Journal of Medical & Health Sciences Review
VOL-1, ISSUE-4, 2024-FALL
Online ISSN : 3007-309X Print ISSN : 3007-3081
https://jmhsr.com/index.php/jmhsr/issue/view/7

Prevalence of High Activated Partial Thromboplastin Time (aPTT) among Patients with Liver Cirrhosis Department of Medicine at Saidu Group of Teaching Hospital, Swat

- **Dr. Nisar Ahmad[1]**
  Internal Medicine, Saidu Teaching Hospital, Swat Email: *Corresponding Author:nisarahmadkhan308@gmail.com
- **Dr. Zahid Ahmad[2]**
  Internal Medicine Saidu teaching hospital swat- Email: zahidahmad614@gmail.com
- **Dr. Muhammad Nisar[3]**
  Internal Medicine, Lady Reading Hospital, Peshawar- Email: nisarsmcite@gmail.com
- **Dr. Inayat Ul Haq[4]**
  Cardiology, Khyber Teaching Hospital, Peshawar- Email: Dr.inpk@gmail.com
- **Dr. Jalwa[5]**
  Khyber Medical College, Peshawar- Email: jalwagul99@gmail.com
- **Dr. Fawad Nasir[6]**
  Khyber Medical College, Peshawar- email: fawadn3@gmail.com

ABSTRACT

Introduction: Chronic liver disease or liver cirrhosis is a disease condition in which fibrosis and the creasing of the liver are not functioning correctly. The severity of cirrhosis depends upon the extent of liver failure. Advanced stages of liver failure that create an abnormal coagulation profile have increased the tendency towards bleeding and have consequently increased the hospitalization rates and mortality among cirrhotic patients. Activated partial thromboplastin time is a test that measures activity of Factors VII, IX, XI, and XII. An increased aPTT is due to decreased synthesis of measuring clotting factors in the sample indirectly decreases synthesis from the liver. Department of Medicine, Saidu Group of Teaching Hospital Swat Duration of study: From 13 August 2020 to 14 Feb 2021. Total 195 cases of cirrhosis are consecutively selected from OPD and activated partial thromboplastin time (aPTT).

Results: The mean age of sample was 45.2 + 7.3 years. 68.2% was male gender while 31.8% is female gender. The mean duration of the disease was 7.1 + 2.5 years. The results showed acute decompensation in 34.9% and 30.8% had hospitalization history due to decompensation. Cardiac drug use history

Journal of Medical & Health Sciences Review
VOL-1, ISSUE-4, 2024-FALL
Online ISSN : 3007-309X Print ISSN : 3007-3081
https://jmhsr.com/index.php/jmhsr/issue/view/7

was present in 34.9%. The results further showed that 45.1% patients were diagnosed with prolonged aPTT.

Conclusion: Prolongation of aPTT is a frequent problem in our local cirrhotic population. Further studies are needed to develop an association of factors that lead to the prolongation of aPTT, its control, and its effect on morbidity and mortality of patients with cirrhosis.

Keywords. Liver cirrhosis, coagulation disorders, activated partial thromboplastin time, acute decompensation

INTRODUCTION

Liver disease usually results in cirrhosis when the liver fibrosis creases to function properly. It has been found in approximately 0.27% of the USA with 69% of these patients unaware of this disease2. In Sweden the crude annual incidence of cirrhosis was estimated at 14.1/1000001, it has been regarded as the most common cause of liver failure in developing countries. Pakistan has been termed a cirrhotic state since it is said to be the second most common country of hepatitis C after Egypt3. It was observed that cirrhosis had affected about 0.27% of the U.S. population, wherein 69% were not even aware of their disease (Scaglicone et al., 2015), with the crude annual incidence of cirrhosis estimated at 14.1 per 100,000, and has been considered one of the leading causes of liver failure in developing countries (Nilsson et al., 2016). The country is termed as a "cirrhotic state" since it ranks as the second most endemic country for hepatitis C after Egypt (Raza et al., 2015). Statistically, the worldwide estimate counts to be about one death in every forty deaths (2.5%) (Perz et al., 2006). It has an estimated mortality rate of two years in cirrhotic patients versus 8.4% in propensity-matched controls.

Moreover, cirrhosis precedes the invasion of more hepatocellular carcinoma (HCC), that might theoretically improve the growth of the tumor through the regeneration of hepatocytes (Bialecki & Di Bisceglie, 2005). The main causes of liver cirrhosis hepatitis B (37.3%), alcoholic liver disease (24.1%), chronic hepatitis C (22.3%), and non-alcoholic fatty liver disease (16.4%) (Perz et al., 2006). The severity of cirrhosis corresponds to the failure degree, but a deranged coagulation profile is commonly implicated.

Journal of Medical & Health Sciences Review
VOL-1, ISSUE-4, 2024-FALL
Online ISSN : 3007-309X Print ISSN : 3007-3081
https://jmhsr.com/index.php/jmhsr/issue/view/7

Coagulopathy is associated with enhanced bleeding tendencies in cirrhotic patients, resulting in higher rates of hospitalization and mortality. Hypercoagulability corresponds with systemic inflammation and mortality at 28 days (45% vs. 16%, P = 0.02), as well as mortality at 90 days (52% vs. 19%, P = 0.01) (Blasi et al., 2018). aPTT measures activities of clotting factors, IX, XI, and XII. Prolonged aPTT reflects a decreased output of clotting factor production by the liver; therefore, it indirectly measures the severity of the disease. For instance, in a study of 50 patients, 34 had PT to be slightly prolonged, 31 had slightly prolonged aPTT, and 35 had prolongation in the clotting profile (Anwar et al., 2016).

Further, 12 subjects had platelet counts of between 20,000 to 100,000/mm3 while 5 had c000/mm3. In the other study, PT was prolonged in 93 cases (71.5%) and aPTT in 60 cases (46.2%) (Cehrukurii 019). Since cirrhosis and its associated mortality are very common, the monitoring of the cy of increased aPTT will be extremely important in such cases. Such results could help to manage the patient by providing fresh frozen plasma or clotting factors in time to reduce associated mortality. These findings would be valuable for our population and would be available online for reference. The outcomes may also help in implementing screening protocols for all cirrhosis patients, making the required intervention and prevention possible at an appropriate time. Frozen plasma or clotting factors to reduce mortality associated with it. The outcome will be evidence in our patients of our population and available online for record and knowledge. Also, the outcome can be used for adopting the screening protocol in every patient of cirrhosis for in-time management and in-time treatment or prevention.

MATERIALS AND METHODS

Study Setting and Design

This is a cross-sectional study carried out at the Department of Medicine, Saidu Group of Teaching Hospital Swat, over six months from 13 August 2020 to 14 February 2021. This study aims at the evaluation of the prevalence of prolonged aPTT in patients with liver cirrhosis diagnosed during the study. A sample size calculation was carried out keeping in consideration the study of

Journal of Medical & Health Sciences Review
VOL-1, ISSUE-4, 2024-FALL
Online ISSN : 3007-309X Print ISSN : 3007-3081
https://jmhsr.com/index.php/jmhsr/issue/view/7

the prior that stated that the prevalence of prolonged aPTT among cirrhotic patients was 46.2% in the current study at a 7% margin of error, this brings the final sample size to 195 patients. Convenience sampling that is non-probability consecutive sampling was used for the recruitment of the patients.

Inclusion and Exclusion Criteria

Inclusion criteria: All the patients between 20 years to 65 years who attend the medical department with a confirmed diagnosis of liver cirrhosis. The patient participating in the study were both males and females. The exclusion criteria would be known abnormalities in coagulation, or hemophilia; suffering from severe infections, such as DIC, or sepsis. For instance, patients with multi-organ failure presentations like over two milligrams of serum creatinine> 2 mg/dL, or more white blood count (TLC > 11,000 cells/mm^3) or more total bilirubin levels above 2mg/dL were not included in this study. Additionally, those patients that decline to participate in this research on their account or that of their families were excluded.

Data Collection and Ethical Approval

After taking approval from the ethical committee of the hospital along with the College of Physicians and Surgeons Pakistan (CPSP), data collection for the study was initiated. The patient was evaluated on proper inclusion and exclusion criteria. Both verbal as well as written consent from the participant was obtained after explanation of the purpose and benefits of the study. Ultrasound of the abdomen and the liver was conducted by a consultant radiologist to establish a diagnosis of cirrhosis of the liver.

Patient Information and Blood Samples

For every patient, comprehensive demographic and clinical information was obtained such as age and gender along with a history of use of cardiac medications like aspirin or clopidogrel. The blood sample drawn from each patient was assayed for aPTT. These specimens were tested in the hospital laboratory and any value that exceeded 40 seconds was taken to represent an abnormal prolongation of aPTT. Such results were recorded on a pre-prepared data collection form or proforma for further analysis. Each patient was managed appropriately according to the hospital protocols for cirrhosis and its

Journal of Medical & Health Sciences Review
VOL-1, ISSUE-4, 2024-FALL
Online ISSN : 3007-309X Print ISSN : 3007-3081
https://jmhsr.com/index.php/jmhsr/issue/view/7

complications.

Data Analysis Techniques

The purpose of this study will be to evaluate the prevalence rate of the prolonged aPTT in cirrhosis patient and to determine whether there is an association, if any with other clinical variables. Data were analyzed on IBM-SPSS software version 22. Qualitative variables gender, use of cardiac medicines, symptoms presented and patients having prolonged aPTT were analyzed by calculation of their frequencies and percentages. The quantitative variables included age, aPTT and the number of previous admissions for acute decompensation and thus summarized in mean values with standard deviations.

Variable Stratification

To control the confounding effects from age, duration since diagnosis, previous hospital admissions, use of cardiac drugs, and reasons for visiting the hospital, data was stratified. The stratified analysis assessed the level of interest variable, prolonged aPTT in subgroups of patients. Each subcategory was tested with the chi-square test in order to identify whether there is an association of such factors with the presentation of prolonged aPTT. The statistical test was performed to determine whether the differences established in the groups were statistically significant or not and the p-value was ≤0.05 .

Analysis of Effect Modifiers

The analysis effect modifiers included the age, duration of illness, previous admissions for acute decompensation, and cardiac medications. The clinical factors were further assessed to see if they were responsible for some effect on the incidence of prolonged aPTT in cirrhotic patients. It was provided in tabular and graphical forms so the associations among the clinical factors and prolonged aPTT were explicitly conveyed. It facilitated analyzing the factors which had the highest correlation with the risk for prolonged aPTT.

Conclusion

The study is well-noted to document the incidence rate of prolonged aPTT in patients diagnosed with liver cirrhosis, and it may also help in making some

Journal of Medical & Health Sciences Review
VOL-1, ISSUE-4, 2024-FALL
Online ISSN : 3007-309X Print ISSN : 3007-3081
https://jmhsr.com/index.php/jmhsr/issue/view/7

associations with age, gender, the duration of illness, and the use of medications. Therefore, these findings are helpful in guiding clinical management towards recognizing patients with cirrhosis, who are at great risk in developing coagulation abnormalities such as prolonged aPTT. Advanced statistical analyses which have culminated in the novel findings in these results may serve as a basis for further research work in this area and may also guide future treatment protocols in cirrhotic patients to diminish the risk of potential bleeding complications.

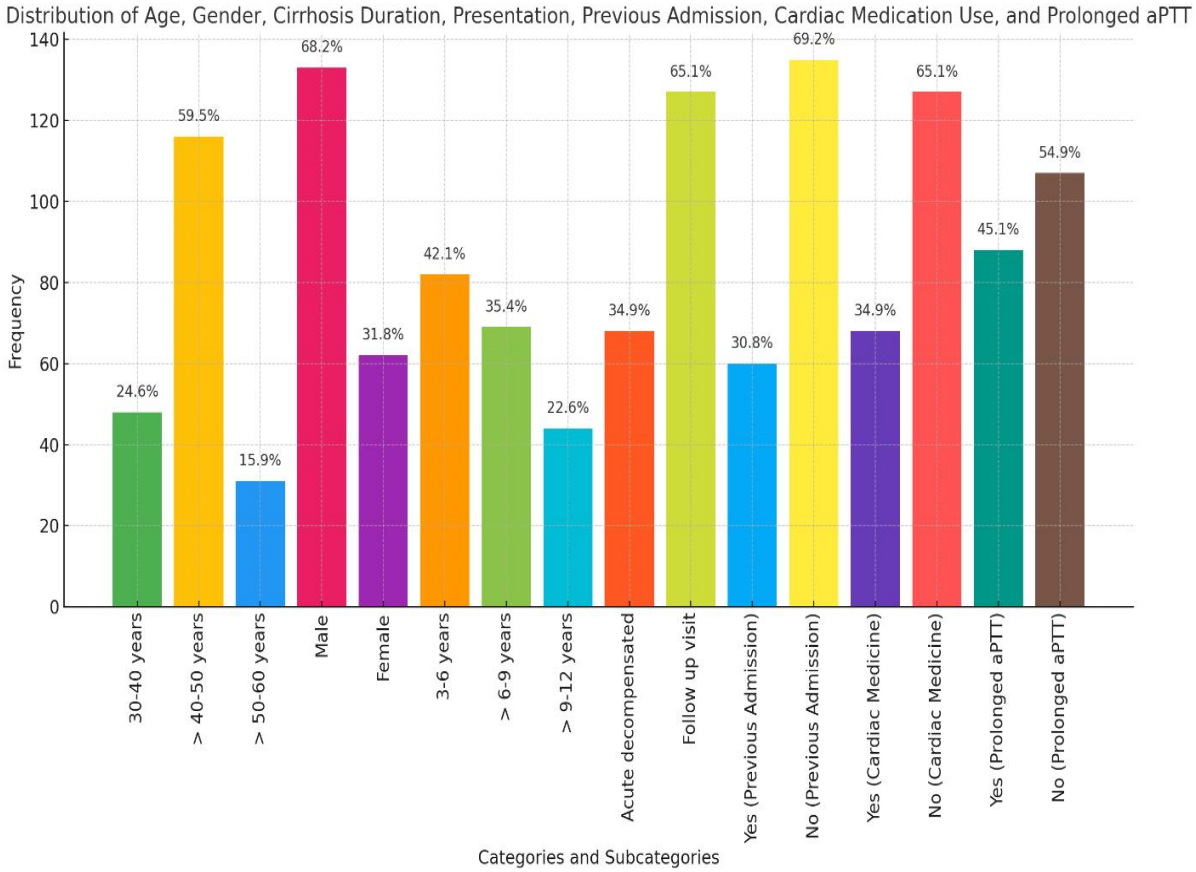
Table 1 Demographic, Clinical, and Coagulation Profile Distribution in Liver Cirrhosis Patients: A Comprehensive Analysis of Age, Gender, Disease Duration, and aPTT Abnormalities

Category	Subcategory	Frequency	Percent (%)
Age	30-40 years	48	24.6
	> 40-50 years	116	59.5
	> 50-60 years	31	15.9
Gender	Male	133	68.2
	Female	62	31.8
Duration of Cirrhosis	3-6 years	82	42.1
	> 6-9 years	69	35.4
	> 9-12 years	44	22.6
Presentation	Acute decompensated	68	34.9
	Follow up visit	127	65.1
Previous Admission	Yes	60	30.8
	No	135	69.2
Use of Cardiac Medicine	Yes	68	34.9
	No	127	65.1
Prolonged aPTT	Yes	88	45.1

Journal of Medical & Health Sciences Review
VOL-1, ISSUE-4, 2024-FALL
Online ISSN : 3007-309X Print ISSN : 3007-3081
https://jmhsr.com/index.php/jmhsr/issue/view/7

	No	107	54.9

The population under study is 195 patients who were suffering from liver cirrhosis. Most patients fell within the age of 40-50 years, at 59.5%, followed by 24.6% aged between 30-40 years, while 15.9% were aged 50-60 years. The population under study is male-dominant, at 68.2%, leaving females at 31.8%. In regard to the duration of cirrhosis, 42.1% were diagnosed with it for 3-6 years, 35.4% for 6-9 years, and 22.6% for 9-12 years. Regarding presentation, 34.9% were on acute decompensation, and 65.1% were on follow-up. Positive history of previous hospital admissions was documented in 30.8% of patients. Of the participants, 34.9% were on cardiac medicines. It also mentioned that prolonged activated partial thromboplastin time occurred in 45.1% of patients which shows that a high number of cirrhotic patients show abnormal coagulation.



Prolongation of Activated Partial Thromboplastin Time: This is a delay in the blood clotting process usually due to deficiency or dysfunction within the

Journal of Medical & Health Sciences Review
VOL-1, ISSUE-4, 2024-FALL
Online ISSN : 3007-309X Print ISSN : 3007-3081
https://jmhsr.com/index.php/jmhsr/issue/view/7

intrinsic and common pathway of the coagulation cascade. Several factors can account for prolonged aPTT levels, including the following:

Liver Disease

Most of the coagulation factors are produced by the liver. These are usually factors I, II, V, VII, IX, X, XI, and XII. Their deficiencies due to liver diseases, particularly cirrhosis reduce the capability of the liver to produce these factors and subsequently prolong aPTT.

Defects in Coagulation Factors

Prolonged aPTT is caused by abnormalities of coagulation factors such as VIII, IX, XI, or XII, which are part of the intrinsic pathway. These deficiencies are mostly congenital and represent the primary cases of hemophilia (factors VIII and IX), but acquired through liver disease or vitamin K deficiency.

Presence of inhibitors

The presence of antibodies or inhibitors that target clotting factors-for example, the lupus anticoagulant, antiphospholipid antibodies-will interfere with normal clotting and therefore lead to prolongation of aPTT. This is generally found in patients suffering from antiphospholipid syndrome.

Heparin Therapy

Heparin is an anticoagulant used commonly for the prevention of blood clots. It enhances the effect of antithrombin III, and the actual effect is the inhibition of thrombin as well as factor Xa. APTT is prolonged, and in patients receiving unfractionated heparin, it is monitored.

Vitamin K Deficiency

Vitamin K is required for activation of many clotting factors. Among them are II, VII, IX, and X. If there is a deficiency in Vitamin K, synthesis of these factors will be reduced. Therefore, it will also prolong aPTT and PT.

DIC

DIC In a patient with DIC, the coagulation system becomes hypercoagulable, in which there is increased consumption of clotting factors and platelets. The condition thus usually presents as an elevated prolonged aPTT due to thrombocytopenia and consumption of clotting factors. Severe Infections or Sepsis Disruption of the coagulation cascade owing to systemic inflammation

Journal of Medical & Health Sciences Review
VOL-1, ISSUE-4, 2024-FALL
Online ISSN : 3007-309X Print ISSN : 3007-3081
https://jmhsr.com/index.php/jmhsr/issue/view/7

caused by infection or sepsis is another common cause of prolongation of PT and aPTT usually ending in DIC.

von Willebrand Disease

Certain disease conditions such as von Willebrand disease result in prolongation of aPTT due to its association with deficiency of factor VIII activity, though claimed to be due to effect on platelet function mainly.

Drugs

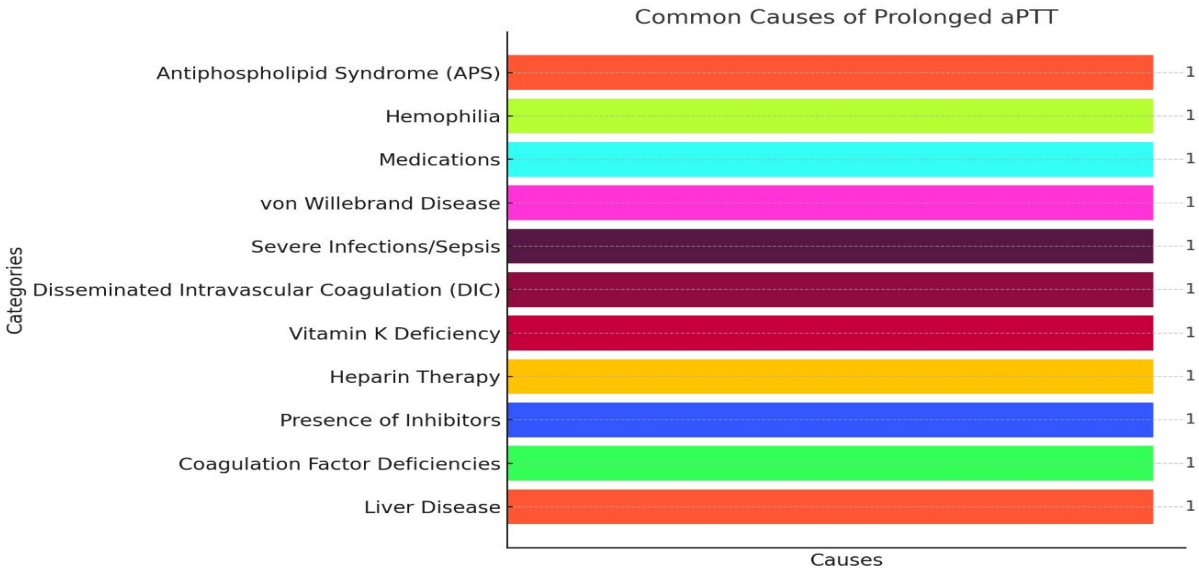
Certain drugs such as certain anticoagulants lead to direct thrombin inhibitors like dabigatran which alters the blood clotting process and hence results in prolongation of aPTT.

Hemophilia

Hemophilia A (factor VIII deficiency) and Hemophilia B (factor IX deficiency) are hereditary bleeding disorders with an abnormal prolongation of aPTT because of a deficiency or absence of functioning intrinsic pathway coagulation factors.

APS

This disease is associated with autoantibodies, like lupus anticoagulant, which acts to target the phospholipid environment and leads to the prolongation of aPTT. This is paradoxical, however, given the increased risk of thrombosis overall.



Journal of Medical & Health Sciences Review
VOL-1, ISSUE-4, 2024-FALL
Online ISSN : 3007-309X Print ISSN : 3007-3081
https://jmhsr.com/index.php/jmhsr/issue/view/7

Discussion

The liver is the central organ in the hemostatic system and not only produces the essential plasma proteins but also multiple coagulation factors, such as Factors I, II, V, VII, VIII, IX, X, XI, XII, and XIII, as well as natural anticoagulants, including proteins C and S. Chronic and acute liver diseases have a very deep impact on hemostatic balance. Traditionally, bleeding in liver disease has been ascribed to decreased production of these hemostatic proteins, coagulopathy, thrombocytopenia, enhanced fibrinolysis, or portal hypertension (McCormick & Murphy, 2000). However, recent research has emphasized that thrombotic events, including deep venous thrombosis and pulmonary embolism, also complicate liver disease, occurring in 0.5% to 1.9% of cases (Northup et al., 2006).

Another population-based study further ascertained an elevated risk of venous thrombosis among patients with liver disease compared to the general population. The prothrombotic tendency is therefore attributed to reduced levels of natural anticoagulants like proteins C and S and antithrombin (Senzolo et al., 2009). This places the patients with liver disease at a risk of both bleeding and thrombotic events, making their clinical management complicated. Thrombocytopenia is yet another common complication of liver disease, which occurs in as many as 76% of cirrhotic patients, quoted in the literature review by Afdhal N et al., 2008. It is mainly caused by splenic sequestration of platelets, bone marrow suppression due to chronic hepatitis C, side effects of antiviral therapy, and low thrombopoietin levels.

Earlier studies conducted by Saray A and Saja MF (2012, 2013) report that an increased aPTT is largely observed in patients suffering from severe liver disease; however, the marker is not sensitive to the extent of liver damage. Global coagulation tests such as prothrombin time and activated partial thromboplastin time do not form any reliable measure to assess hemorrhagic potential in cirrhotic patients, though prothrombin time continues to be an important prognostic indicator of liver function (Tripodi et al., 2007). Al-Ghumlas AK et al. (2005) reported that an extended thrombin time (TT) indicates a disorder of quantity or quality of fibrinogen. The acute-

Journal of Medical & Health Sciences Review
VOL-1, ISSUE-4, 2024-FALL
Online ISSN : 3007-309X Print ISSN : 3007-3081
https://jmhsr.com/index.php/jmhsr/issue/view/7

phase reactant released from the liver is fibrinogen.

It is normal or increased in chronic disease of the liver but often decreased in diseases with reduced synthesis by the liver, DIC, or increased fibrinolysis. Lower plasma levels of protein C are associated with more severe liver disease, as evidenced by higher Model for End-Stage Liver Disease (MELD) scores according to Zocco MA et al. (2009). Higher FDPs and D-dimers levels in chronic liver disease were observed to be associated with increased plasminogen activation, elevated tissue plasminogen activators concentrations, and a reduced clearance of these activators (Dahlbäck, 2004). The hyperfibrinolytic state in cirrhotic patients can be at least partly explained by the depletion of their main plasmin inhibitor, α-2 antiplasmin (Tripodi et al., 2006).

Early detection of the patients who are prone to bleeding along with suitable therapeutic interventions in the form of blood product substitution, would prevent complications and improve outcomes in cirrhotic patients (Amitrano et al., 2002). However, in the current study, no fixed transfusion thresholds were allowed in such patients. Coagulation product substitution in cirrhotic patients is much debated, with the risks of transfusion highly relevant to this debate. Active bleeding would not be counterindicated by a liberal transfusion strategy for correction of coagulation abnormalities in patients (Gajic et al., 2006). More research is needed to determine more specific transfusion thresholds that must balance the benefits of substitution in opposition to risks of transfusion within this population (Shawcross et al., 2011).

It should be reminded that PT, INR, and aPTT were first developed for routine coagulation testing in monitoring anticoagulant therapy and single-factor deficiencies rather than mimicking in vivo coagulation (Ng, 2009). They measure only the levels of procoagulant factors and do not represent plasma levels of the natural anticoagulants, such as proteins C and S. Patients with liver disease can also find it challenging to standardize PT through INR due to differences between laboratories, thus making the assay less reliable (Magnusson et al., 2013). Also, these assays have a low sensitivity to thrombin

Journal of Medical & Health Sciences Review
VOL-1, ISSUE-4, 2024-FALL
Online ISSN : 3007-309X Print ISSN : 3007-3081
https://jmhsr.com/index.php/jmhsr/issue/view/7

activated by platelets and do not take into account the role of endothelium from blood vessels in the process of coagulation through interactions with thrombomodulin and glycosaminoglycans, which interacts with activation of proteins C and antithrombin (Huntington, 2003). Therefore, though PT/INR and aPTT are often used in practice, their inadequacies in the treatment of liver disease are only now better realized as clinical knowledge regarding the coagulation mechanism advances (Reverter, 2006).

CONCLUSION

One of the common problems in our local patients with cirrhosis is the prolongation of aPTT. Future studies are needed to shape an association of factors that cause a prolongation of aPTT, how it can be controlled, and its effect on the morbidity and mortality of such patients who have cirrhosis.

Conflict of interest statement

The authors declare that there is no conflict of interest in connection with the publication of this paper.

REFERENCES

1. Scaglicone S, Kliethermes S, Cao G, Shaham D, Durazo R, Luke A, et al. The epidemiology of cirrhosis in the United States: A population-based study. J Clin Gastroenterol. 2015;49(8):690-6.
2. Nilsson E, Anderson H, Sargent K, Lindgren S, Prytz H. Incidence, clinical presentation and mortality of liver cirrhosis in southern Sweden: a 10-year population-based study, Aliment Pharmacol Ther. 2016;43(12):1330-9.
3. Raza H, Ahmad T, Afzal MS. Hcv, interferon therapy response, direct-acting antiviral therapy revolution, and Pakistan: Future perspectives. Asian Pac. J Cancer Prev. 2015;16(13):5583-4.
4. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol. 2006;45(4):529- 38.
5. Bialecki ES, Di Bisceglie AM, “Clinical presentation and natural course of hepatocellular carcinoma. Eur J Gastroenterol Hepatol. 2005;17(5):485-9.
6. Hsiang J, Bai W, Raos Z, Stableforth W, Upton A, Selvaratnam S,

et al.

7. Epidemiology, disease burden and outcomes of cirrhosis in a large secondary care hospital in south Auckland, New Zealand Intern Med J. 2015;45(2):160-9.
8. Sabia RS, Sibia P, Sharma H, Choudhary A, Kaur C, Ydav S. Frequency, determinants and outcome of upper gastrointestinal bleeding among patients with liver cirrhosis Int J Curr Res Med Sci 2017;3(6):20-6.
9. Blasi A, Calvo A, Prado V, Reverter E, Reverter JC, Hemindez-Tejero M, et al. Coagulation failure in patients with acute or chronic failure and decompensated cirrhosis: Beyond the international normalized ratio. Hepatology. 2018;68(6):2325-37.
10. ANWR SBN, CHEEMA F, S WASEEM H. Coagulopathy in patients of chronic liver disease admitted in Sir Ganga Ram Hospital (SGRH). J Fatima Jinnah Med Univ. 2016;10(1).
11. Cehrukurii VR, Gupta NS. Hematological and coagulation abnormalitiesin cirrhosis with decompensation. Int J Sci Res. 2019;8(3).
12. Befeler AS, Palmer DE, Hoffman M, et al. The safety of intra-abdominal surgery in patients with cirrhosis: a model for end-stage liver disease score
13. is superior to Child-Turcotte-Pugh classification in predicting outcome. Arch Surg. 2005 Jul. 140(7):650-4; discussion 655.
14. Teh SH, Nagorney DM, Stevens SR, et al. Risk factors for mortality after surgery in patients with cirrhosis. Gastroenterology. 2007 Apr. 132(4):1261-9.
15. Morlock CG, Hall BE. Association of cirrhosis, thrombocytopenia, and hemorrhagic tendency. Arch Intern Med. 1943;72:69–77. [
16. Mammen EF. Coagulation abnormalities in liver disease. Haematol Oncol Clin North Am. 1992;6:1247–57.
17. McCormick PA, Murphy KM. Splenomegaly, hypersplenism, and coagulation abnormalities in liver disease. Bailliere's Clin Gastroenterol. 2000;14:1009–31.
18. Lisman T, Leebeek FWG, de Groot PG. Hemostatic abnormalities in patients with liver disease. J Hepatol. 2002;37(2):280–87.

19. Witters P, Freson K, Verslype C, Peerlinck K, Hoylaerts M, Nevens F, et al. Review article: blood platelet number and function in chronic liver disease and cirrhosis. Aliment Pharmacol Ther. 2008;27(11):1017–29.
20. Bakker CM, Knot EA, Stibbe J, Wilson JH. Disseminated intravascular coagulation in liver cirrhosis. J Hepatol. 1992;15(3):330–35.
21. Northup PG, McMahon MM, Ruhl AP, Altschuler SE, Volk-Bednarz A, Caldwell SH, et al. Coagulopathy does not fully protect hospitalized
22. cirrhosis patients from peripheral venous thromboembolism. Am Gastroenterol. 2006;101(7):1524–28.
23. Senzolo M, Sartori MT, Lisman T. Should we give thromboprophylaxis to patients with liver cirrhosis and coagulopathy? HPB (Oxford)2009;11(6):459–64
24. Gulley D, Teal E, Suvannasankha A, Chalasani N, Liangpunsakul S. Deepvein thrombosis and pulmonary embolism in cirrhosis patients. Dig Dis Sci. 2008;53(11):3012–17.
25. Garcia-Fuster MJ, Abdilla N, Fabia MJ, Fernandez C, Oliver V, Forner MJ. Venous thromboembolism and liver cirrhosis. Rev Esp Enferm Dig. 2008;100(5):259–62.
26. Sogaard KK, Horvath-Puho E, Gronbaek H, Jepsen P, Vilstrup H, Sorensen HT. Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case-control study. Am J Gastroenterol. 2009;104(1):96–101.
27. Afdhal N, McHutchison J, Brown R, Jacobson I, Manns M, Poordad F. Thrombocytopenia associated with chronic liver disease. Journal of Hepatology. 2008;48(6):1000–07.
28. Papatheodoridis GV, Papakonstantinou E, Andrioti E, Cholongitas E, Petraki K, Kontopoulou I, et al. Thrombotic risk factors and extent of liver fibrosis in chronic viral hepatitis. Gut. 2003;52(3):404–09.
29. Zocco MA, Di Stasio E, De Cristofaro R, Novi M, Ainora ME, Ponziani F, et al. Thrombotic risk factors in patients with liver cirrhosis: correlation with MELD scoring system and portal vein thrombosis development. J Hepatol. 2009;51(4):682–89.

30. Saray A, Mesihovic R, Vanis N, Gornjakovic S, Prohic D. Clinical significance of hemostatic tests in chronic liver disease. Med Arh. 2012;66(4):231–35.

31. Saja MF, Abdo AA, Sanai FM, Shaikh SA, Gader AG. The coagulopathy of liver disease: does vitamin K help? Blood Coagul Fibrinolysis. 2013;24:10–17.

32. Tripodi A, Caldwell SH, Hoffman M, Trotter JF, Sanyal AJ. The prothrombin time test is a measure of bleeding risk and prognosis in liver disease. Aliment Pharmacol Ther. 2007;26(2):141–48.

33. Al Ghumlas AK, Abdel Gader AG, Al Faleh FZ. Hemostatic abnormalities in liver disease: could some hemostatic tests be useful as liver function tests? Blood Coagulation and Fibrinolysis. 2005;16:329–35

34. Amitrano L, Guardascione MA, Brancac-Cio V, Balzano A. Coagulation disorders in liver disease. Semin Liver Dis. 2002;22(1):83–96.

35. Abdo AA, Sanai FM, Azzam N, Al Sawat K, Al Dukhayil M, Al GhumlasA, et al. Natural anticoagulants can be useful predictors of severity in chronic liver disease. Blood Coagul Fibrinolysis. 2010;21(2):122–27

36. Ahmadhameed SN, Khursheed ASSI, Hamid A, Naveed I. An assessment of coagulation parameters in liver cirrhosis. Biomedica. 2006;22:74–77.

37. Shawcross DL, Sharifi Y, Canavan JB, Yeoman AD, Abeles RD, Taylor NJ, et al. Infection and systemic inflammation, not ammonia, are associated with grade 3/4 hepatic encephalopathy, but not mortality in cirrhosis. J Hepatol 2011; 54: 640- 649.

38. Tripodi A, Primignani M, Chantarangkul V, Lemma L, Jovani M, Rebulla P, et al. Global hemostasis tests in patients with cirrhosis before and after prophylactic platelet transfusion. Liver Int 2013; 33: 362- 367.

39. Tripodi A, Chantarangkul V, Primignani M, Clerici M, Dell'Era A, Aghemo A, et al. Thrombin generation in plasma from patients with cirrhosis supplemented with normal plasma: considerations on the efficacy of treatment with fresh-frozen plasma. Intern Emerg Med 2012; 7: 139- 144.

40. Khan H, Belsher J, Yilmaz M, Afessa B, Winters JL, Moore SB,

et al.

41. Fresh-frozen plasma and platelet transfusions are associated with the development of acute lung injury in critically ill medical patients. Chest 2007; 131: 1308- 1314.
42. Gajic O, Dzik WH, Toy P. Fresh frozen plasma and platelet transfusion for nonbleeding patients in the intensive care unit: benefit or harm? Crit Care Med 2006; 34: S170- S173.
43. Tripodi A, Primignani M, Chantarangkul V, Clerici M, Dell'Era A, Fabris F, Salerno F, Mannucci PM. Thrombin generation in patients with cirrhosis: the role of platelets. Hepatology. 2006; 44:440–445.
44. Trotter JF, Brimhall B, Arjal R, Phillips C. Specific laboratory methodologies achieve a higher model for end-stage liver disease (MELD) scores for patients listed for liver transplantation. Liver Transpl. 2004;10:995–1000.
45. Reverter JC. Abnormal hemostasis tests and bleeding in chronic liver disease: are they related? Yes. J Thromb Haemost. 2006;4:717–720
46. Magnusson M, Sten-Linder M, Bergquist A, Rajani R, KechagiasS, Fischler B, Németh A, Lindahl TL. The international normalized ratio according to Owren in liver disease: interlaboratory assessment and determination of international sensitivity index. Thromb Res. 2013;132:346–351.
47. Ng VL. Prothrombin time and partial thromboplastin time assay considerations. Clin Lab Med. 2009;29:253–263.
48. Dahlbäck B. Progress in the understanding of the protein C anticoagulant pathway. Int J Hematol. 2004;79:109–11
49. Huntington JA. Mechanisms of glycosaminoglycan activation of the serpins in hemostasis. J Thromb Haemost. 2003;1:1535–1549.