

# Thrombosis Associated with Viral Hepatitis

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## Abstract

Viral hepatitis may promote the development of venous thromboembolism (VTE) and, more specifically, portal vein thrombosis (PVT). In this narrative review, we summarize the clinical data and discuss the possible pathogenetic roles of cytomegalovirus (CMV), Epstein-Barr virus (EBV), and hepatitis A, B, and C viruses (HAV, HBV, HCV) in the occurrence of VTE. CMV is the first qualified candidate to enter the list of VTE minor risk factors, and in the rare case of fulminant infection, both EBV and CMV, like any severe infection or inflammatory disease, increase risk for thrombosis. In chronic hepatitis B and C, it remains controversial whether antiphospholipid antibodies are important for thrombotic complications or merely an epiphenomenon. Retinal vein occlusion described in chronic hepatitis C is usually attributed to the treatment with interferon. Eltrombopag, used for HCV-related thrombocytopenia, has been associated with increased thrombotic risk. The imbalance between procoagulant and anticoagulant factors associated with chronic liver disease may have clinical implications. This may help to explain why these patients are not protected from clinical events such as VTE, PVT, and the progression of liver fibrosis. © 2014 The Second Affiliated Hospital of Chongqing Medical University. Published by XIA & HE Publishing Ltd. All rights reserved.

## Introduction

Viral hepatitis is a major health problem worldwide, and infected patients are at high risk of morbidity and mortality. Although acute arterial and venous thrombosis are not classically described as possible complications of viral hepatitis,<sup>1,2</sup> both cardiovascular complications are multicausal diseases. Acute infections have been linked to a transient increased risk for both myocardial infarction and venous thromboembolism (VTE).<sup>3</sup>

Multiple factors can lead to hemostatic abnormalities, and it is well known that inflammation, and in particular some

viral infections, can play a key role. These alterations can range from relatively insignificant laboratory changes to severe disseminated intravascular coagulation.<sup>4</sup> Coagulation can be activated at either the systemic or local level via two main processes: systemic inflammation and direct infection of endothelial cells. Viruses can down-regulate physiological anticoagulant mechanisms and inhibit fibrinolysis and tissue factor (TF)-mediated thrombin generation.<sup>4,5</sup>

Hepatitis viruses may increase thrombosis risk by several mechanisms. Acute viral hepatitis can induce inflammatory changes in surrounding tissues, in particular the endothelium of the portal vein system, leading to activation of the coagulation system by inflammation and increasing the risk of portal vein thrombosis (PVT). Furthermore, antiphospholipid antibodies (aPL) may be involved in thrombosis pathogenesis.<sup>6</sup> These antibodies, as well as other autoimmune phenomena, have been associated with chronic hepatitis C infection. Lastly, particular attention must be paid to chronic liver disease. Although it is classically seen as a coagulopathy leading to bleeding, there is recent evidence suggesting that in patients with chronic liver disease the risk for thrombosis may even outweigh that due to bleeding.<sup>7</sup>

On the atherothrombotic side, likewise, viral infections may contribute to atherosclerosis either through direct infection of endothelial cells or indirectly via cytokines or acute phase proteins induced by systemic inflammation. A recent review of the literature suggests a relationship between different infective pathogens and atherothrombosis: rather than the effects of a single microorganism, the aggregate burden of chronic infections might contribute to atherosclerosis and its thrombotic complications.<sup>8</sup> However, the real role of infection in atherosclerosis remains under debate.

In this review, we summarize current evidence on the relationship between viral hepatitis and thrombosis.

## Methods

We identified and reviewed published clinical studies examining the link between viral hepatitis and thrombosis. This is an update of our previous review published in 2012.<sup>9</sup> Overall, we searched the literature from 1966 to the second week of September 2014 using the MEDLINE electronic database. The following search terms (text words and medical subject headings (MeSH) terms) were used for the search: "viral hepatitis", "hepatitis A", "hepatitis B", "hepatitis C", "cytomegalovirus", "Epstein-Barr virus" and "thrombosis". The search was performed without any language restriction or exclusion criteria based on study design. Case series and case reports were included, and systematic reviews were considered the highest level of available evidence. When epidemiological studies were lacking, case reports are discussed.

**Keywords:** Hepatitis; Thrombosis; Cytomegalovirus; Epstein-Barr virus; Hepatitis A, B and C virus.

**Abbreviations:** APC, activated protein C; aPL, antiphospholipid antibodies; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; PARs, protease activated receptors; PVT, portal vein thrombosis; RVO, retinal vein occlusion; TF, tissue factor; VTE, venous thromboembolism.

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## Cytomegalovirus

Cytomegalovirus (CMV) is a herpesvirus that may usually be asymptomatic or cause few symptoms with no long-term health consequences. CMV infection is common worldwide, and humans can acquire it even prior to birth. After the initial infection, CMV often becomes latent without detectable damage or clinical illness, but immunosuppression by medications or disease may allow the virus to reactivate and become symptomatic. Active CMV infection manifests as flu-like symptoms or by a mononucleosis-like syndrome, with prolonged fever, cervical lymphadenitis, and arthralgia.<sup>10</sup> Occasionally, it may present with more severe symptoms, such as pneumonia, hepatitis, myocarditis, pericarditis, colitis, or hemolytic anemia.<sup>10</sup>

In recent years, CMV infection has been linked to the development of venous thrombosis.<sup>5,9,11</sup> CMV seems to directly interfere with the hemostatic system.<sup>5</sup> The activation of CMV-infected endothelial cells induces membrane perturbation and expression of adhesion molecules that, consequently, enhance platelet and leukocyte adhesion. The subsequent local inflammatory response<sup>12,13</sup> and tissue-factor exposure to the bloodstream may promote thrombin generation.<sup>5,14</sup> Furthermore, the envelope of CMV has intrinsic procoagulant properties, probably acquired after infection of endothelial cells,<sup>5</sup> which may promote thrombin generation via factor X activation, surface tissue-factor activity, and procoagulant phospholipid expression.<sup>15-17</sup> During CMV infection, increases in von Willebrand factor and factor VIII levels have been observed, and this may also promote thrombosis.<sup>18,19</sup> In addition, CMV has been proposed to transiently increase aPL.<sup>20,21</sup>

Clinical characteristics of patients with CMV-associated venous thrombosis were summarized by Justo and colleagues.<sup>21</sup> This meta-analysis, including 64 immunocompetent patients and 33 immunocompromised patients with mean age 39.7±14.9 years, showed that lower limb venous thrombosis and PE were the most frequently affected sites (53.6%) in CMV-associated thrombosis. This was followed by splanchnic thrombosis (25.8%), with a relatively high frequency for thrombosis in unusual sites. This meta-analysis, however, did not specifically look at CMV hepatitis, but the unusually high relative risk for developing splanchnic vein thrombosis during CMV-infection suggested that viral hepatitis might play a key pathogenic role in this type of thrombosis. The inflammatory changes in the surrounding tissues, and in particular in the endothelium of the portal vein system, that could be associated with viral acute hepatitis, can activate the coagulation system and lead to splanchnic vein thrombosis.<sup>22</sup>

Recently, Para and colleagues published a community prospective study on thrombosis following acute CMV infection.<sup>23</sup> The 6-month incidence of VTE and/or arterial thrombosis was higher in patients with acute CMV infection (tested positive for CMV-IgM antibodies) relative to CMV-IgMseronegative patients. The observed VTE incidence among CMV-IgM seropositive and seronegative patients was 0.306% and 0.136%, respectively (odds ratio (OR) 2.25; 95% confidence intervals (95% CI) 1.38-3.66;  $p=0.003$ ), showing an independent association between VTE and CMV-IgMseropositivity after adjustment for age, sex, and other confounders.<sup>23</sup> Although several cases of CMV-associated arterial thrombosis (or embolism) have been previously reported,<sup>21,24-25</sup> no association between arterial thrombosis and CMV-IgMseropositivity was demonstrated in this large community based cohort.<sup>23</sup>

## Epstein-barr virus

Epstein-Barr virus (EBV), also known as human herpesvirus 4, is, like CMV, a member of the herpes virus family. It is one of the most common human viruses, with seroprevalence rates of 90 to 95% in adults.<sup>9</sup> EBV infection can cause the mononucleosis infectious syndrome, consisting of hepatosplenomegaly, pharyngitis, cervical lymphadenopathy, hepatitis, atypical lymphocytosis, and monocytosis, but it is usually asymptomatic or associated with flu-like symptoms only.<sup>9</sup>

In contrast to CMV, the association between VTE and EBV has rarely been described. Justo and colleagues identified only two reports of immunocompetent patients who developed EBV-associated VTE in addition to their described cases.<sup>26</sup> The mechanisms by which EBV infection might promote thrombosis are not fully understood.<sup>26</sup> Plausible mechanisms include transient elevation of aPL antibodies<sup>27</sup> and EBV-induced oxidative endothelial cell injury.<sup>28</sup> Overall, there is insufficient information available showing any clinically relevant association between EBV and thrombosis.

## Hepatitis A virus, hepatitis B virus, and hepatitis C virus

### Hepatitis A virus

Hepatitis A virus (HAV) causes an acute infectious disease of the liver that is asymptomatic in the majority of children (70%), but usually in adults produces a self-limited disease with nausea, anorexia, fever, malaise, or abdominal pain and jaundice, which does not result in chronic infection or chronic liver disease.<sup>9</sup>

To our knowledge, the report of a young woman with a cerebral venous thrombosis is the only case of VTE related to HAV to have been described in the literature.<sup>29</sup>

### Hepatitis B virus, hepatitis C virus and PVT

Hepatitis B virus (HBV) can cause both acute and chronic hepatitis. In the United States alone, there were approximately 38,000 new infections in 2010, with 1.2 million people affected by chronic HBV infection. The acute illness causes liver inflammation, vomiting, jaundice, and rarely, death. Chronic HBV infection, which occurs in 5% of infected adults and older juveniles, may eventually lead to cirrhosis.<sup>9</sup> Hepatitis C is an infectious disease that primarily affects the liver and is caused by the hepatitis C virus (HCV).<sup>9</sup> There are approximately 180 million people infected worldwide.<sup>30</sup> Most people with acute infection are asymptomatic, with only 20-30% of newly infected persons developing symptoms. About 75-85% of newly infected persons will develop a chronic infection, which can be asymptomatic or lead to fibrosis of the liver and ultimately, after many years, to cirrhosis. In some cases, both HBV and HCV-related cirrhosis will progress to liver failure or other complications of cirrhosis, including liver cancer or life-threatening esophageal varices and gastric varices.<sup>9</sup>

It is well known that PVT is a possible complication of hepatic cirrhosis and liver transplantation. Major risk factors for PVT are portal hypertension and consequent venous stasis. However, recently, the focus has shifted on the possible role of the prothrombotic state related to chronic liver disease.<sup>7,31-33</sup> Indeed, despite chronic liver disease being classically seen as a

**Table 1. Haemostasis imbalance in chronic liver disease**

	Coagulation factors	Anticoagulant factors	Platelet	Fibrinolysis	Other
Pro-thrombotic	High von Willebrand factor and factor VIII	Low antithrombin and protein C		Low plasminogen, high PAI	Elevated aPL
Pro-haemorrhagic	Low fibrinogen, factors II, V, VII, IX, X, XI		Low platelet count	High tPA, low TAFI, low plasmin inhibitor	

Summarized from refs. 7, 37–39.

PAI, plasminogen activator inhibitor; tPA, tissue plasminogen activator; TAFI, thrombin-activatable fibrinolysis inhibitor; aPL, antiphospholipid antibodies.

coagulopathy leading to bleeding, it is now appreciated that there exists a delicate hemostatic balance (see Table 1) between reduced production of procoagulant factors and platelets and decreased levels of anticoagulants (such as protein C and antithrombin) in cirrhosis.<sup>7</sup> Tripodi *et al.*<sup>38</sup> demonstrated *in vitro* that the activated protein C (APC) resistance test was impaired in cirrhotic patients and worsened with progressive deterioration of liver disease from Child Pugh Class A to C. This resulted in a hypercoagulable state similar to that conferred by congenital protein C deficiency or Factor V Leiden mutation.<sup>38,39</sup> A recent *in vitro* study showed that the procoagulant imbalance decreased when exogenous purified protein C was added to restore levels to normal.<sup>40</sup> Furthermore, chronic liver disease was associated with normal, or even increased, thrombin generation.<sup>7</sup>

It is uncertain whether HBV and HCV themselves cause PVT. There is some evidence suggesting that chronic viral infection is a thrombotic risk factor, perhaps by infection-mediated inflammation and hemostatic impairment. aPL<sup>32,33</sup> and pro-thrombotic state associated with chronic liver disease<sup>7</sup> seems to play an important role in virus-associated thrombosis. aPL are classically described in association with viral infections<sup>32</sup> and can affect up to 33% of patients with hepatitis C,<sup>34</sup> but the real etiology and thrombogenic potential of these autoantibodies in this setting are still largely unknown.<sup>35</sup> Even though aPL may be just an epiphenomenon of chronic viral hepatitis, several authors have suggested that they may be responsible for thrombotic events occurring in patients with chronic hepatitis.<sup>36,37</sup>

### HBV, HCV, and arterial and venous thrombosis

The risk of developing other arterial and venous thromboembolic events in patients with chronic liver disease is not well defined. Only recently it was suggested that the incidence of thrombotic events other than PVT is increased in these patients. Enger and colleagues calculated the incidence of venous and arterial thromboembolic events among patients with hepatitis C virus (HCV) infection ( $n=22,733$ ) and matched comparators ( $n=69,198$ ) as well as patients with cirrhosis ( $n=15,158$ ) and matched comparators ( $n=45,473$ ).<sup>31</sup> The incidence for any thromboembolic event was 233.4 events per 10,000 person-years for the HCV cohort and 138.5 per 10,000 person-years for the comparators, with an adjusted incidence rate ratio for any thromboembolic event of 1.62 (95% CI: 1.48–1.77). The incidence of any thromboembolic event was 561.1 per 10,000 person-years for the cirrhosis patients and 249.7 per 10,000 person-years for the comparators, with an adjusted incidence rate ratio of 2.28 (95% CI: 2.11–2.47).<sup>31</sup>

### Drug-related thrombosis

The conventional treatment for hepatitis C infection is a combination of pegylated interferon- $\alpha$ -2a or pegylated interferon- $\alpha$ -2b and the antiviral drug ribavirin for a period of 24 or 48 weeks, depending on the HCV genotype.<sup>9</sup> Chronic liver disease associated with HCV infection can often be complicated by thrombocytopenia, and its severity is usually correlated with liver disease severity and the presence of portal hypertension.<sup>41–43</sup> Pegylated interferon and ribavirin can induce bone marrow suppression, thereby causing further reduction of platelet counts<sup>44</sup> and leading to treatment discontinuation or dose reduction.

Eltrombopag, an oral thrombopoietin receptor agonist, was recently approved in the United States for treatment of thrombocytopenia in patients with chronic hepatitis C in order to allow for the initiation and maintenance of interferon-based therapy. Eltrombopag was shown to increase platelet numbers in thrombocytopenic patients with HCV and advanced fibrosis and cirrhosis. This allowed ineligible or marginal patients to begin and maintain antiviral therapy.<sup>45</sup> However, there is concern growing about the safety of these drugs in patients with cirrhosis associated coagulation alterations. As mentioned earlier, these patients have lower concentrations of coagulation factors and inhibitory factors, leading to a less balanced coagulation system. Indeed, eltrombopag has been found to cause thromboembolism, especially PVT at normal or even subnormal platelet levels.<sup>46–52</sup> Data from ENABLE-1 and ENABLE-2 study<sup>45</sup> showed that during the antiviral phase, there were 34 thromboembolic events in 31 eltrombopag patients (3%) and only five in placebo patients (1%). PVT was the most common event in both treatment groups ( $n=12$ , 1% eltrombopag;  $n=2$ , <1% placebo).<sup>45</sup> Thus, eltrombopag should only be used after a careful assessment of the benefit and risk profile, particularly in those patients with clear evidence of hepatic impairment.

It is unclear how eltrombopag promotes thromboembolism despite normal or subnormal platelet counts. It is unlikely that eltrombopag therapy itself produces any ill effects on platelet function, as platelets in HCV-related thrombocytopenia, such as in patients with primary chronic immune thrombocytopenia, are thought to become more 'sticky' and more prone to aggregate and form a thrombus.<sup>49,50</sup> There are, however, no clear data in the literature demonstrating whether eltrombopag increases the physiological tendency of platelets to adhere or aggregate, and more studies are needed to resolve this controversy. Finally, rapid increase in platelet count induced by eltrombopag and chronic liver disease-associated endothelial dysfunction may contribute to the increased thrombotic risk.

**Table 2. Viral hepatitis and thrombosis – possible underlying mechanisms**

Virus	Prothrombotic mechanism
CMV	Endothelial dysfunction with increased TF exposure and increased leukocyte adhesion; increased TF exposure in CMV-infected monocytes; procoagulant properties of CMV envelope; aPL
EBV	aPL, oxidative endothelial cell injury
HAV, HBV, HCV	Cirrhosis-related prothrombotic state; aPL; drugs

CMV, cytomegalovirus; TF, tissue factor; aPL, antiphospholipid antibodies; VTE, venous thromboembolism; EBV, Epstein-Barr virus; HAV, HBC, HCV, hepatitis A, B, C virus.

In addition to interferon- $\alpha$ -related retinopathy, some cases of retinal vein occlusion (RVO) have been described in chronic hepatitis C patients on interferon and ribavirin combination therapy.<sup>53-58</sup> Since there are few cases available regarding RVO in patients on interferon and ribavirin, it is uncertain whether the treatment or the underlying condition cause the complication.<sup>53</sup> The precise mechanisms underlying the development of RVO in these patients are not established yet, but it is possible that interferon favours the formation of aPL and the induction of plasma-activated complement C5a, a potent intravascular aggregator of granulocytes.<sup>59-60</sup>

Ischemic colitis is another rare complication of interferon treatment. To date, 12 cases have been described in eight papers.<sup>61-68</sup> The pathophysiology of interferon-related ischemic colitis is not clear. Possible mechanisms of action are the following: gastrointestinal vasculitis secondary to the immune-modulating effects of interferon, a direct vasospastic effect by interferon leading to a decrease in blood flow to the colon,<sup>67</sup> or hypotension, a known rare adverse effect of interferon treatment.<sup>69</sup>

**Liver fibrosis and the coagulation system**

The development of hepatic fibrosis in patients with chronic liver injury represents a complex disease trait that is modulated by the interaction of host genetic factors and environmental influences, in which the coagulation system may play a relevant role.<sup>70</sup> Thrombin not only has procoagulant function, but it also binds to several receptors called protease activated

receptors (PARs). The presence of these thrombin receptors has been associated with increased severity of liver disease.<sup>71</sup> Moreover, coagulation cascade activity mediated by activated-factor X may favor hepatic fibrosis.<sup>72,73</sup>

A recent retrospective multicenter study evaluated the role of daily low-dose aspirin (75 or 100 mg) in fibrosis progression in liver transplant recipients with recurrent HCV infection.<sup>74</sup> In total, 188 HCV-positive patients who had undergone liver transplantation between 2000 and 2010 were included. Liver fibrosis was assessed by histological evaluation. Progression to fibrosis  $F \geq 2$  was analyzed with a multistate model with time-dependent variables. In the multivariate analysis, younger recipient age and aspirin intake (hazard ratio 0.65, CI 0.47-0.91) were associated with slower fibrosis progression.<sup>74</sup> To the best of our knowledge, there are no intervention studies available regarding the effect of platelet aggregation inhibitors, such as aspirin, or anticoagulant therapy on fibrosis progression.

**Conclusions**

There is mounting evidence suggesting that viral hepatitis may increase thrombotic risk (see Table 2 and Table 3). CMV is the first qualified candidate to enter the list of VTE minor risk factors: both clinical and laboratory data suggest a causative role. Although CMV is certainly not a major risk factor, the multicausal nature of VTE may predispose patients with CMV hepatitis to cross the thrombosis threshold in the presence of other risk factors.<sup>1</sup> The link between HBV/HCV and VTE and

**Table 3. Viral hepatitis and thrombosis – clinical evidence**

Virus	Best available level of evidence	Findings
CMV	Systematic review <sup>21</sup>	CMV is not a VTE major risk factor, but it is a good VTE minor risk factor candidate. Splanchnic vein thrombosis was the second most prevalent thrombosis associated with acute CMV infection, after lower limbs DVT and PE.
EBV	Case report <sup>26</sup>	Association with VTE was rarely described, mostly in immunocompromised patients. Mechanisms by which EBV infection might trigger thrombosis not fully understood.
HAV	Case report <sup>29</sup>	Only one case reported of a cerebral venous thrombosis assumed as related to HAV hepatitis
HBV	Cross-sectional study <sup>77-78</sup>	It is uncertain whether HBV itself cause VTE or PVT, but chronic viral infection may be an additional thrombotic risk factor. Some studies suggest that HBV is the major risk factor for PVT in Southeast Asian populations, where PVT mainly occurs in patients with post-hepatitis B liver cirrhosis.
HCV	Cohort study <sup>31</sup>	Patients with HCV and cirrhosis are at increased risk of thromboembolic events, even though it is uncertain whether HCV itself cause VTE or PVT. The increasing numbers of treatment available for chronic hepatitis C may shift the hemostatic balance from hemorrhagic to thrombotic complications

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HAV, HBC, HCV, hepatitis A, B, C virus; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; PVT, portal vein thrombosis.

PVT is more ambiguous. There are some indications, however, that there is a connection.<sup>31,75–76</sup> The increasing number of treatments available for chronic hepatitis C may shift the haemostatic balance from hemorrhagic to thrombotic complications.<sup>77</sup> The procoagulant state associated with chronic liver disease has a direct clinical consequence: the unrestricted use of plasma infusion to correct the results of conventional coagulation tests in patients undergoing invasive procedures may be useless, or even harmful.<sup>7</sup> Indeed, the guidelines of the American Association for the Study of Liver Diseases warns against the indiscriminate use of plasma therapy before liver biopsy.<sup>78</sup> Finally, the activation of the coagulation system may be directly detrimental on the progression of liver disease, with mounting evidence suggesting that liver fibrosis deposition is also mediated by coagulation factor activation.

Several issues remain unresolved. First, would be a benefit to cirrhotic inpatients of routine thromboprophylaxis; second, would patients with an apparently “unprovoked” VTE and a concomitant CMV or EBV infection be redefined as a “provoked” VTE event; and, finally, which, if any, antithrombotic drugs would be beneficial in limiting liver fibrosis.

### Conflict of interest

None

### Author contributions

Drafting of manuscript (LG, AS), critical revision (VEAG, LG).

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