic balance between bleeding and clotting (Adams GL *et al.,* 2007).Normal hemostasis is explained in two steps, firstly the *primary hemostasis* and secondly the *secondary hemostasis.* The process of coagulation takes place in two different pathways, called the *extrinsic* and *intrinsic* pathways illustrated in Fig 1. Both pathways end at the common production of factor Xa. Further process of coagulation is common for both pathways, so then it's called *common pathway* of coagulation.

Any pathology of the liver and biliary system will affect the physiological functions of hepatocyte. Liver disorders affect the synthesis of coagulation factors, and results in coagulopathies. Liver diseases have multiple etiologies. Level of abnormalities in hemostatic balance occurs according to different etiological liver disorders. Coagulation disorders in acute liver failure are somewhat different than chronic liver failure. Even in chronic failure, there is a difference between patients with cholestatic and non-cholestatic liver disease. For example, clotting factors deficiency is more severe, thrombocytopenia is less common in acute liver failure as compare to liver cirrhosis. Fibrinolysis is usually normal or hyper fibrinolysis occur in cirrhosis while inhibited in acute liver failure (Lisman *et al.,* 2001). Any pathology in the liver system can be classified as liver disease. Here we discussed only those major liver diseases, which can result in a prominent coagulation disorder based on various routine coagulation tests like prothrombin time (PT)/international normalized ratio (INR), activated partial thromboplastin time (APTT) and platelets count.

Pakistan carries one of the world's highest burdens of chronic hepatitis and mortality due to liver failure and hepatocellular carcinomas. However, national level estimates of the prevalence of and risk factors for hepatitis B and hepatitis C are currently not available. Methodological differences in studies made it inappropriate to conduct a formal meta-analysis to determine accurate national prevalence estimates, but the likely range of prevalence were estimated in different population sub-groups. A weighted average of hepatitis B antigen prevalence in pediatric populations was 2.4% (range 1.7–5.5%) and for hepatitis C antibody was 2.1% (range 0.4–5.4%). A weighted average of hepatitis B antigen prevalence among healthy adults (blood donors and non-donors) was 2.4% (range 1.4–11.0%) and for hepatitis C antibody was 3.0% (range 0.3–31.9%. Rates in the high-risk subgroups were far higher(Ali *et al.*, 2009).The aim of this study was to determine the frequency of the common coagulation disorders like abnormal prothrombin time/international normalized ration (PT/INR), abnormal Activated partial thromboplastin time(APTT) and decreased Platelets count in patients having liver diseases diagnosed at tertiary care hospital Hayatabad Medical complex, Peshawar.

Materials and methods

This study was conducted in Hayatabad Medical Complex (HMC) which is a tertiary care hospital located at Hayatabad Peshawar, Pakistan. Written informed consent was taken and were explained the objectives of the study to included patients. Patients confidentiality was maintained.

Inclusion Criteria

All those patients admitted to the hospital of HMC diagnosed as liver disease were included in this study.

Exclusion Criteria

All those patients (liver disease) with known history of coagulation disorders like inherited bleeding disorders or thromboembolism were excluded.

Clinical data of the patients admitted to the Gastroenterology ward HMC Peshawar were collected from the history chart during the period April 2012 to October 2012. Total 278 samples were collected from liver disease patients. The venous blood samples were transferred to vacutainer having anti-coagulants trisodium citrate and another vacutainer containing anticoagulant Ethylene diamine tetra acetic acid (EDTA). The blood sample anticoagulated with EDTA were analyzed for complete blood count (platelet count) in an automatic hematological analyzer while for PT and ATTP the samples were anticoagulated with trisodium citrate. For PT and ATTP, the samples were first centrifuged at 2000 rpm for 15 minutes. The reagents for prothrombin time test used were Neoplastine R and the Kit had two vials of reagents. One of the reagents was consisted of lyophilized thromboplastin prepared from human recombinant TF and from phospholipids. It also contained a specific inhibitor of heparin. The other reagent was a solvent containing calcium with sodium azide as a preservative. For APTT, the reagent used was C.K. PREST and this Kit also consisted of two reagents. One reagent was Cephalin (Platelet substitute) prepared from rabbit brain and was freeze-dried while the other reagent was an activator and a buffered suspension of Kaolin. Both the PT, APTT reagents were loaded to the coagulation analyzer after matching the barcode. Calcium Chloride was loaded separately. The centrifuged plasma samples were loaded then to the analyzer. All the remaining process was done by the machine automatically, giving results on a screen. The results were recorded on daily basis.

Data analysis

Data was analyzed in SPSS (Statistical Packages for Social Sciences) version 13. Mean ± Standard Deviation was calculated for numerical variables.

Results

Data of 278 patients were collected including both adult male and female admitted to the gastroenterology ward of HMC Peshawar for the evaluation of frequency, percentage and extent of abnormality of coagulation disorders in liver disease patients.

Table 1. Distribution of Age of the patients with liver disorder.

Valid	278
Missing	0
Mean	51.90
Mode	60
Std. Deviation	14.174
Minimum	12
Maximum	95

Table 2. Percentages of prolonged PT in patients with Acute and Chronic Hepatitis**.**

Disease ^PT Cross tabulation				
		PT		Total
		NORMAL PT	PROLONDED PT	
Disease acute	Count	11	53	64
	% within DISEASE	17.2%	82.8%	100.0%
	% within PT	47.8%	20.8%	23.0%
Chronic	Count	12	202	214
	% within DISEASE	5.6%	94.4%	100.0%
	% within PT	52.2%	79.2%	77.0%
Total	Count	23	255	278
	% within DISEASE	8.3%	91.7%	100.0%
	% within PT	100.0%	100.0%	100.0%

The frequencies and percentages were calculated for descriptive purposes. The data was analyzed for prothrombin time (PT), INR, Activated Partial Thromboplastin Time (APTT), APTT Range, Platelet Count, results of coagulation disorders in liver disease patients (male: female), Acute vs Chronic Hepatitis and Gastrointestinal Bleeding (GIB). Out of 278 patients, 145 were male and 133 were female patients. The age of patients was 12 to 95, with mean age of 51.9 ±14 (Table 1).

Prothrombin time (PT)

The normal range for the reagent used in this study was 10-14 seconds. Out of 278 patients, 91.7% patients were having prolonged PT, which was more than 14 seconds (mean ± SD = 28.6 ± 15.1 sec). 8.3% patients were having normal Prothrombin Time (PT) less than 15 seconds (mean ± SD = 13.57± 0.99 sec) (Fig.2).

International normalized ratio INR

Percentages of different INR in this study shows the severity of the disorder. Out of 278 patients 254 patients had INR more than 1. Out of these 254 patients, 170 patients had INR 1.1-2.0, which is 61% of the total 278 patients. The remaining 84 patients were categorized as; INR = 2.1-3.0 (17.6%), INR=3.1-4.0 (6.8%), INR=4.1-5.0(3.6%), INR=5.1-6.0(1.1%), INR> 6.0 (1.1%) (Fig.3). It showed that more than 78% of patients (prolonged PT) had INR within 3.0, the PT up to 42 seconds.

Table 3. Percentages of prolonged APTT in patients with Acute and Chronic Hepatitis.

Disease ^APTT Cross tabulation				
		APT		Total
		NORMAL APTT	PROLONDED APTT	
Disease acute	Count	15	49	64
	% within DISEASE	23.4%	76.6%	100.0%
	% within APTT	45.5%	20.0%	23.0%
Chronic	Count	18	196	214
	% within DISEASE	8.4%	91.6%	100.0%
	% within APTT	54.5%	80.0%	77.0%
Total	Count	33	245	278
	% within DISEASE	11.9%	88.1%	100.0%
	% within APTT	100.0%	100.0%	100.0%

Activated partial thromboplastin time (APTT) and APTT range

Out of 278 patients, 88% had prolonged APTT with mean ± SD = 50.6 ± 19 sec (Fig. 4). Within total patients, 236 patients (84.89%) were having both prolonged PT and APTT. The different ranges of APTT in patients with prolonged APTT are shown in the Fig. 5.

Platelet count

Out of 278 patients, 164 patients (59%) have low platelet count. The different ranges of low platelet count patients are displayed in Fig 6.

Among 278 patients, 145 were male and 133 were female. Within male patients 91% and female patients 92.5% were having prolonged PT. In case of APTT, 90% of male patients and 85.7% of female patients were having prolonged APTT.

Table 5. Comparison with other studies in tabular form as follow.

Studies	Sample size	Prolonged PT	Prolonged APTT
Hameed *et al.*, 2006	50	Mean PT=28 Sec	Mean APTT= 51 Sec
Siddique *et al.*, 2005	171	88%	71%
Malik *et al.*, 1999	36	94.4%	82.6%
Bajaj *et al.*, 2001	36	83%	67%
Henao *et al.*, 2005		88%	71%
Devrajani *et al.*, 2012	118	INR 2-3= 17.8%	51%
Current study 2012	278	91% Mean PT= 28 Sec INR 2-3= 17.6%	88% Mean APTT=50 Sec

When analyzed for platelet count, 62% of males and 58% of females were having low platelet count. Thus, no significant difference between male and female having disordered coagulation regarding PT, APTT and platelet count, was found.

Acute vs chronic hepatitis

Among patients, 214 were having chronic hepatitis, and 64 patients with acute hepatitis. The results indicated that the PT and APTT were affected in both Acute and Chronic cases, with a little more percentage in chronic as compared to Acute cases.

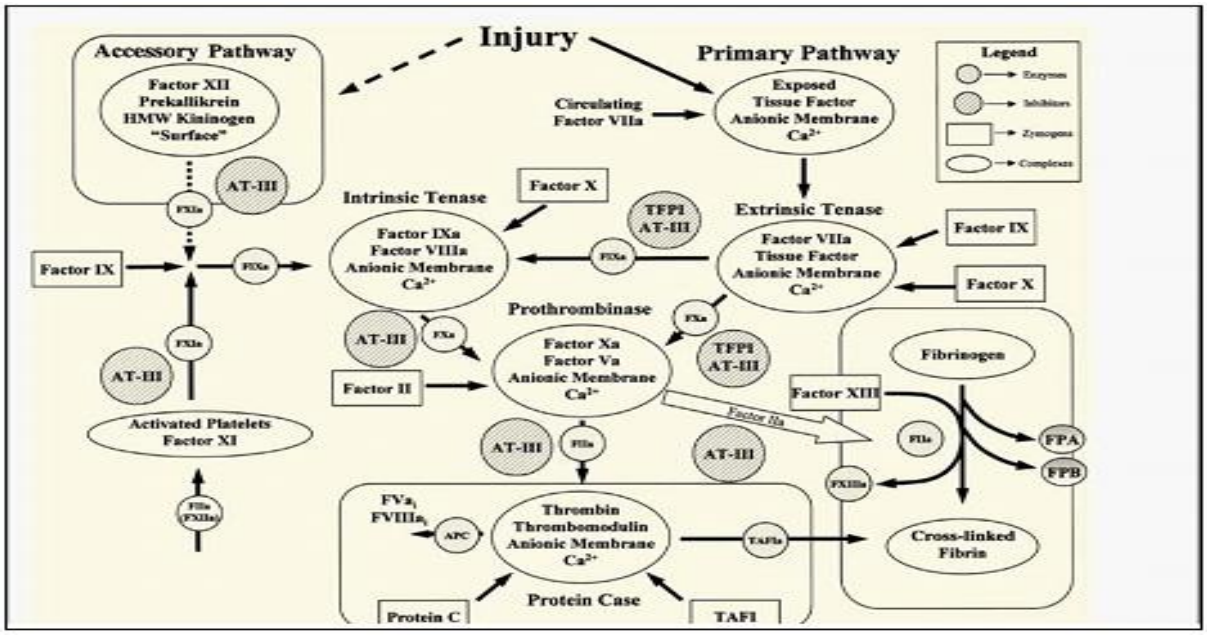

Fig. 1. Coagulation cascade (21).

In acute cases, percentage of prolonged PT, prolonged APTT and low platelet count are 82.8%, 76.6% and 32.8%, respectively. While in chronic cases, 94.4 % prolonged PT, 91.6% prolonged APTT and 68.2% low platelet counts were estimated. But there is much difference in decrease in the platelet count.

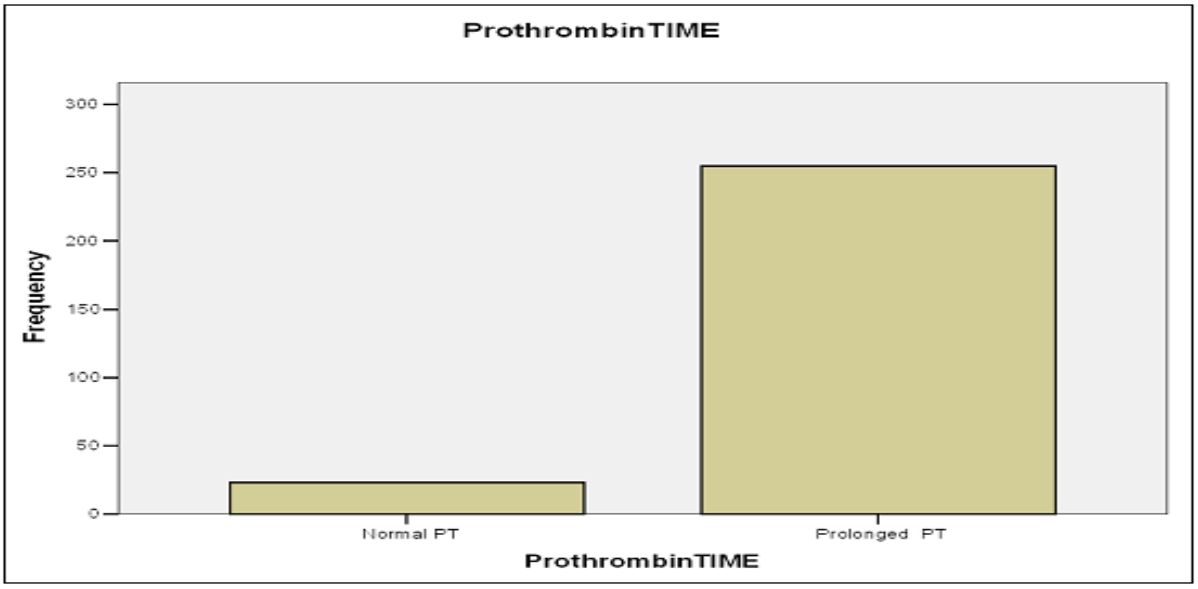

Fig. 2. Graph of patients with normal and prolonged PT.

As the platelet count was found to be more affected in chronic liver disorder as compared to acute hepatitis excluding fulminant hepatic failure. The results are summarized in the tables 2, 3 and 4.

Gastrointestinal bleeding (GIB)

Out of 278 patients with liver disease, 36 patients (13%) were having some form of (GIB). Out of 36 patients with G.I. bleeding, only one patient (2.8%) was having normal PT and normal platelet count. All the remaining 35 patients were having prolonged PT or low platelet count or both (Fig. 7).

Discussion

Data of 278 patients collected contain both adult male and female with a ratio 1.09: 1 indicates that there is about equal incidence of liver disorders regarding gender.

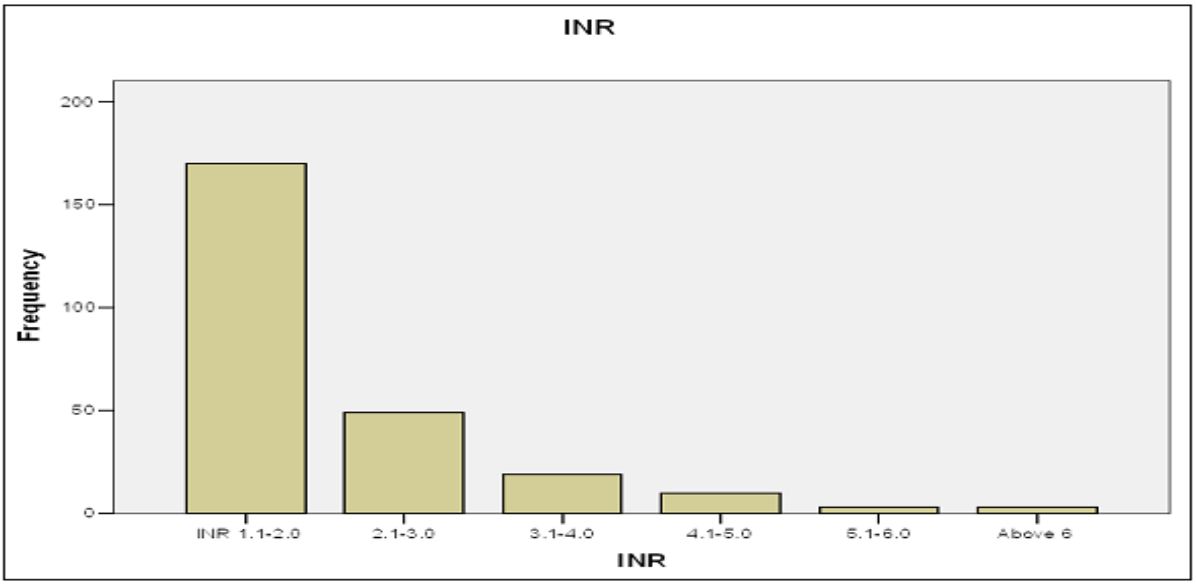

Fig. 3. Graph of different ranges of INR in patients having prolonged PT.

The age range is 12-95, with mean age 51.9 ±14 and the mode is 60 years. It means all age groups are affected but with more tendency in fifties and above. The statistics show that there is about equal percentage of male and female with coagulation abnormalities in liver diseases. Similar results regarding age and gender of the patients were reported in a study conducted by Siddique *et al*, 2005.

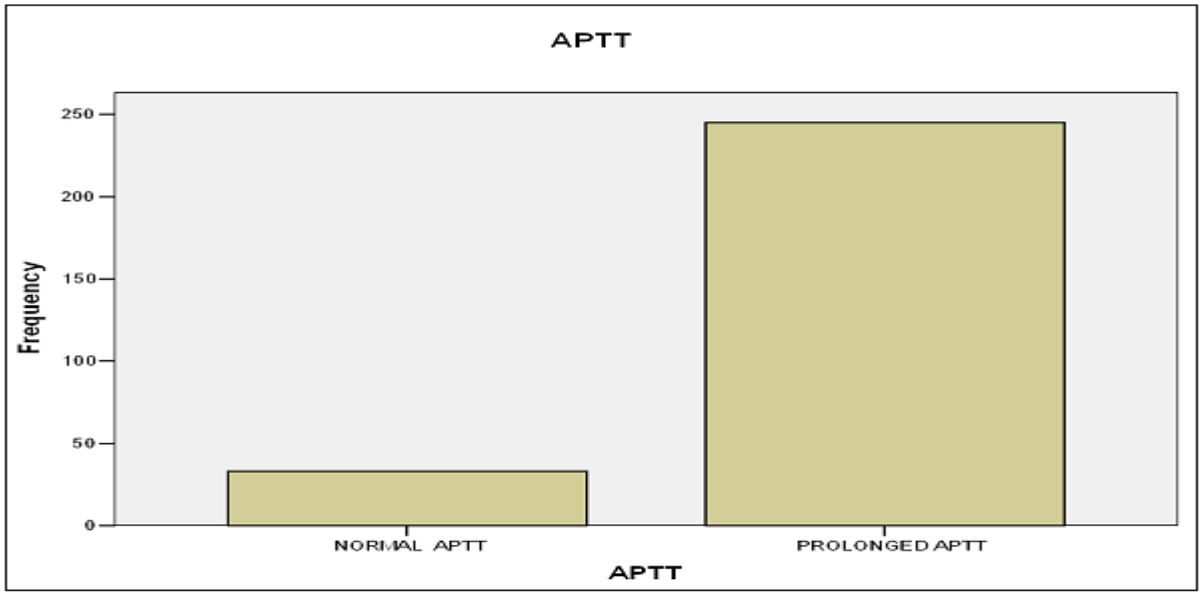

Fig. 4. Graph of patients with normal and prolonged APTT.

This study includes both types of hepatitis patients in acute or chronic conditions. Most of studies carried out in the past on this topic, were on chronic liver diseases or a type of chronic liver disease like cirrhosis and End Stage Liver Disease (ESLD). These results indicate that the PT and APTT are affected in both Acute and Chronic cases, with a little more percentage in chronic as compare to Acute cases, except for acute liver failure, where the abnormalities in PT and APTT were much severe. But there is much difference in decrease in the platelet count.

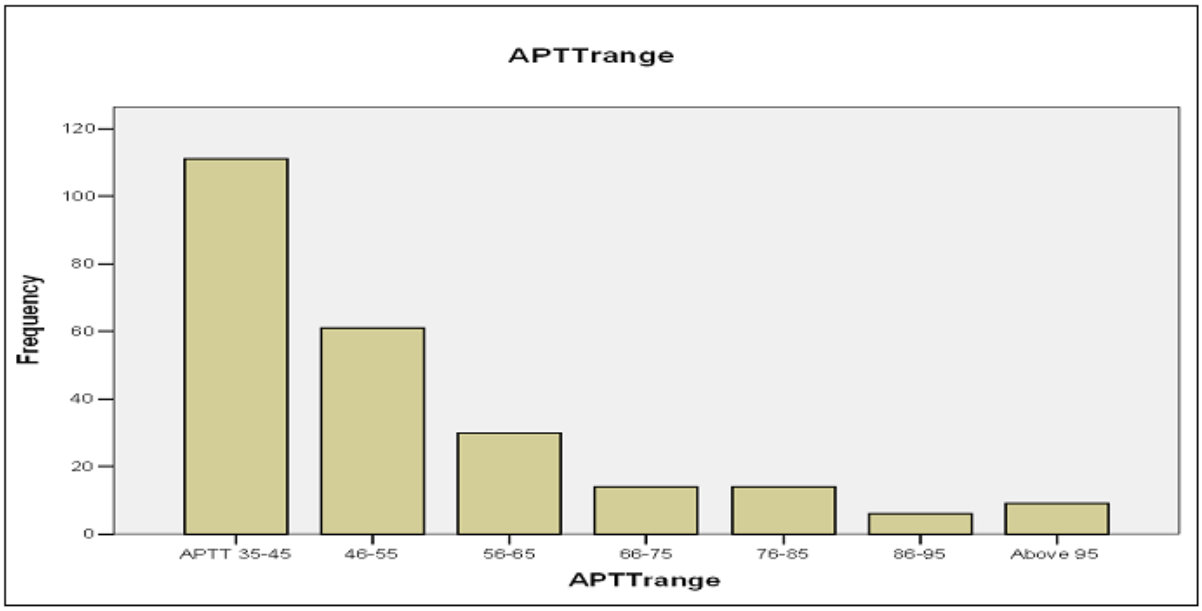

Fig. 5. Graph showing different ranges of APTT in patients with prolonged APTT.

As the platelet count is more affected in chronic liver disorder as compare to Acute hepatitis. The results of this study and all those studies carried out in Pakistan or other countries have clear outcome, that the laboratory results of routine coagulation tests are significantly abnormal. These results indicate that coagulation system is disturbed in all type of liver disorders depending on the severity of the diseases. The prothrombin time test in this study of 278 patients shows a high percentage of abnormality.91.7% patients have prolonged PT (abnormal), PT (mean ± SD = 28.6 ± 15.1 sec). While the APTT, have similar high percentage of abnormality. The percentage of prolonged APTT in this study is 88.1%, with (mean ± SD = 50.6 ± 19 sec). The percentage of patients having prolonged PT and APTT was 84.89%. These results showed a high significance of coagulation disorders in liver disease.

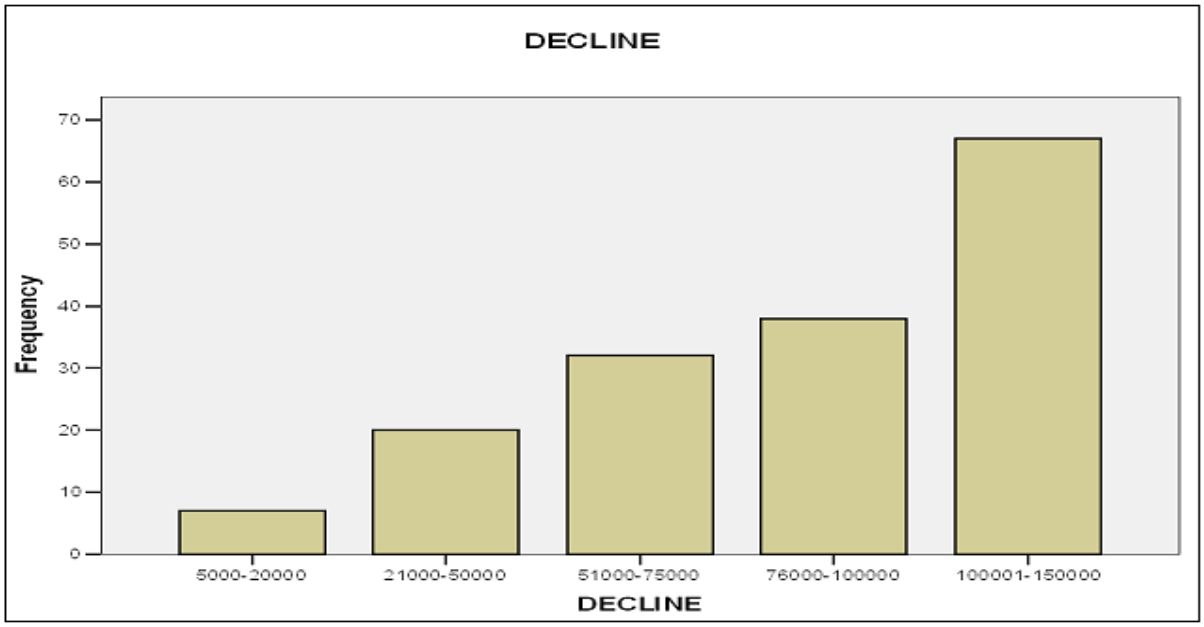

Fig. 6. Graph showing different ranges of low platelet count patients.

There is little difference with results of some studies, and the reason of those differences is either in the sample size, or some studies are restricted to a specific liver disorder, while this study includes all the patients having any type of liver disease. Similarities with other studies carried out are as in accordance with literature review by Henao *et al.* 2011, at Colombia, the results are very close to this study. They reported as prolonged PT= 88 % and prolonged APTT= 71%, comparing with this result as 91% and 88%. Hameed *et al.,* 2006, conducted a study which concluded the mean PT to be 28 seconds and mean APTT was 53 seconds, having a close similarity with this study which resulted in 28 seconds of mean PT and 51 seconds of mean APTT. A study carried out by Lloyd-Donald *et al.,* 2017 included 34 patients, concluded that all the coagulation test had abnormal results showing prolonged PT, increased INR, prolonged ATTP and decreased fibrinogen and platelet count. Siddique *et al.,* 2005, conducted a study on chronic cases only, have result of prolonged PT in 88% patients and APTT in 71% patients, prolonged PT and APTT both were in 67% patients. And the low platelet count in 37% patients. The sample size of that study was 171, much less than the sample size in current study. The PT and APTT results are close to this study but there is little difference regarding platelet count as 37% and 59%. Comparison of this study was made with other studies conducted on same topic in Table 5.

Coagulation disorders are disturbing the balance of hemostasis, either toward bleeding or thrombosis. The abnormal bleeding or spontaneous bleeding depends on the extent of the abnormality of the disorder.

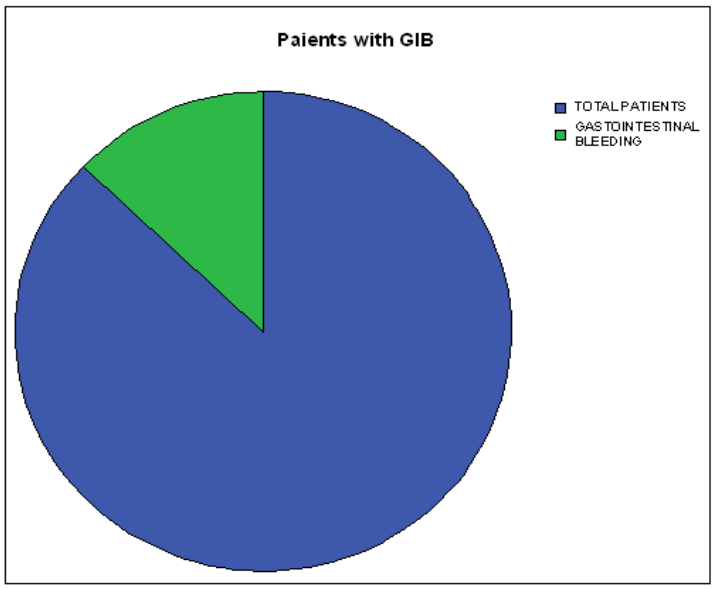

Fig. 7. Pie chart of patients with Gastrointestinal Bleeding.

The spontaneous bleeding might occur when the INR is above 5, (Prothrombin Time> 70 seconds). Out of 278 subjects enrolled in this study, only 2.2% patients were having INR>5. The PT is frequently more prolong in acute liver failure than in patients having cirrhosis, but spontaneous bleeding episodes are relatively uncommon (estimated at about 5%). Surgical procedure like indwelling venous catheter or an intra cranial pressure monitor may result in serious bleeding, as reported by Munoz *et al.* 2009. In their study, they had included three patients with acute liver failure, having PT 42,68 and 100 seconds, very prolong but they had no history of spontaneous bleeding.

The *in vitro* test of PT can give information for the function of clotting factors in extrinsic pathway of hemostasis like FVII, FV, X, FII and Fibrinogen (FI). But it is not the real picture of the *in vivo* coagulation system, as the *in vivo* coagulation consists of the role of anticoagulants like thrombomodulin and protein C. These are the reasons that there was no history of any spontaneous bleeding in the patients included in this study. The remaining 97% having INR < 5 and >1 were at risk for abnormal bleeding after any surgery, trauma or other associated disease like renal failure, splenomegaly, encephalopathy. 61.2% of patients were having PT of 15-28 Seconds. The APTT measure the activities of clotting factors involved in the intrinsic pathway of hemostasis.

The factors are FXII, FXI, FIX, FVIII, and the factors involved in the common pathway. Results of the study showed some prolongation of APTT. About 40% patients had APTT between 35-45 Seconds. 10.4% patients had APTT> 75 seconds. These results showed that the syntheses of clotting factors involved in intrinsic pathway of hemostasis is equally affected in the liver disease patients. Patients with GIB were 13%. The bleeding was more due to portal hypertension. As coagulation disorder is only a factor in the G.I. bleeding. Portal hypertension is the main complication of chronic liver disorder, which cause esophageal varices, and result in GIB. Only one patient (2.8%) out of 36 patients with GIB was having normal PT and platelet count. All the remaining 35 patients were having abnormal PT or platelet count.

The results of PT, APTT and Platelet count showed a bleeding tendency. But the procoagulant and anticoagulants both are affected in the liver disorders, so it may rebalance the hemostasis up to some extent. But this balance is less stable as compare to balance of hemostasis in healthy individuals. It can be easily disturbed by minor stimulants. Complications of liver diseases like bacterial infections, renal failure and portal hypertension can easily disturb it, and the balance leans toward a bleeding tendency. It can flip to either side; bleeding or thrombosis depends on the disorder of factors involved.

Patients having some form of thrombocytopenia were 59%. Synthesis of Thrombopoietin is affected by hepatocellular injury, and splenomegaly and or hypersplenism due to associated portal hypertension lead to increased platelet destruction in liver disease patients. The percentage of patients having platelet count < 20,000 was estimated to be 2.5%, which is categorized as very low platelet count and a risk for spontaneous bleeding. Patients at risk for abnormal bleeding after minor injury or surgery were 7.2% with platelet count 21000-50000. All the remaining patients having platelet count below normal range were at risk for abnormal bleeding after major surgery, trauma or secondary infections.

In hepatocellular injury, antithrombin, protein C, protein S, plasminogen synthesis is reduced. In recent studies, the deep vein thrombosis (DVT) and pulmonary embolism (PE) do develop in patients with liver disease at appreciable rate, between 0.5% and 1.9% Northup *et al* 2006. The patients of liver disease if suffered from myocardial infarction or strokes are in emergencies and brought to cardiac care unit (CCU) or intensive care unit (ICU) instead of gastroenterology ward, so the patients included in this study have no history of any thromboembolism. To detect the percentage of thromboembolism in liver disease patients, a further research is required study, on patients having thromboembolism and associated liver disorder.

Conclusion

Although the percentage of prolonged PT was very high as 91%, but more than 78% patients hadPT less than 43 Seconds (INR =3). INR = 3 is not dangerous for spontaneous bleeding but is at risk for abnormal bleeding after major trauma, major surgery or other pathological conditions so patients would need prophylaxis before going through any surgical procedure. Patients having platelet count less than 20,000 were 2.5% at risk for spontaneous bleeding and between 21,000- 50,000 were 7.2% at risk for abnormal bleeding after minor trauma or minor surgery. The remaining 90% patients having low platelet count were at risk for abnormal bleeding after major trauma or major surgery only.

There was no difference found between male and female having liver disease regarding disturbance of coagulation system PT, APTT and Platelet count was affected in both acute and chronic hepatitis with little more percentage in chronic cases (excluding acute liver failure).Patients having GIB, 97% were having abnormal PT and or low platelet count. It indicated the role of coagulation disorder in bleeding due to esophageal varices.

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