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Review

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Local and systemic thrombotic complications in cirrhotic patients with hepatocellular carcinoma

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Abstract

Venous thromboembolic events (VTE) represent a significant and common complication in patients with hepatocellular carcinoma (HCC) in the context of cirrhosis. While some patient-related risk factors for VTE are shared with the non-cirrhotic population, the presence of HCC amplifies the risk, potentially due to the pro-thrombotic paraneoplastic alterations associated with the tumor. This review aims to examine the current evidence regarding hemostatic disorders observed specifically in cirrhotic patients with HCC. Additionally, the review comprehensively examines VTE events in cirrhotic patients with HCC, specifically emphasizing portal vein thrombosis (PVT). PVT is the most common thrombotic complication in this population and can have significant implications for the eligibility and success of treatment modalities such as liver transplants or surgical interventions. Identifying risk factors associated with PVT occurrence in these patients is essential to guide preventive measures and enhance patient outcomes. This review aims to provide a clear background for further research and investigations into effective prevention and treatment strategies for VTE in cirrhotic patients with HCC by comprehensively revising the current evidence on these topics.

Keywords: Hepatocellular carcinoma, portal vein thrombosis, anticoagulation, cirrhosis, deep vein thrombosis, venous thrommboembolism

INTRODUCTION

Venous thromboembolic events (VTE) represent a significant and common complication in patients with hepatocellular carcinoma (HCC) in the context of cirrhosis. While some patient-related risk factors for VTE are shared with the non-cirrhotic population, the presence of HCC amplifies the risk, potentially due to the pro-thrombotic paraneoplastic alterations associated with the tumor. This review aims to examine the current evidence regarding hemostatic disorders observed specifically in cirrhotic patients with HCC. Additionally, the review comprehensively examines VTE events in cirrhotic patients with HCC, specifically emphasizing portal vein thrombosis (PVT). PVT is the most common thrombotic complication in this population and can have significant implications for the eligibility and success of treatment modalities such as liver transplants or surgical interventions. Identifying risk factors associated with PVT occurrence in these patients is essential to guide preventive measures and enhance patient outcomes. This review aims to provide a clear background for further research and investigations into effective prevention and treatment strategies for VTE in cirrhotic patients with HCC by comprehensively revising the current evidence on these topics.

HEMOSTATIC DISORDERS IN ONCOLOGIC PATIENTS

Approximately 10%-15% of oncology patients develop a VTE during the disease[1], with incidence rates ranging from 0.1% to 60%, depending on patients and cancer-specific risk factors. Although most VTE events manifest within the first 3 to 6 months after cancer diagnosis[2], concurrent detection of VTE with cancer is not uncommon. Therefore, unprovoked VTE should be considered a possible indirect signal of an underlying malignancy, warranting a comprehensive investigation. A recent meta-analysis found a mortality rate of 1.9 fatal recurrent cancer-related VTE cases per 100 patient-years, with a higher mortality rate for recurrent VTE (15%) than for bleeding events (9%)[2]. Given its adverse prognostic implications, thromboprophylaxis is frequently advocated in the oncologic setting[3,4].

The Khorana risk score, which takes into account factors such as cancer site, platelet count, hemoglobin levels, the use of erythropoiesis-stimulating agents, leukocyte count, and body mass index, helps identify patients who may benefit from primary VTE prevention[5]. Currently, the American Society of Clinical Oncology (ASCO)[6] advises pharmacological prophylaxis for specific patient categories: those with active malignancy and acute medical illness or limited mobility during hospitalization, as well as individuals with locally advanced or metastatic cancer who are undergoing systemic anti-cancer therapy and have an intermediate-to-high risk of VTE (Khorana score ≥ 2).

Indeed, malignancies are often associated with pro-thrombotic paraneoplastic syndrome, which can manifest directly with overt thrombotic events or be subclinical and detected only through coagulation tests. The tumor type typically represents the primary determinant of the kind and degree of coagulative alterations, as some tumors may display a more proinflammatory or secretory phenotype (e.g., tissue factor (TF), growth factors, pro/antiangiogenic factors). In contrast, other tumors may cause endothelial dysfunction or mechanically cause blood stasis through extrinsic vascular compression[7]. Hemocoagulative impairment usually intensifies with disease progression, increasing to a greater extent in the metastatic stage of the disease[8]. Nevertheless, early stages of various malignancies often reveal subtle hemostatic changes, such as slightly elevated levels of plasmatic coagulation markers [including prothrombin fragment 1+2 (F1+2), fibrinopeptide A (FPA), thrombin-antithrombin complex (TAT), and D-dimer], acquired protein C resistance, and an increased presence of circulating microvesicles (MV) originating from both tumor and blood cells[7,9,10]. In the metastatic stage, various elements of the hemostatic system, such as thrombin, TF, activated factor VII (FVIIa), factor Xa (FXa), fibrinogen, and vascular cells, contribute to tumor progression, as evidenced by experiments conducted in both in vitro and in vivo tumor models[7]. Risk

factors for cancer-associated venous thromboembolism are summarized in Table 1[11-16].

HEMOSTATIC DISORDERS IN CIRRHOTIC PATIENTS

Patients with cirrhosis exhibit complex hemostatic alterations, challenging VTE management. Although routine diagnostic tests suggest a bleeding tendency, it is now accepted that these tests do not accurately reflect hemostatic competence in this population. Blood coagulation in such patients is rebalanced due to the parallel reduction of procoagulant factors (e.g., low fibrinogen, factors II, V, VII, IX, X, XI, low platelet count, low plasmin inhibitor) and anticoagulant factors (e.g., low antithrombin, protein C and S, low heparin cofactor II, low plasminogen), along with high levels of von Willebrand factor and factor VIII[16]. Thus, the observed bleeding tendency in cirrhotic patients cannot solely be attributed to reduced coagulation capabilities but should also be attributed to other mechanisms influenced by underlying conditions that increase the risk of hemorrhage. These conditions include hemodynamic changes resulting from portal hypertension, endothelial dysfunction, bacterial infections, and renal failure. Furthermore, the relative deficiency of key factors in the coagulation system renders the balance delicate in these patients, and it may shift toward either hemorrhage or thrombosis based on the prevailing risk factors at any given moment[17].

HEMOSTATIC DISORDERS IN CIRRHOTIC PATIENTS WITH HCC

HCC in cirrhotic patients is associated with pro-thrombotic changes[18], enhancing hypercoagulability and the risk of thrombosis. These changes include elevated platelet adhesive glycoprotein Von Willebrand factor, increased thrombin generation, reduced activation of fibrinolysis, higher levels of pro-thrombotic circulating MV including those bearing TF, increased circulating fibrinogen, production of thrombopoietin by HCC cells, thrombocytosis, increased platelet activation and aggregation, and increased markers of neutrophil extracellular traps (NETs)[19]. Previous studies have documented elevated levels of plasmatic fibrinogen in patients with HCC, especially those with extensive tumor burden[20-21], which could be due to widespread inflammation[22] or direct synthesis by hepatoma cells[23].

A comprehensive study delved into changes in blood clotting and clot breakdown mechanisms in cirrhosis patients with HCC, revealing that HCC was linked to a substantial rise in thrombin generation, indicating heightened clot-forming ability, and decreased activation of fibrinolysis[24]. Moreover, these patients display an elevated concentration of pro-thrombotic microvesicles, including those originating from the endothelium, platelets, and leukocytes, particularly those carrying TF, compared to cirrhotic patients without HCC and healthy individuals[25].

The prevalence of thrombocytosis (conventionally defined as a platelet count > 450 x 10^9/L) has been estimated to be 3%-9% in patients with cirrhosis and HCC[26], placing this malignancy among those with a low prevalence of thrombocytosis[27]. However, these rates might be underestimated due to hypersplenism secondary to portal hypertension[28-30], suggesting a need to redefine the threshold for thrombocytosis in these patients. Notably, a platelet count > 450 x 10^9/L in HCC patients has been associated with larger tumor volume, increased vascular invasion, extrahepatic metastases, high serum α-fetoprotein, and worse overall survival[31]. Indeed, it has been demonstrated that hepatoma cells can produce thrombopoietin, thus promoting platelet production[32], and platelet count and serum thrombopoietin levels decrease after surgical resection of the tumor or transarterial chemoembolization, re-elevating when the tumor recurs, concomitantly with a new increase in levels of α-fetoprotein[33]. Moreover, recent studies have demonstrated that platelet count may be a predictor of survival in HCC patients, with the degree of platelet activation correlating with poor outcomes[27,34]. Finally, a substantial elevation in Von Willebrand factor levels is also associated with the presence of HCC; however, its prognostic role still needs to be defined[35]. Further studies

Table 1. Risk factors for cancer-associated venous thromboembolism

Patient-related	Cancer-related	Treatment-related
Female sex	Site of cancer: high risk in brain, pancreas, kidney, stomach, lung, bladder, gynecologic, and hematologic malignancies	Prolonged hospitalization
Ethnicity: lower risk in Asians, higher in African-Americans	Stage of cancer	Surgery: open surgery > minimally invasive surgery
Old age	Histological type: adenocarcinoma lung cancer > squamous cell carcinoma[9]	Chemotherapy and hormonal therapy
Obesity	Hypersecretory type: unregulated secretion of proinflammatory cytokines	Antiangiogenic therapy
	Thrombocytosis and increased platelet activation	Erythropoiesis stimulating agents
	Increased soluble tissue factor expression by tumor cells	Blood transfusions
		Central venous line

are needed to clarify hemostatic balance and platelet count thresholds in these patients according to tumor burden and liver disease severity, and their ability to predict VTE and prognosis.

VENOUS THROMBOEMBOLISM IN PATIENTS WITH HCC

Numerous studies have indicated that individuals with cirrhosis and HCC face an elevated risk of developing VTE. These studies have also explored potential risk factors associated with this heightened risk [Tables 2 and 3]. Interestingly, HCC has not been classified as high-risk in studies validating the Khorana score, likely due to its unique thrombosis mechanisms. HCC patients frequently have cirrhosis and portal hypertension, resulting in low platelet counts that can mask thrombocytosis or pancytopenia, limiting the score's accuracy, which primarily considers systemic inflammatory markers in the absence of portal hypertension. While Wang *et al.* study on 270 HCC patients (16 with VTE) may be underpowered[40], similar studies in non-HCC cancers have also shown limitations in the score's predictive value.

Despite the considerable heterogeneity among the cohorts described in the studies evaluating VTE risk in HCC patients and differences in inclusion criteria, the commonly detected risk factors are summarized in Tables 2 and 3[36-42]. The reported prevalences of VTE ranged between 1.7%-4.6%[36,38,41].

The reported VTE prevalence in this population ranges from 1.2% to 18.6%, with the highest incidences reported in studies with more advanced cancer stages or extrahepatic metastases. Advanced cancer features such as multiple hepatic lesions or metastasis carry high odds ratios (up to 12), underscoring the increased thrombotic risk when HCC is extensive. Liver-related factors like hypoalbuminemia and hepatic encephalopathy also appear to significantly elevate VTE risk, reflecting the contribution of advanced liver dysfunction. Major comorbidities, particularly cardiovascular events and diabetes, add further risk. Moreover, demographic characteristics like female sex, age over 60, and higher BMI appear to be also associated with increased VTE likelihood. However, HCC itself does not consistently emerge as an independent predictor of VTE across all studies, possibly due to the variability in sample composition and study power regarding HCC-specific risk. Indeed, the reliability of these findings varies among studies. While the large-scale analyses by Abou Yassine *et al.* (157,400 patients, 2015-2020)[37] and Faccia *et al.* (7,445 patients, 1982-2017)[38] offer strong statistical power and extended observation periods, the first one lacks tumor stage or histotype data, and the majority of patients do not have cirrhosis, which may limit direct relevance to HCC-specific VTE risk. Although specifically selecting HCC patients, the study by Faccia *et al.*[38] utilized ICD-9 coding, minimizing misclassification but lacking detailed anticoagulant use data that could affect VTE incidence. Among studies specifically focused on HCC, only two[39,40] include liver disease staging, a key variable for interpreting VTE risk, and all the studies are retrospective, limiting the collection

Table 2. Risk Factors associated with VTE occurrence in patients with cirrhotic patients HCC

	Risk Factors	OR	Author
Cancer-related	HCC extrahepatic metastasis	12; 2.11	Wang *et al.*, 2018, Al-Taee *et al.*, 2019[40,41]
	HCC	3.6; 1.98; 0.176	Wang *et al.*, 2018, Faccia *et al.*, 2022, Lesamana *et al.*, 2010[36,38,40]
	Extrahepatic tumors	2.48	Faccia *et al.*, 2022[38]
	Liver cancer (not specified)	1.47	Abou Yassine *et al.*, 2022[37]
Liver disease-related	Hypoalbuminemia	3.83	Abou Yassine *et al.*, 2022[37]
	Hepatic encephalopathy	3.21	Faccia *et al.*, 2022[38]
	Portal vein thrombosis	NA	Connolly *et al.*, 2008[39]
Patient-related – medical history	Extrahepatic comorbidities	9.03; 1.26	Chen *et al.*, 2021, Al-Taee *et al.*, 2019[41,42]
	Acute Miocardial Infarction/Stroke	7.86	Faccia *et al.*, 2022[38]
	Diabetes mellitus	3.88; 1.31	Lesamana *et al.*, 2010, Abou Yassine *et al.*, 2022[36,37]
	Infection	3.01	Faccia *et al.*, 2022[38]
	Cardiac/Respiratory Insufficiency	2.4	Faccia *et al.*, 2022[38]
	Long hospitalization	2.05	Al-Taee *et al.*, 2019[41]
Patient-related - demographics	Sex (F *vs.* M)	13.96	Chen *et al.*, 2021[42]
	BMI (> 25-30)	4.22; 1.62	Chen *et al.*, 2021, Abou Yassine *et al.*, 2022[37,42]
	Age (> 60-65)	3.03; 1.23	Chen *et al.* 2021, Al-Taee *et al.*, 2019[41,42]
	Non-Caucasians	1.22	Abou Yassine *et al.*, 2022[37]
	Black *vs.* White	1.20	Al-Taee *et al.*, 2019[41]

VTE: venous thromboembolic event; HCC: hepatocellular carcinoma; BMI: body mass index.

of relevant data. These limitations suggest that while associations between VTE risk and HCC-related factors are evident, further prospective studies specifically designed to evaluate VTE in HCC across varying stages of liver disease and treatment conditions would refine our understanding.

PVT IN PATIENTS WITH HCC

Among cirrhotic patients with HCC, non-neoplastic PVT stands out as the most frequent thrombotic complication, with 1-year prevalence rates varying from 7% to 24%[43,44], The A-VENA criteria provide a key diagnostic framework to differentiate non-neoplastic from tumoral invasion of the portal vein in HCC patients (neoplastic PVT), achieving high specificity and sensitivity by integrating radiological characteristics with AFP levels. These criteria assess: A - arterial hypervascularization in the thrombus, detectable via Doppler or MRI, indicating tumor-driven angiogenesis; V - thrombus growth, with neoplastic thrombi typically enlarging, unlike stable benign thrombi; E - direct vascular invasion, where tumor thrombi may infiltrate nearby vessels; N - thrombus morphology, with neoplastic thrombi appearing irregular and heterogeneous, often with neovascularization; and A - exclusion of other thrombosis causes, increasing suspicion of a neoplastic thrombus[45]. Nevertheless, neoplastic PVT, which involves neoplastic invasion of the portal vein and is not an actual thrombus[46,47], will not be discussed in this paper. From now on, we will refer to non-neoplastic PVT simply as PVT. Nonami *et al.*[48] highlighted the heightened risk of both intrahepatic and extrahepatic PVT in HCC patients (34.8%) compared to those without HCC (11.4%) ($P < 0.001$). Similarly, Davidson *et al.*[49] found that patients with HCC who underwent liver transplantation (LT) experienced a notably greater occurrence of PVT compared to those without liver malignancies (27% *vs.* 9%, $P < 0.05$). This finding was also confirmed by Ravaioli *et al.*[50], who reported a prevalence of PVT reaching 40.8% in recipients with HCC, compared to recipients without HCC, where it was 30.7% ($P = 0.05$). Furthermore, Zanetto *et al.*[20] conducted a prospective comparative analysis between HCC and non-HCC cirrhotic patients matched for underlying liver disease severity, revealing that within 1 year, the occurrence

Table 3. Risk Factors associated with VTE occurrence in cirrhotic patients with HCC

Studies considering patients with and without HCC				
Author, Year	**Type of study (time of inclusion)**	**Patients (n)**	**VTE**	**Risk Factors associated with VTE occurrence**
Lesamana *et al.*, 2010[36]	Case-control study (2004-2007)	87 cirrhotics (+ HCC), 169 cirrhotics (-HCC)	HCC (+) prevalence 4.6% *vs.* HCC (-) prevalence 4.7%	Diabetes mellitus (OR = 3.88, *P* = 0.031) HCC is not a risk factor for VTE (OR = 0.176, *P* = 0.099)
Abou Yassine *et al.*, 2022[37]	Retrospective cohort study (2015-2020)	157,400 with cirrhosis (7% with overall liver cancer) and 9,832,890 without cirrhosis		Cirrhosis (OR = 0.921, *P* < 0.001) Liver cancer (OR = 1.47, *P* < 0.001) Hypoalbuminemia (OR = 3.83, *P* < 0.001) Diabetes Mellitus (OR = 1.31, *P* < 0.001) BMI > 30 (OR = 1.62, *P* < 0.001) Non-Caucasians (OR = 1.22, *P* < 0.001)
Faccia *et al.*, 2022[38]	Retrospective Cohort study (1982-2017)	7,445 hospitalized cirrhotic patients (1,524 + HCC) 1,524 cirrhotics (+ HCC); 5,921 cirrhotics (-HCC)	HCC (+) prevalence 1.7%, HCC (-) prevalence 1.2%	HCC (OR = 1.98, *P* = 0.002) Hepatic Encephalopathy (OR = 3.21, *P* < 0.0001) Extrahepatic tumors (OR = 2.48, *P* = 0.0007) Infection (OR = 3.01, *P* = 0.0001) Cardiac/respiratory insufficiency (OR = 2.40, *P* = 0.003) AMI/Stroke (OR = 7.86, *P* = 0.003)
Studies considering only patients with HCC				
Connolly *et al.*, 2008[39]	Retrospective (1998-2004)	194 with cirrhosis (CHILD A/B/C 60/87/46) + HCC	Incidence of 6.7%	Concomitant presence of PVT (11.5% *vs.* 4.4 %, *P* = 0.04)
Wang *et al.*, 2018[40]	Retrospective (2000-2015)	270 with HCC (229 with cirrhosis CHILD A/B/C 97/89/43)	2- years cumulative incidence 5.93% 75% of VTE occurring within 3 months of diagnosis of HCC	>3 hepatic lesions *vs.* single lesion (OR = 3.6, *P* = 0.048); Multi-organ extrahepatic metastasis (OR = 12, *P* = 0.028)
Al-Taee *et al.*, 2019[41]	Retrospective study (2008-2013)	54,275 with HCC	2.8% prevalence	age ≥ 65 (OR = 1.23, *P* = 0.0004) African ethnicity (OR = 1.20, *P* = 0.002) Metastatic disease (OR = 2.11, *P* < 0.0001) Higher Elixhauser comorbidity index* (OR = 1.26, *P* < 0.0001) Longer hospital stay (OR = 2.05, *P* < 0.0001)
Chen *et al.*, 2021[42]	Retrospective study (2016-2020)	355 consecutive patients with HCC who underwent laparoscopic hepatectomy	Incidence of 18.6%	Age > 60 (OR = 3.03, *P* = 0.008) Sex F *vs.* M (OR = 13.96, *P* < 0.001) BMI > 25 (OR = 4.22, *P* = 0.005) Comorbidities (OR = 9.03, *P* < 0.001)

*Elixhauser comorbidity index: method of categorizing comorbidities of patients based on ICD. VTE: venous thromboembolic event; HCC: hepatocellular carcinoma; OR: odds ratio; BMI: body mass index; PVT: Portal vein thrombosi.

of PVT was over twice as high among individuals with cancer compared to those without (24.4% *vs.* 11.4%; *P* = 0.05). The factors that increase the risk of PVT in patients with HCC are outlined in Supplementary Table 1 and Table 4[20,38,44,48-52].

The only prospective study addressing PVT prevalence at HCC diagnosis and incidence during follow-up is by Senzolo and Shalaby *et al.*[44], which reports an 11.7% PVT prevalence in a cohort of patients with a first

Table 4. Risk factors for PVT in cirrhotic patients with HCC

Group	Risk factor	OR/HR	Author
Cancer-related	HCC features	HR: 10.34; HR: 1.81; NA; OR: 4.59	Zanetto *et al.*, 2017, Ravaioli *et al.*, 2011, Cagin *et al.*, 2016, Faccia *et al.*, 2022[20,38,50,51]
	Liver cancer	NA	Davidson *et al.*, 1994[49]
	Chronic active hepatitis	NA	Davidson *et al.*, 1994[49]
Liver disease-related	Encephalopathy	OR: 13.98; NA	Faccia *et al.*, 2022, Nonami *et al.*, 1992[38,48]
	Clinically significant portal hypertension	OR: 1.33	Faccia *et al.*, 2022[38]
	Ascites	NA	Nonami *et al.*, 1992[48]
	Gastrointestinal bleeding	NA	Nonami *et al.*, 1992[48]
Abnormal tests	Thromboelastography (MCF > 25mm)	HR: 6	Zanetto *et al.*, 2017[20]
	Annexin A5/PS ratio (< 00277264) PS + MPs (> 38.7 nmol/L)	NA	Serag *et al.*, 2020[52]
	Portal flow velocity (< 15cm/sec)	NA	Serag *et al.*, 2020[52]
Patient-related	Abdominal surgery/invasive procedure	OR: 2.03	Faccia *et al.*, 2022[38]
	Diabetes	OR: 1.68	Faccia *et al.*, 2022[38]
	Splenectomy	NA	Nonami *et al.*, 1994[48]

HCC: hepatocellular carcinoma; HR: hazard ratio; NA: not Available; OR: odds ratio; MCF: maximum clot firmness.

HCC diagnosis and undergoing microwave ablation as a first treatment. The incidence during follow-up was 4.1% for active HCC and 6.9% for the entire cohort, including complete responders. Notably, PVT progression was more common in patients with incomplete tumor control, suggesting a link between treatment response and PVT progression[44]. Nevertheless, the presence and progression of PVT significantly affected prognosis independently of HCC progression, highlighting the need for prompt treatment to prevent thrombosis progression in HCC patients and the importance of future research to refine treatment thresholds and approaches[44]. Interestingly, the performance status was not associated with the risk of PVT occurrence or progression. While locoregional treatments can induce intrahepatic thrombosis near the treated area, these typically resolve spontaneously without progressing to the main portal branches. Although the actual impact of HCC treatments on overall PVT incidence remains unclear, in Senzolo and Shalaby *et al.*[44] study, PVT progression was linked to incomplete response to treatment, highlighting the importance of the procoagulant role of active tumors rather than treatment schedule. Future prospective studies specifically assessing this issue should clarify this further.

ANTICOAGULANT TREATMENT IN PATIENTS WITH HCC

The perceived risk of bleeding in cirrhosis and the need for invasive treatments for HCC have historically led to the underuse of thromboprophylaxis and undertreatment of thrombotic complications. However, as previously discussed, patients with cirrhosis are not naturally anticoagulated[24], especially in the presence of HCC. Moreover, anticoagulant drugs have shown potential benefits in advanced liver disease beyond thrombosis treatment, including the reduction of liver fibrosis, portal hypertension, and improved survival[44], and bleeding complication rates are comparable to those reported for the general population[44]. According to this evidence, current practice guidelines endorse anticoagulation for cirrhotic patients with atrial fibrillation and VTE[53,54]. European guidelines[54] recommend low molecular weight heparin (LMWH) for decompensated patients, while direct oral anticoagulants (DOACs) are recommended only in those with Child-Pugh class A and B cirrhosis, preferring unfractionated heparin in cases of renal failure. Indeed, due to the possibility of accumulation, DOACs should be used with caution in Child-Pugh class B patients and those with creatinine clearance below 30 ml/min[54].

While the efficacy of anticoagulation for VTE is well established, experts still emphasize the need for additional research to ascertain the true efficacy of anticoagulation in the treatment of PVT, as up to 60% of patients may not respond to this treatment[44]. Indeed, although PVT may frequently self-resolve when partial at diagnosis and anticoagulation may be more efficient than no treatment at all[55,56], the pathophysiology of PVT is still unknown and portal vein peculiar features have prevented its extensive study so far. Current clinical guidelines[57,58] recommend considering anticoagulation therapy for cirrhotic patients with PVT who are potential candidates for LT to prevent its progression; however, for those with extensive/progressive PVT who do not respond, there remains a significant need to escalate to invasive treatments. Moreover, studies that consider the efficacy and safety of anticoagulation in patients with HCC are limited. A recent study[44] reported the evolution pattern of PVT in a small group of patients with HCC treated with anticoagulation. Among 83 patients with cirrhosis and PVT diagnosed in the presence of HCC, 22 were anticoagulated for a median of 10 months (IQR: 8-18), while the others were not. No patients discontinued anticoagulation due to complications. At the end of follow-up, PVT improved by 50%, progressed by 9.1%, and remained stable in 40.9% of anticoagulated patients, compared to 6.6%, 62.3%, and 31.4% of untreated patients, respectively. This suggests that anticoagulation may be effective in preventing PVT progression, though the sample size is too small to draw definitive conclusions. Another small study of 51 patients with HCC and PVT, 12 of whom were treated with anticoagulation, found no significant difference in PVT progression between treated and untreated groups, with anticoagulation discontinued in three patients due to complications[56]. These results do not allow conclusions to be drawn on the efficacy and safety of anticoagulation in patients with PVT and HCC, and future research should include these patients in the analyses to allow specific recommendations to be made for this specific population.

CONCLUSIONS

VTE is prevalent in patients with cirrhosis, presenting significant management challenges, especially in those with HCC. While common patient-related risk factors overlap with those in the general population, the presence of HCC amplifies the risk of VTE due to pro-thrombotic alterations associated with tumor activity. Current evidence suggests that anticoagulation therapy can offer benefits beyond thrombosis treatment, including reducing liver fibrosis and portal hypertension and improving survival.

PVT is the most frequent thrombotic complication in cirrhosis, and its occurrence and evolution correlate with tumor activity in patients with HCC. However, the pathophysiology of PVT remains under-explored, and the efficacy and safety of anticoagulation in cirrhotic patients with HCC require further investigation. Future studies should focus on refining treatment thresholds and approaches, considering the unique hemostatic challenges posed by HCC and cirrhosis, aiming to improve prophylaxis and treatment strategies for thrombotic complications in cirrhotic patients with HCC, ultimately enhancing patient outcomes.

DECLARATIONS

Authors' contributions

Selection and interpretation of data, drafting the article and revising it critically for important intellectual content: Zanatta E

Conception and design of the study, selection and interpretation of data, drafting the article and revising it critically for important intellectual content, final approval of the version to be published: Shalaby S

Critical revision of the manuscript for important intellectual content: Zanetto A, Burra P

Selection and interpretation of data, drafting the article and revising it critically for important intellectual content, final approval of the version to be published: Senzolo M

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