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REVIEW ARTICLE

The prothrombotic tendency of metabolic-associated fatty liver disease

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Abstract

Our understanding of the function of the liver has evolved over the centuries. Early theories proposing that the liver could be used to divine the future have been superseded by our current knowledge of the importance of the liver in processes such as digestion and detoxification. Similarly, although liver disease was previously associated with only an increased risk of bleeding, there is now a substantial body of evidence demonstrating an increased thrombotic potential in patients with this disease. Metabolic-associated fatty liver disease (MAFLD) is increasing in frequency and is likely to overtake alcoholic liver disease as the primary indication for liver transplant in the future. In this review, we discuss the evidence linking liver disease, and MAFLD in particular, with arterial and venous thromboembolic disease. We review the safety and efficacy of anticoagulation in advanced liver disease and consider whether antithrombotic agents could slow or halt the progression of fibrosis in MAFLD.

KEYWORDS
anticoagulation, bleeding, direct oral anticoagulants, liver disease, thrombosis

1 | INTRODUCTION

The attributed roles of the liver have changed over the history of mankind. Until the 17th century, the liver was believed to be the single site of origin of blood based on the teachings of Galen [1]. Before the honor was usurped by the heart, the liver was also considered by the followers of "hepatocentrism" to be the seat of the soul [1,2]. Since no 2 livers looked the same, divination was believed possible through examination of the liver surface, details of which were included in "textbooks" for priesthood [2–4]. The transition in history of the roles of the liver has also happened in the niche area of the liver and coagulation.

Until the 21st century, abnormal hemostasis tests in the context of liver disease were thought to be associated with bleeding risk. In this century, due to important works by Lisman et al. [5] and Tripodi et al. [6], we now understand that the abnormal laboratory coagulation profile in liver disease is not associated with bleeding and that a rebalanced state exists where procoagulant and anticoagulant factors keep hemostatic equity. Similar to the change in the liver's allocation as the blood-forming organ and seat of the soul, to a digestive and synthetic organ, we have realized that liver disease may be hypercoagulable and associated with thrombosis rather than bleeding [7].

This article aims to overview this changing paradigm. MEDLINE and Embase were searched for publications in English using the following key words: chronic liver disease (CLD), metabolic-associated fatty liver disease (MAFLD)/nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH), cirrhosis, thrombosis, and anticoagulation. The historical aspect presented in the article was researched separately.

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2 | LIVERPOOL AND AUTOANTICOAGULATION IN CLD

The first record of the city of Liverpool, known worldwide as The Beatles' birthplace, is around the 12th century as "Liuerpul", thought to derive from the Old English terms "lifer," meaning clotted/muddy water, and "*pōl*," meaning a pool of water that flowed slowly (due to excess liverwort into the Mersey River) [8]. A similar connection for the word "liver" to "clotted mud" exists in the *Oxford English Dictionary* as a version of its use in "blood-liver," meaning a "clot of blood" and in the adjective, "livery" denoting "coagulated, clotted" [9].

In the medical parlance, the role of this organ in synthesizing coagulation proteins was recognized around the dawn of the 19th century. Indeed, the prothrombin time (PT) was devised by Quick [10] using blood obtained from patients with obstructive jaundice. An interesting historical event of note here is that Quick's mentors, Bancroft and Stanley-Brown, were hoping for their new recruit to study blood coagulation with the aim of dealing with postoperative thrombosis and *not* bleeding [11]. Soon after PT discovery and its use in determining the extent of anticoagulation in patients receiving coumarins, this test was employed to identify bleeding risk in various clinical conditions, including in the setting of liver disease. Indeed, PT expressed as international normalized ratio (INR), which was meant to standardize the laboratory variations in patients receiving vitamin K antagonists, started being (erroneously) used in scoring systems for determining the severity of liver disease, such as the Child-Pugh (CP) and model for end-stage liver disease (MELD) scores [12].

3 | REBALANCED HEMOSTASIS IN CLD

The liver is the site of synthesis of the majority of coagulation factors, fibrinolytic proteins, and thrombopoietin [13]. Simultaneous changes in both procoagulant and anticoagulant pathways in liver disease result in "rebalanced hemostasis." Thrombocytopenia and platelet function defects are balanced by increased levels of von Willebrand factor and reduced ADAMTS-13 [5]. Diminished coagulation factors are balanced by a reduction in natural anticoagulants, protein C (PC), protein S, and antithrombin (AT), with a resultant preservation of thrombin generation seen [14]. Multiple studies have even demonstrated enhanced thrombin generating capacity in patients with cirrhosis [15]. Fibrinogen defects are present in liver disease, with defective fibrinogen-fibrin conversion seen, but increased clot strength noted [16]. Fibrinolysis is also altered by as yet incompletely understood complex mechanisms, with a hypofibrinolytic state particularly in the sickest patients [17].Therefore, despite obvious perturbations to standard coagulation parameters, hemostasis may be preserved or even hyperactive in these patients.

4 | FOIE GRAS AND MAFLD

The Greeks considered the liver to be the focal point of the soul and hence used the word "hèpar" derived from "hèdar" (root is "hedoné," meaning "pleasure") to denote liver [2,18]. However, when it came to the Romance languages, an entirely different epithet started being used. Riva et al. [2] describe this in their interesting discourse on the modern names for the liver. They explain that the use of the term "iecur" in Medieval Latin was gradually replaced by "iecur ficatum," which indicated the fattening liver of an animal with figs [2]. Force-feeding figs to poultry makes them too heavy to fly, while these fruits, rich in carbohydrates, can lead to adipose tissue accumulation in the liver of these birds [2]. This *foie gras* (from foie, liver, and gras, fat) eventually became the "The Dish of Kings" in France [19].

The English physician, Thomas Addison, first described cases of fatty degeneration of the liver, related to ethanol excess in 1836 [20,21]. In 1980, Jurgen Ludwig introduced the term "nonalcoholic steatohepatitis" (NASH) based on analysis of 20 patients with obesity, diabetes, and hepatomegaly or cholelithiasis [22]. In the last 2 decades, there have been increasing calls to replace the terminology of NASH with "metabolic steatohepatitis," "metabolic-associated fatty liver," and "metabolic syndrome steatohepatitis" [20]. Following a Delphi method, a consensus was reached by international experts to use MAFLD as the accepted nomenclature based on strict diagnostic criteria [23]. The majority of patients previously classified as having NAFLD will fall under the umbrella of MAFLD based on the new criteria. A small proportion, previously considered to have "lean NAFLD," who lack features of the metabolic syndrome, will not meet the criteria for MAFLD. A significant proportion of the evidence we discuss within this review was published prior to the reclassification. We use the terms MAFLD and NAFLD interchangeably here as we believe that the hemostatic findings will be largely applicable to either nomenclature.

5 | PROTHROMBOTIC STATE IN MAFLD

MAFLD may be considered to be the hepatic manifestation of metabolic syndrome. Insulin resistance promotes storage of free fatty acids in nonadipose tissue, including the liver. It promotes *de novo* lipogenesis by hepatocytes and increases movement of free fatty acids to the liver secondary to impaired inhibition of lipolysis [24]. This is compounded by decreased availability of adiponectin, which usually inhibits lipogenesis, alongside increased systemic inflammation and oxidative stress [25].

Patients with MAFLD are at an increased risk of both arterial and venous thrombotic disease. A positive correlation between the severity of liver histology in patients with MAFLD and markers of early atherosclerosis, such as greater carotid artery wall thickness [26] and lower endothelial flow-mediated vasodilation, was noted early on [27]. There were also studies suggesting that MAFLD may actually mediate development of atherosclerosis [28,29]. It may seem that since both cardiovascular disease (CVD) and MAFLD share similar risk factors like type 2 diabetes, dyslipidemia, and obesity, the higher arterial thrombotic risk is merely a result of the similar contributing factors. However, a direct mechanistic relationship between MAFLD and CVD has been shown by several groups prompting the latest guidelines to recommend screening of the cardiovascular (CV) system in all patients with MAFLD [30,31].

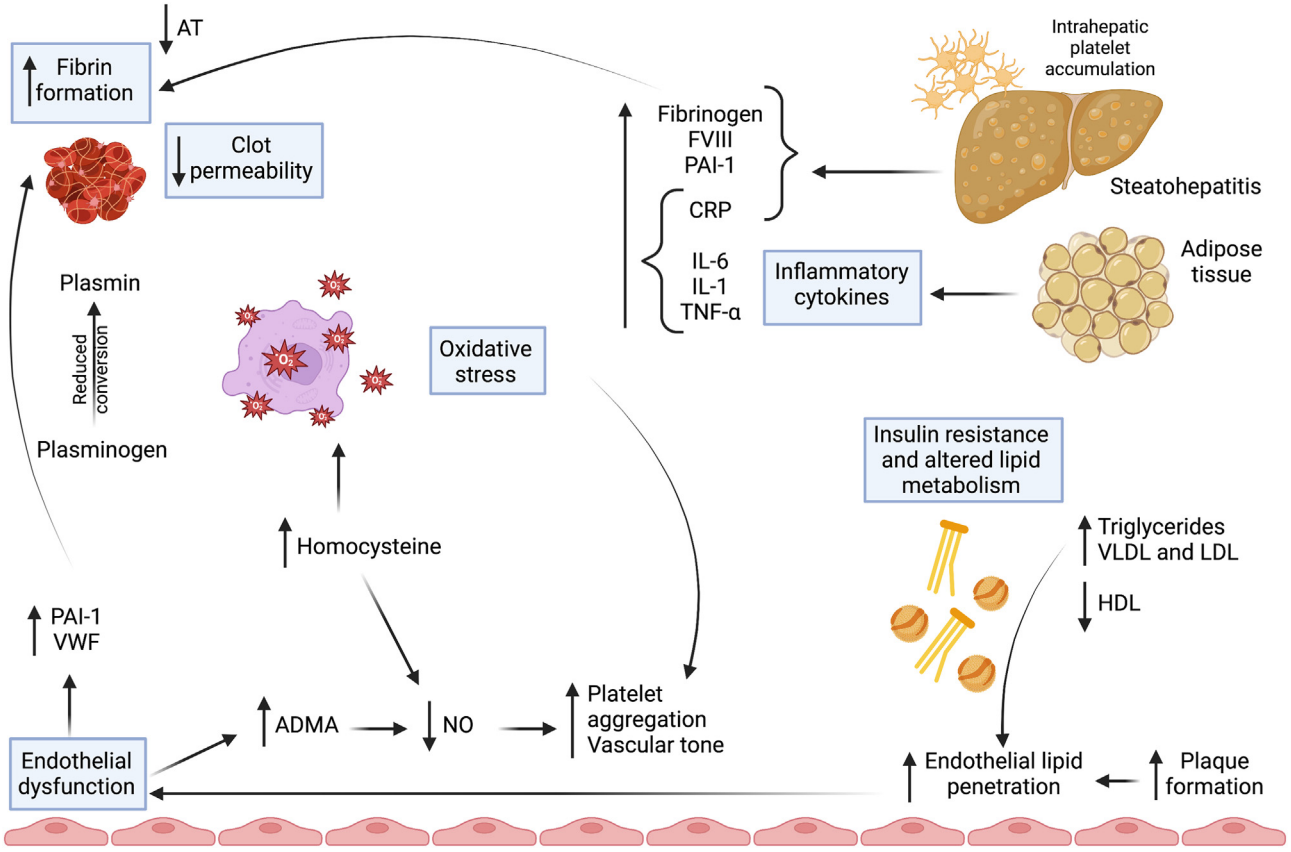

FIGURE 1 Factors contributing to increased arterial and venous thrombotic events in metabolic-associated fatty liver disease. ADMA, asymmetric dimethyl arginine; AT, antithrombin; CRP, C-reactive protein; FVIII, factor VIII; HDL, high density lipoprotein; IL-1, interleukin-1; IL-6, interleukin-6; LDL, low-density lipoprotein; NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1; TNF-α, tumor necrosis factor-α; VLDL, very low–density lipoprotein; VWF, von Willebrand factor.

Thrombosis is a multifactorial process. It may be the endpoint of derangements in a number of interlinking factors and processes including hemostatic components, blood cells, immune and inflammatory mediators, and the endothelium. MAFLD is a complex disease that may impact this sensitive homeostasis in a variety of ways that we do not yet fully understand. Important factors that contribute to increased CV risk include endothelial dysfunction, increased oxidative stress, a systemic inflammatory state, altered lipid metabolism with increased production of more atherogenic lipids, insulin resistance, and inhibition of fibrinolysis [31–33]. Patients with MAFLD have dysfibrinogenemia and elevated levels of plasminogen activator inhibitor-1, impairing fibrinolysis, alongside increased production of factor VIII (FVIII) and von Willebrand factor. Compared with lean controls and patients with alcoholic cirrhosis, individuals with MAFLD have been shown to have decreased clot permeability and hypofibrinolysis [34]. This complex interplay is described in a highly simplified form in Figure 1.

5.1 | CVD

CVD represents the most common cause of death in patients with MAFLD after cirrhosis [35]. A meta-analysis of >34 000 patients reported a higher risk of nonfatal and fatal CV events in patients with MAFLD (odds ratio[OR], 1.64 for all patients with MAFLD and 2.58 for those with "severe disease") [36]. A retrospective analysis of 286 patients with type 1 diabetes mellitus, of whom 150 had evidence of MAFLD at baseline, identified a higher incidence of CV events in the MAFLD cohort (17.3% vs 1.5%), despite the shared risk factor of diabetes. This association remained significant after adjustment for other CV risk factors (hazard ratio [HR], 6.73) [37]. CVD mortality has also been shown to be higher in patients with MAFLD-related cirrhosis than in patients with hepatitis C cirrhosis [37].

5.2 | Atrial fibrillation

A review of 1727 patients with cirrhosis reported an incidence of atrial fibrillation (AF) of 11%. Increasing MELD scores were predictive of higher rates of AF in this group, although only 17% of the cohort had MAFLD [38]. A population-based study of nearly 700 000 patients with cirrhosis found that AF is associated with increased in-hospital mortality rates and stroke. The proportion of patients with MAFLD was not stated [39]. A recent meta-analysis by Jaiswal et al. [40] of more than 18 million patients identified statistically significantly increased rates of AF (relative risk [RR], 1.42) and CV mortality (RR, 3.10) in patients with MAFLD. The patients with MAFLD were more

likely to have concomitant hypertension and diabetes mellitus, which may have confounded results [40]. Two recent studies in diabetic patients reported that features of MAFLD on ultrasonography were associated with a 3- to 5-fold increased risk of AF [41,42]. MAFLD has been shown to be independently associated with cardiac structural and functional abnormalities [43]. Patients with MAFLD, without other traditional cardiac risk factors, have increased epicardial fat accumulation and impaired left ventricular (LV) metabolism, compared with matched controls [44]. This has also been shown in type 2 diabetes, wherein higher myocardial fat levels correlated with increased hepatic steatosis. In this study, myocardial fat deposition was associated with LV diastolic dysfunction [45]. Of note, marked LV diastolic dysfunction has been observed in patients with MAFLD without hypertension or diabetes [46].

5.3 | Ischemic stroke

The presence of MAFLD may be associated with increased risk and severity of ischemic stroke. In a cohort of 200 patients with acute ischemic stroke, of which 43% fulfilled the criteria for MAFLD, the patients with liver disease had significantly higher National Institutes of Health Stroke Scale and modified Rankin Scale scores, indicative of greater neurological severity [47]. In a population-based study including nearly 80 000 individuals without a history of stroke, cancer, or myocardial infarction, the risk of ischemic stroke was 16% higher in those with evidence of MAFLD at baseline, with a trend toward increasing risk with severity of MAFLD [48]. In another population-based study of over 120 000 adults with a diagnosis of MAFLD, after adjustment for age and smoking status, MAFLD conferred an increased risk of stroke (HR, 1.18; 95% CI, 1.11-1.24); however, statistical significance was lost after adjusting for additional CV risk factors (HR, 1.04; 95% CI, 0.99-1.09) [49]. Jaiswal et al. [40] also reported an increased rate of stroke in patients with MAFLD vs patients without MAFLD (RR, 1.26) in their meta-analysis.

5.4 | Venous thromboembolism

Patients with liver disease are also at increased risk of venous thromboembolism (VTE). A meta-analysis including 695 012 patients with cirrhosis reported an OR for VTE of 1.7 (95% CI, 1.3-2.2) in the cirrhosis cohort [50]. A study of 290 patients with cirrhosis, of whom 145 had VTE, identified MAFLD (OR, 2.46), a personal history of VTE (OR, 7.12), and presence of portal vein thrombosis (PVT) (OR, 2.18) as statistically significant risk factors for VTE after matching for age, sex, and MELD score [51]. Another case-control study assessed 138 patients with VTE, and 276 matched controls for features of MAFLD. Evidence of MAFLD by ultrasound was identified in 81% of the VTE group compared with 30% of controls. After adjusting for the presence of inherited thrombophilia, MAFLD conferred an OR for VTE of 1.8 (95% CI, 1.2-2.7) in this study [52]. PVT, a sequela of cirrhotic liver disease, is more frequently seen in patients with MAFLD. Stine et al. [53] reviewed all patients undergoing liver transplantation in the United States over a 10-year period. Incidence of PVT at the time of transplantation was higher in the MAFLD group at 10.1% vs 6% in patients with other disease etiologies. Moreover, MAFLD cirrhosis was identified as the strongest predictor of PVT on multivariable analysis (OR, 1.55) [53]. Another retrospective review of patients awaiting transplantation identified MAFLD, increased body mass index, diabetes, and hepatocellular carcinoma (HCC) as risk factors for PVT-development. The authors noted an increase in PVT incidence during the 12-year study period, potentially relating to the increasing population incidence of MAFLD [54]. Despite the increased risk of VTE in MAFLD, the various risk-assessment models available have mostly been derived from populations that excluded CLD. The Padua prediction score has been shown to predict VTE in patients with CLD; however, 52% of the cohort had hepatitis C cirrhosis, 23% had alcoholic liver disease, and 25% had other causes of CLD. The role of this score in MAFLD is therefore unclear [55].

6 | SAFETY OF ANTICOAGULATION IN LIVER DISEASE

The use of anticoagulation in advanced liver disease is hampered by a lack of randomized controlled trial (RCT) evidence as CLD is frequently specified within exclusion criteria. Lack of rigorous data is compounded by fear of bleeding in patients with laboratory abnormalities suggestive of coagulopathy, such as thrombocytopenia or PT prolongation. MAFLD encompasses a spectrum of diseases ranging from “fatty liver” to steatohepatitis, cirrhosis of varying severity, and HCC. Patients with early MAFLD often have normal liver function with no overt evidence of coagulopathy. Several scoring systems are available to grade disease severity. The steatosis, activity, fibrosis score requires histological assessment; however, there are also a large number of biopsy-free scoring systems, with associated strengths and weaknesses, described in a recent review [56]. These scores can distinguish between early and advanced MAFLD. Individuals with early-stage disease will likely have been included in the registration trials for the various anticoagulants, with no subanalysis regarding their outcomes available. In this section, we consider the efficacy and safety of anticoagulation primarily in the context of cirrhosis, which is graded by the CP system, irrespective of the etiology of liver disease.

6.1 | Warfarin

Warfarin is metabolized in its entirety by the liver [57], which does not make it an ideal anticoagulant in this setting. It can be monitored by the INR but with obvious limitations in patients with baseline PT prolongation. Additionally, patients with liver disease receiving warfarin spend less time in the therapeutic range than those without liver disease, which carries an increased risk of bleeding and thrombosis [58]. A retrospective review of 2694 US veterans with cirrhosis and AF reported reduced rates of ischemic stroke (HR, 0.29) and mortality (HR, 0.65) in patients receiving warfarin compared with those in matched,

unanticoagulated controls [59]. A population-based study from Taiwan analyzed the outcomes of >10 000 patients with cirrhosis and AF, who received either warfarin, aspirin, or no antithrombotic agent. Patients with cirrhosis had higher incidence rates of ischemic stroke and intracranial hemorrhage (ICH) than noncirrhotic controls. Warfarin use was associated with a reduction in the incidence of ischemic strokes (HR, 0.76) without any increase in bleeding [60]. These studies neither discuss severity of cirrhosis, or MAFLD specifically. One group analyzed outcomes of 321 patients with AF and cirrhosis, according to whether they had early (CP A), or advanced (CP B or C) cirrhosis. Warfarin reduced the risk of ischemic stroke (1.5%/year vs 4.7%/year) without increasing major bleeding in early disease. Conversely, in advanced cirrhosis, warfarin use led to a significant increase in major bleeding (9.6% vs 6.2%) with no survival benefit seen [61].

In their 2022 guideline, the European Association for the Study of the Liver (EASL) have recommended warfarin be used with caution in patients with cirrhosis, due to the impact of liver disease on the INR. They have suggested limiting use to CP class A disease, whereas other groups are less restrictive [62–64].

6.2 | Low-molecular-weight heparin

There are little data specific to the use of low-molecular-weight heparin (LMWH) in liver disease. LMWHs are predominantly renally excreted; however, their *in vitro* effect appears to be increased in plasma from cirrhotic patients [65]. Monitoring via the anti-Xa assay can also be unreliable in liver disease [66]. In a study of 84 patients with cirrhosis receiving LMWH at either therapeutic or prophylactic doses, anti-Xa levels inversely correlated with disease severity according to the CP and MELD scores, in an AT-dependent fashion. Only 3 patients in this cohort had MAFLD, however, reduction in AT levels has previously been demonstrated in patients with MAFLD [31]. An analysis of 353 patients with cirrhosis and PVT assessed the rates of recanalization and bleeding in patients treated with LMWH, warfarin, or no anticoagulation. The number of patients with MAFLD and the severity of liver disease were not stated. Overall, recanalization occurred significantly more often in patients who received anticoagulation than in those who did not (71% vs 42%). On multivariate analysis, LMWH, but not warfarin, was associated with complete resolution of PVT. Bleeding was not significantly increased by either anticoagulant [67]. A retrospective review of patients with primarily viral cirrhosis (approximately 50% of whom had CP A cirrhosis) reported no improvement in safety and a lower rate of PVT recanalization after treatment with a reduced dose of dalteparin than after treatment with the standard regimen [68]. The recent IMPORTAL study reviewed outcomes from 500 patients treated across 5 studies, of which 41% received anticoagulation with LMWH and/or warfarin. Eleven percent of anticoagulated and 15% of nonanticoagulated patients had liver disease of "other" etiology, and approximately two-thirds of each cohort had CP B/C disease. The authors reported higher rates of recanalization (OR, 3.45) and reduced mortality (HR, 0.59) but increased nonportal hypertension–related bleeding in the anticoagulation arm [69]. The relative contributions of LMWH and warfarin to patient outcomes were not assessed.

Based on the available albeit limited evidence, EASL has advised that LMWHs are reasonable options for use in cirrhosis, irrespective of severity [64]. Standard therapeutic doses of LMWH are recommended in the absence of evidence for intermediate dose schedules.

6.3 | Direct-acting oral anticoagulants

Direct-acting oral anticoagulants (DOACs) have differing pharmacokinetics affecting their safety in liver disease. Apixaban has the highest hepatic clearance at 75%, followed by rivaroxaban at 65%, edoxaban at 50%, and dabigatran at 20%. DOACs with high plasma protein binding capacity are also prone to increased free drug levels in situations where circulating plasma albumin is reduced, such as CLD [62]. Despite the exclusion of patients with CLD from the seminal RCTs of DOACs [70–73], DOAC use in the management of AF and VTE in this cohort has been steadily growing [74].

A meta-analysis of studies in which the primary safety outcome was International Society on Thrombosis and Haemostasis–defined major bleeding, reviewed 683 patients with cirrhosis, receiving anticoagulation for VTE or AF. Risk of major bleeding was not significantly different between the DOAC and traditional anticoagulation arms, with a trend toward safety for the DOAC group seen (OR, 0.55; 95% CI, 0.28-1.07). Across the studies, the most commonly used DOACs were apixaban and rivaroxaban, with no individual subanalysis according to DOAC choice available [75]. In this study, only 4% of the DOAC arm and 6% of the traditional anticoagulation arm had CP class C disease, with the majority of patients having class A disease. A large meta-analysis reviewed 43 532 patients with alcoholic liver disease or cirrhosis, who required anticoagulation for either AF or VTE. Sixty-three percent of the participants were treated with a DOAC (choice not specified) and 37% with warfarin or LMWH. There was a statistically significant reduction in major bleeding, ICH, and recurrent deep vein thrombosis in favor of the DOAC arm, which was not impacted by the severity of liver disease (HR, 0.39, 0.48, and 0.18, respectively) [76]. A similar meta-analysis of nearly 20 000 patients with cirrhosis and AF reported a reduction of bleeding in patients prescribed DOACs compared with those receiving warfarin [77]. Again, neither the choice of DOAC nor the proportion of patients with MAFLD was specified. A further meta-analysis of 41 954 patients with liver disease and AF treated with a DOAC or warfarin also reported reduced major bleeding (RR, 0.68) and ICH (RR, 0.49), with comparable rates of stroke and systemic embolism in favor of DOAC use. Once again, the cause of liver disease was not stated, with considerable heterogeneity present among studies [78].

Specifically considering PVT, 2 RCTs have been conducted. The first compared edoxaban with warfarin in 50 patients (5 had CP C cirrhosis). Edoxaban was superior in terms of reducing thrombus volume at 6 months, with a nonsignificant increase in gastrointestinal bleeding [79]. In the second, 84 CP A/B patients received either rivaroxaban or warfarin. The DOAC-treated arm had superior clot

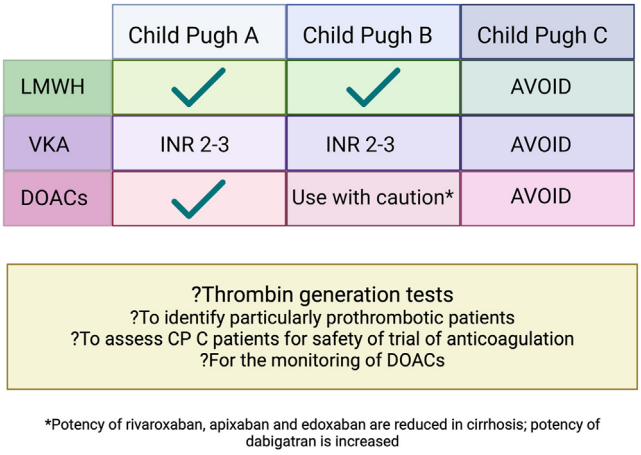

FIGURE 2 Use of anticoagulation in patients with cirrhosis. CP; Child-Pugh; DOAC, direct-acting oral anticoagulant; INR, international normalized ratio; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist.

resolution, reduced bleeding events, and improved survival (20.4 vs 10.6 months) in this small study [80].

Based on the accumulating real-world evidence, the American Society of Gastroenterology has recently recommended that DOACs may be used in CP class A cirrhosis and should be avoided in most patients with class B cirrhosis and all patients with class C cirrhosis. EASL has stated that DOACs may be used in CP A and B cirrhosis in the context of thromboprophylaxis. For the treatment of VTE, DOACs may be used in patients with CP A cirrhosis but should be used only with caution in patients with CP B cirrhosis and/or patients with a creatinine clearance of <30 mL/min [64,81].

We have summarized these recommendations in Figure 2 and have suggested possible future uses for thrombin generation tests. Management of patients with advanced cirrhosis who require anticoagulation is clearly a challenging area. This is particularly relevant for those with indications for long-term anticoagulation. The decision to continue anticoagulation beyond the acute phase in higher-risk patients needs to be carefully considered, keeping the patient informed of their risks of bleeding and systemic thrombosis. Reduction of bleeding risks associated with varices, via endoscopic techniques or transjugular intrahepatic portosystemic shunting in certain cases, should proceed as per international guidelines. A possible, opinion-based approach to this situation is shown in Figure 3. This algorithm is based on the authors' opinions, given the available published evidence.

7 | LABORATORY MONITORING OF COAGULATION AND ANTICOAGULANTS IN LIVER DISEASE: THE ROLE OF THROMBIN GENERATION

7.1 | Coagulation

It is well established that standard laboratory coagulation tests are of limited utility in patients with CLD, in whom a state of balanced hemostasis may exist despite marked abnormalities of PT, activated partial thromboplastin time, or blood count. Thrombin generation tests can be used to provide a measure of global hemostasis, taking into account changes in the levels of both procoagulants and anticoagulants. Key measures provided include the peak thrombin generated and endogenous thrombin potential (ETP) (total amount of thrombin generated). These tests can be measured with or without the addition of exogenous thrombomodulin (TM), the physiological activator of PC, which is predominantly present on endothelial cells rather than in the plasma. The ratio of ETP (with-to-without TM) has been proposed as a global measure of the procoagulant imbalance epitomized by the increased FVIII (one of the most potent procoagulants) and reduced PC (one of the most important anticoagulants), which are typical features of cirrhosis. Studies showed that the ETP-TM ratio is increased in patients with cirrhosis of viral/alcoholic origin [6] and also in patients with metabolic cirrhosis [33]. In the latter study, the increased ETP-TM ratio correlated with the ratio of FVIII to PC and was associated with the typical manifestations of metabolic syndrome (ie, higher intima-media thickness, and fibrosis). However, in a subsequent study, Potze et al. [34] reported a relatively normal ETP-TM ratio when measured in a population of patients with MAFLD, even though elevated levels of FVIII and reduced PC were present in their patients. The reasons for this discrepancy probably rest on the characteristics of the investigated population and on the thrombin generation procedures in the 2 studies [82,83]. Whatever the value of the ETP-TM ratio, it is important to realize that this parameter reflects the *in vitro* imbalance of FVIII/PC, but evidence from prospective clinical trials in favor or against its association with thrombosis or hemorrhage in cirrhosis remain unknown.

7.2 | Anticoagulants

The effect of the DOACs on thrombin generation parameters has been assessed, although mostly using healthy volunteers. Factor Xa inhibitors and direct thrombin inhibitors produce different effects on thrombin generation studies. Thrombin generation is delayed and ETP is reduced in a dose-dependent manner for all agents, with direct thrombin inhibitors exerting a greater effect on results at lower concentrations than the factor Xa inhibitors [84]. Clinical correlation between measures of thrombin generation and bleeding or thrombotic events is lacking. One study reported that patients receiving rivaroxaban who developed minor bleeding had delayed thrombin generation (based on a prolonged lag time) and reduced peak thrombin generation, compared with non-bleeding subjects [85]. Whether thrombin generation tests could be used to identify patients with MAFLD at increased risk of thrombosis or hemorrhage or to monitor dosing of therapeutic anticoagulation is an attractive but as yet untested prospect.

8 | CAN ANTICOAGULATION LIMIT PROGRESSION OF LIVER FIBROSIS?

There is accumulating evidence that intrahepatic thrombosis contributes to disease progression, and that antithrombotic agents may

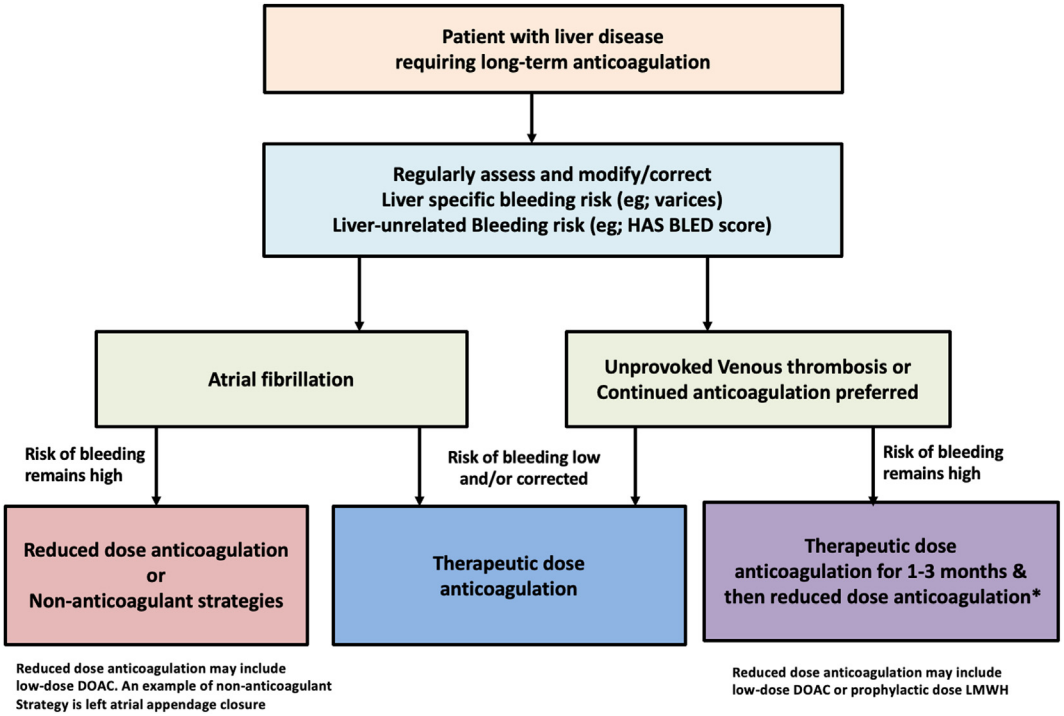

FIGURE 3 A possible approach to the patient requiring long-term anticoagulation. DOAC, direct-acting oral anticoagulant; HAS BLED, Hypertension, Abnormal liver/renal function, Stroke history, Bleeding predisposition, Labile INR, Elderly, Drug/alcohol usage; LMWH, low-molecular-weight heparin.

abrogate this process. Microthrombi were initially identified in murine models of liver disease, with preclinical evidence generated suggesting that anticoagulation may reduce fibrosis, portal pressures, and inflammation [86]. In MAFLD, Kopec et al. [87] showed that the thrombin inhibitor dabigatran reduced weight gain, liver injury, steatosis, and improved glucose handling in obese mice. Another mouse model was used to investigate the role of platelets in progression of MAFLD. The authors identified increased platelet number and activity in MAFLD mice, with accumulation of platelets within the liver, leading to intrahepatic cytokine and chemokine release, fat accumulation, and liver damage. They subsequently demonstrated that antiplatelet therapy with aspirin, clopidogrel, or ticagrelor could prevent the development of steatohepatitis and HCC by minimizing hepatic platelet accumulation [88]. Moreover, in clinical practice, the IMPORTAL study showed improved survival in patients who received anticoagulation for PVT compared with those who did not. This survival advantage was independent to PVT recanalization [69].

Rate of progression of fibrosis has been found to be elevated in patients who are heterozygous for factor (F)V Leiden, whereas a comparison of patients with chronic hepatitis C infection with or without hemophilia showed significantly lower fibrosis scores and less histological evidence of advanced disease in the bleeding disorder cohort [89,90]. A study of 70 patients with CP B or C cirrhosis randomised to receive 48 weeks of prophylactic enoxaparin or placebo reported PVT at the end of follow-up in 8.8% of the patients in the enoxaparin group compared with 27.7% of the patients in the control group. Rates of liver decompensation were also lower in the treatment arm (11.7% vs 59.4%; $P < .0001$) with a survival benefit seen (8 deaths vs 13; $P = .02$) and no increased bleeding reported [91]. A multicenter randomized study aiming to assess the impact of rivaroxaban on disease progression and survival in cirrhosis is ongoing (NCT02643212, the CIRROXABAN study).

There are several hypotheses regarding the mechanisms underlying the association between intrahepatic activation of coagulation and disease progression. Initial theories focused on the potential for fibrin-containing thrombus to impede blood flow through the microcirculation, leading to down-stream tissue ischemia and cell death [92]. In opposition to this theory, a murine model of fibrosis using mice expressing a mutant fibrinogen, which is insensitive to thrombin-mediated proteolysis, found neither the evidence of decreased fibrin deposition nor decreased liver fibrosis [93]. In the study by Kopec et al. [87], coagulation activation was shown to promote liver injury via fibrin-mediated attraction of inflammatory macrophages. Blocking this interaction protected mice from diet-induced MAFLD.

Another hypothesis concerns the activation of hepatic stellate cells (HSCs) by coagulation proteases. HSCs comprise approximately 10% of liver cells. They normally maintain a quiescent nonproliferative phenotype but transdifferentiate into myofibroblasts when activated, producing extracellular matrix contributing to the development of fibrosis [94]. Thrombin interacts with HSCs through binding to proteinase-activated receptors (PARs). HSCs express PAR-1, PAR-2, and PAR-4. Exposure to thrombin stimulates HSC proliferation, contraction, and collagen synthesis and release, which can be abrogated by the addition of a PAR-1 antagonist, reducing collagen

deposition [95]. PAR-1 knockdown in a murine model of fibrosis led to reduced HSC activation and collagen deposition [96]. However, PAR-1 was not shown to have a role in lipid accumulation or animal weight gain in MAFLD. PAR-2 deficiency reduces the progression of liver fibrosis in murine models [97], and PAR4 is involved in thrombo-inflammation [32]. Aspirin was shown to ameliorate MAFLD in a murine model by inhibiting lipid biosynthesis and inflammation through PAR-activation [98].

Antithrombotic agents could therefore potentially limit disease progression in MAFLD and other forms of CLD through reduction of physical vessel blockade and also by preventing HSC activation and extracellular matrix production. A study of aspirin in patients with MAFLD and early-stage fibrosis is under recruitment (NCT04031729).

9 | CONCLUSION

Theories underpinning the role of the liver have changed dramatically over the centuries. From the poetic early hypotheses, which centered around the liver as the seat of the soul and the origin of emotional and mental activity, modern understanding of liver function has switched to the more prosaic and practical considerations of digestion, detoxification, and production of hemostatic regulators. Similarly, the wisdom that all liver impairment leads to a hemorrhagic phenotype is now being superseded by a body of evidence that connects liver disease to an increased risk of CV and thrombotic sequelae. Anticoagulation will likely form an important aspect of therapy; however, our knowledge of the potential safety concerns surrounding these drugs in liver disease remains limited by recruitment criteria in randomized studies and by the invalidity of the commonly available laboratory tests. Moreover, early use of anticoagulants may abrogate further hepatic decline. As rates of MAFLD continue to increase worldwide, the importance of finding answers to these important questions becomes ever more pressing.

Addendum: Subsequent to the acceptance of this paper for publication, the European Association for the Study of the Liver (EASL) announced updated nomenclature for MALFD at the EASL Congress, 2023. The global hepatology community has chosen the term 'metabolic dysfunction-associated steatotic liver disease' (MASLD) to encompass patients with hepatic steatosis and cardiometabolic risk factors. This term will largely replace MAFLD, where it has been used within the manuscript.

AUTHOR CONTRIBUTIONS

D.S. wrote the manuscript. T.L. and A.T. provided expert appraisal. J.T. conceived the manuscript and provided expert review.

DECLARATION OF COMPETING INTERESTS

J.T reports honoraria from Leo Pharma, Bayer, BMS-Pfizer, Boehringer, and Daiichi. The other authors have no competing interests to disclose.

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