The risks of venous thrombosis and thromboembolism in cirrhotic patients: An integrative review

https://doi.org/10.56238/sevened2024.012-038

Maria Eduarda de Jesus[1], Ageu Nunes Dourado[2], Fernando Daniel Pereira Barbosa[3], Monalisa Horner Santine[4], Mateus Flores Matsuda[5], Breno Gonçalves Marchezan[6], Anderson Henrique Rocha Brito[7], Maria Luisa Perosa Guerra[8] and Mariana Yukari Aguena[9]

ABSTRACT

The present study employed the integrative literature review methodology to examine the risks of deep vein thrombosis and venous thromboembolism in patients with liver cirrhosis. Different data sets were collected, all related to this specific theme. The discussion addressed and analyzed the risks of developing deep vein thrombosis and venous thromboembolism in patients with different degrees of liver cirrhosis, the occurrence of thrombotic events in these patients was also analyzed, it was also observed that deep venous thrombosis and thromboembolism are less common in alcoholic cirrhosis than in non-alcoholic cirrhosis. It is concluded that the understanding of these risks is still limited and there is a lack of more in-depth and complete studies and research, since there is a general reluctance to use anticoagulation for fear of hemorrhagic complications when there is an indication for the use of anticoagulants, such as venous thromboembolism (VTE) and deep vein thrombosis (DVT), which makes it impossible to carry out clinical trials to understand these risks and make use of an effective therapy.

Keywords: Risks, Deep vein thrombosis, Pulmonary thromboembolism, Liver cirrhosis.

[1] Graduating in Medicine
Institution: University of Rio Verde (UNIRV)
E-mail: mariaedupinho@gmail.com
[2] Graduating in Medicine
Institution: University of Rio Verde (UNIRV)
E-mail: ageununes99@gmail.com
[3] Graduating in Medicine
Institution: University of Rio Verde (UNIRV)
E-mail: fernandodpbarbosa@gmail.com
[4] Graduating in Medicine
Institution: Anhanguera University - UNIDERP
E-mail: mona.ruiz@hotmail.com
[5] Graduating in Medicine
Institution: Anhanguera University - UNIDERP
E-mail: mateusmatsuda0@gmail.com
[6] Graduating in Medicine
Institution: University of Rio Verde (UNIRV)
E-mail: brenomarchezan@hotmail.com
[7] Graduating in Medicine
Institution: Anhanguera University - UNIDERP
E-mail: anderhbrito@icloud.com
[8] Graduating in Medicine
Institution: Anhanguera University - UNIDERP
E-mail: maluperosaguerra@gmail.com
[9] Graduating in Medicine
Institution: Anhanguera University - UNIDERP
E-mail: marianaaguena16@gmail.com

INTRODUCTION

Liver cirrhosis is the advanced stage of a progressive fibrosis in the liver, characterized by changes in liver structure and formation of regenerative nodules. Generally considered irreversible in advanced stages, liver transplantation is often the only viable treatment option. However, in the early stages, reversal of cirrhosis is seen in various liver diseases after treatment of the underlying cause. Patients with cirrhosis face a variety of complications and experience a significant reduction in life expectancy (Golberg et al., 2023).

In patients with cirrhosis, significant changes in the hemostatic system, evident in basic hemostasis tests, such as normalized international prothrombin time (IPT), activated partial thromboplastin time (aPTT), and platelet count during screening are common. Historically, these changes were associated with a higher risk of hemostasis-related bleeding. However, it is now widely recognized that basic hemostasis tests, such as prothrombin time and aPTT, do not fully reflect the hemostatic system. In addition, it is understood that although patients with liver disease may experience bleeding complications, many of these cases are not attributed to hemostatic dysfunctions, but rather to factors such as deep hypertension or mechanical vascular injuries, such as accidental punctures during invasive procedures. It has also been established that patients with cirrhosis are not exempt from thrombotic episodes and may require anticoagulant therapy for prevention or treatment. However, there is a paucity of data on the risk of bleeding and thrombosis in critically ill patients with cirrhosis, and knowledge about the efficacy of pro- and anti-hemostatic interventions in these situations is limited (Villa et al., 2022).

Perceived risk factors for deep vein thrombosis in cirrhosis include slow blood flow, vessel wall damage, and hypercoagulability, which constitute the classic triad of mechanistic factors for venous thromboembolism identified by Virchow. Deep vein thrombosis (DVT) is uncommon in the general population, but occurs more frequently in cirrhotic patients, especially in advanced stages of the disease. The prevalence of DVT increases as cirrhosis progresses, being less than 1% in patients with compensated disease, but ranging from 8% to 25% in liver transplant candidates, and increasing further in cases complicated by the presence of hepatocellular carcinoma. (Primignani et al., 2015)

The challenge persists in the use of procoagulant therapies in patients with advanced cirrhosis, and there are concerns about the increased risk of thrombosis in this population. In a study of 347 patients with cirrhosis who received prothrombin complex (CCP) concentrates for prevention or treatment of bleeding, CCP administration was identified as the only factor associated with thromboembolic events (5.5%) at a short-term follow-up. In addition, isolated cases of coagulopathy similar to disseminated intravascular coagulation have been reported in patients with decompensated cirrhosis following CCP administration. Patients with chronic Deep Vein Thrombosis (DVT) may present with clinical manifestations related to underlying conditions that predispose them to DVT,

such as cirrhosis. They may be asymptomatic due to thrombosis, especially if they have underlying cirrhosis (Tischendorf et al., 2019; Sanyal, 2023).

Regarding the above, the role of this literature review is to analyze the risks of thromboembolism and venous thrombosis in patients with liver cirrhosis.

MATERIALS AND METHODS

To carry out this narrative review of the literature, the following scientific databases were used: Latin American and Caribbean Health Sciences Literature (LILACS); Scientific Electronic Library Online (SCIELO); National Library of Medicine (MEDLINE) on the UpToDate platform, with the PUBMED, LILACS and MEDLINE databases being consulted by the Virtual Health Library (VHL).

In the choice of articles to compose the research, the following inclusion criteria were adopted: articles in Portuguese, Spanish and English; a time sample between 2015 and 2024; Publications with abstract and title. Articles that were not covered by the theme and those that were outside the temporal sample were excluded from the study, in addition to articles that were not available electronically and were not free.

In addition, descriptors were used in the PUBMED platform ((thrombosis) AND (thromboembolism)) AND (hepatical cirrhosis). Hepatology and cardiology guidelines were also used to conceptualize terms. Thus, 10 articles that met the inclusion criteria were selected in order to analyze and extract data that would support the hypothesis of this integrative review. After data collection, the information was interpreted and analyzed.

RESULTS AND DISCUSSIONS

The impacts of deep thrombosis on the natural progression of cirrhosis is a controversial topic, as several studies that examined the clinical outcome of cirrhotic patients after the diagnosis of DVT presented discrepant results. In fact, some research suggests that DVT may advance to complete occlusion and/or extend to other splanchnic vessels in 40%-70% of cases. Patients with DVT appear to have a more than three-fold increased risk of uncontrolling variceal bleeding and have a reduction in post-transplant survival, indicating an association between the presence of DVT in advanced stages of liver disease and critical outcomes. On the other hand, a recent multicenter study, involving a large series of patients, revealed that the incidence of DVT, mainly non-occlusive, had no impact on the clinical outcome and was associated with a high rate of spontaneous recanalization (Primignani et al., 2015).

Thrombotic events, such as deep vein thrombosis and venous thromboembolism, have been observed less frequently in alcoholic cirrhosis compared to nonalcoholic cirrhosis. However, the

higher in-hospital mortality rate associated with deep vein thrombosis in alcoholic cirrhosis highlights the importance of a careful approach in the management of these cases (Fan et al., 2019).

Observational data have suggested that anticoagulation may be beneficial for patients with cirrhosis and deep vein thrombosis. In a meta-analysis of eight studies involving 353 patients with cirrhosis and DVT, patients treated with anticoagulants (such as low molecular weight heparin or warfarin) had higher rates of partial or complete recanalization compared with untreated patients (71% versus 42%; OR 4.8, 95% CI 2.7-8.7). The overall rate of hemorrhage, including minor and major episodes, was similar in the anticoagulated and untreated patients (11% in both groups). The risk of variceal bleeding was assessed in four studies involving 158 patients, and the rate of variceal bleeding was lower in anticoagulated patients compared with untreated patients (2% versus 12%; OR 0.23, 95% CI 0.06-0.94) (Loffredo et al., 2017).

For the treatment of venous thromboembolism (VTE) in patients with cirrhosis, vitamin K antagonists (for Child A), low molecular weight heparin (for Child A, B, C), unfractionated heparin (for those with renal insufficiency), and direct-acting oral anticoagulants (DOAC for CTP A) have been recommended. These guidelines are valuable and can guide healthcare professionals in the prevention and management of these complications in patients with cirrhosis. Although comprehensive, the recommendations, as underscored by the guidelines, were mostly based on retrospective and observational studies of quality that do not yet reach optimal status. It is important to note that randomized controlled trials may not be feasible in patients at low risk of bleeding, due to the need for a large number of participants to demonstrate benefits or the lack thereof in preventing post-procedure bleeding. In addition, both patients and healthcare professionals may be reluctant to participate in such studies, due to fears of the risk of bleeding without the use of blood agents. Nevertheless, it is crucial to recognize the clinical importance of these issues and the need for guidance based on the best available evidence, since conducting large randomized trials may be unlikely and impractical (Kulkarni; K Rajender Reddy, 2023).

In a meta-analysis (PASTA et al., 2023) on the efficacy of venous thromboembolism prophylaxis showed that the rate of VTE is low (2.8%) in patients with cirrhosis, which accompanies the specifications mentioned when they are small, single-center studies, and even more so when considering the heterogeneous nature of patients with cirrhosis in terms of the etiology of the disease, stage and presence of acute diseases (such as infection, renal failure). Therefore, patients at higher risk of bleeding may not receive VTE prophylaxis, regardless of the perceived risk of thrombosis. Nevertheless, it is possible to perceive that there is a potential for prophylaxis for these patients and they deserve to be analyzed in clinical trials later.

CONCLUSION

To conclude, the evidence found in the current literature suffers from high heterogeneity and limited quality. However, it was analyzed that there is no significant risk for the development of bleeding in the prophylaxis of thrombosis and thromboembolism in cirrhotic patients. However, efficacy still remains largely uncertain and future studies are needed to guide clinicians dealing with this delicate clinical issue.

REFERENCES

1. Cool, J., et al. (2018). Deep vein thrombosis prevalence and associated mortality in cirrhosis in a nationally representative inpatient cohort. *Journal of Gastroenterology and Hepatology*, 34(6), 1088–1092. https://doi.org/10.1111/jgh.14501. Acesso em: 25/04/2024.

2. Fan, X., et al. (2019). Deep vein thrombosis prevalence and mortality among alcoholic cirrhosis in a nationwide inpatient cohort. *European Journal of Gastroenterology & Hepatology*, 32(9), 1160–1167. https://doi.org/10.1097/MEG.0000000000001624. Acesso em: 27/04/2024.

3. Goldberg, E., & Chopra, S. (2023, January 23). Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis. *UpToDate*. Retrieved March, 2024, from https://www.uptodate.com/contents/cirrhosis-in-adults-etiologies-clinical-manifestations-and-diagnosis.

4. Kulkarni, A. V., & Reddy, K. R. (2023). Bleeding risk and thrombosis in cirrhosis: a paradox with a need to address them. *Hepatobiliary Surgery and Nutrition*, 12(3), 410–412. https://doi.org/10.21037/hbsn-23-138. Acesso em: 27/04/2024.

5. Pasta, A., et al. (2023). Safety and efficacy of venous thromboembolism prophylaxis in patients with cirrhosis: A systematic review and meta-analysis. *Liver International*, 43(7), 1399–1406. https://doi.org/10.1111/liv.15609. Acesso em: 27/04/2024.

6. Primignani, M., et al. (2015). Therapeutic and clinical aspects of deep vein thrombosis in patients with cirrhosis. *World Journal of Hepatology*, 7(29), 2906. https://doi.org/10.4254/wjh.v7.i29.2906. Acesso em: 25/04/2024.

7. Sanyal, A. J. (2023, January 30). Chronic deep vein thrombosis in adults: Clinical manifestations, diagnosis, and management. *UpToDate*. Retrieved March, 2024, from https://www.uptodate.com/contents/chronic-deep-vein-thrombosis-in-adults-clinical-manifestations-diagnosis-and-management.

8. Tischendorf, M., et al. (2019). Use of prothrombin complex concentrates in patients with decompensated liver cirrhosis is associated with thromboembolic events. *Journal of Hepatology*, 70(4), 800–801. https://doi.org/10.1016/j.jhep.2018.11.019. Acesso em: 25/04/2024.

9. Villa, E., et al. (2022). EASL Clinical Practice Guidelines on prevention and management of bleeding and thrombosis in patients with cirrhosis. *Journal of Hepatology*, 76(5), 1151–1184. https://doi.org/10.1016/j.jhep.2021.09.003. Acesso em: 25/04/2024.