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Stroke and Liver Cirrhosis: A Brief Review of Current Evidence

Kexin Zheng, Xiaozhong Guo, Xinhong Wang and Xingshun Qi

Abstract

Stroke and liver cirrhosis are common in our everyday clinical practice, both of which can lead to serious complications. Their association is unclear. In this chapter, we briefly summarized the epidemiology of liver cirrhosis in stroke, reviewed the current evidence regarding the association between liver cirrhosis and stroke, and discussed the potential mechanisms for explaining such an association, such as coagulopathy, hypoperfusion, cardiac diseases, diabetes, and dyslipidemia.

Keywords: liver cirrhosis, stroke, review, mechanisms, epidemiology

1. Introduction

Stroke and liver cirrhosis are two leading causes of death worldwide [1]. Patients with liver cirrhosis often have coagulopathy, hypoperfusion, cardiac diseases, diabetes, and dyslipidemia, which are associated with the development of stroke. Recent evidence also suggests a higher risk of stroke in liver cirrhosis. In the present chapter, we reviewed the current evidence regarding epidemiology of stroke in liver cirrhosis, association of stroke with liver cirrhosis, and their potential mechanisms.

2. Stroke

Stroke is the second leading cause of death and disability worldwide, which is defined as an acute episode of focal dysfunction of the brain, retina, or spinal cord [2]. It is often divided into hemorrhagic and ischemic stroke. Hemorrhagic and ischemic stroke leads to 2978 and 3348 thousands people dying until 2015, respectively [1]. Over two thirds of stroke-related deaths occur in developing countries in the world [3], especially in low-income and middle-income countries [4]. Burden of stroke in Asia is heavier than Europe or North America [5]. Patients with stroke are more susceptible to suffer systemic complications, including cardiac, pulmonary, gastrointestinal, genitourinary, musculoskeletal, and neuropsychiatric systems, venous thromboembolism, and so on [6, 7]. Prognosis of stroke is poor. About 20–30% of patients died 6 months after stroke, 20–30% had moderate to severe disability, and 20–25% had mild to moderate disability [8]. Traditional risk factors of stroke are hypertension, decreased physical activity, increased ratio of lipoprotein (Apo)B/ApoA1 and waist-to-hip, unhealthy diet, depression status, smoking, cardiac disease, alcohol intake, and diabetes mellitus [4, 9]. Additionally, our clinical practice suggested that acute upper gastrointestinal bleeding would lead to stroke [10]. Several possible explanations are as follows. First, massive blood loss

leads to reduced blood supply to the brain secondary to cerebral vessel vasoconstriction. Second, massive blood loss sometimes leads to reactive thrombocytosis [11], thereby resulting in potential hypercoagulability. Third, hemocoagulase is occasionally employed for the treatment of gastrointestinal bleeding, which could reduce fibrinogen concentration [12]. Fourth, blood transfusion is an important treatment of upper gastrointestinal bleeding [13], but the ischemia reperfusion injury of brain cannot be ignored.

3. Liver cirrhosis

Liver cirrhosis is an end stage of liver disease [14]. Histologically, it is characterized by diffuse fibrosis within hepatic tissue, false lobular formation, and regenerative nodules [14, 15]. It is the 17th cause of death globally [16], and the mortality has increased steadily over the past 30 years, especially in Central Asia, North Africa, and the Middle East [17]. The major causes of liver cirrhosis are chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, alcoholism, nonalcoholic steatohepatitis (NASH), drug abuse, and cholestasis [18–20]. The major complications are variceal hemorrhage [21], ascites [22], cirrhotic cardiomyopathy [23], hepatic encephalopathy [24], hepatocellular carcinoma [25, 26], portal vein thrombosis [27], and other common venous thromboembolism [28]. Up-to-date concept suggests a tendency towards both bleeding and thrombotic events in cirrhotic patients due to decreased levels of both procoagulant and anticoagulant factors [29, 30].

4. Association between stroke and liver cirrhosis

Overall, it remains unclear about whether liver cirrhosis increases or reduces the risk of ischemic stroke. A majority of studies [31–35] indicated an obviously higher risk of overall, ischemic, and/or hemorrhagic stroke after adjusting the covariates in cirrhotic patients than non-cirrhotic patients. By contrast, another two studies by Chen [36] and Solaymani-Dodaran [37] suggested the protective role of liver cirrhosis in the development of ischemic stroke. Heterogeneous results regarding this association among the studies might be attributed to the selection of patients. The characteristics of study population were different. Studies by Chen and Solaymani-Dodaran et al. focused on patients with nonalcoholic cirrhosis and primary biliary

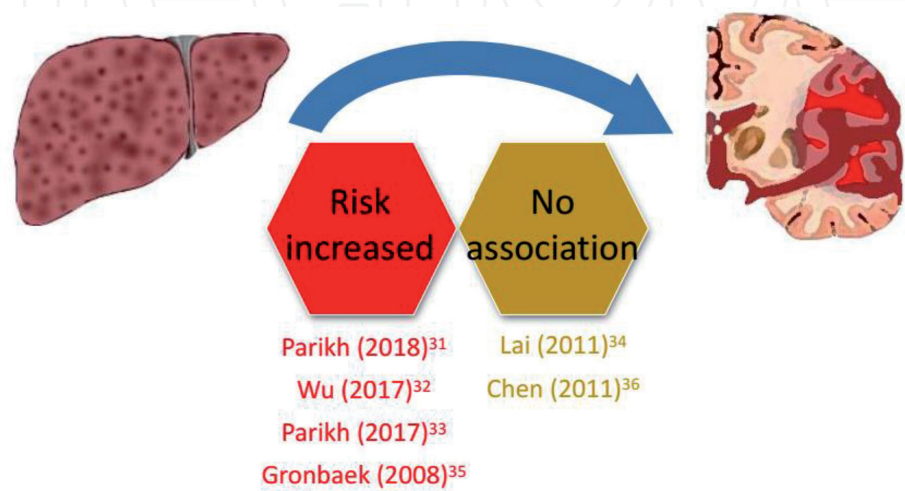


Figure 1.
The association between liver cirrhosis and hemorrhagic stroke.

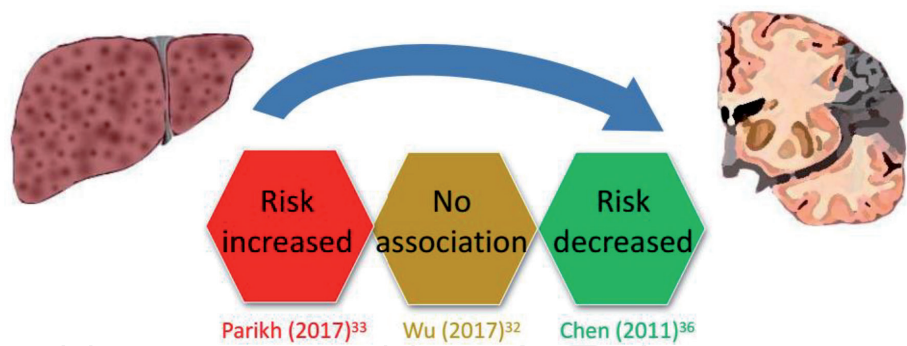


Figure 2.
The association between liver cirrhosis and ischemic stroke.

cirrhosis, respectively. By comparison, the study population had unspecified liver cirrhosis in other studies. The association between liver cirrhosis and stroke was outlined according to the evidence from abovementioned studies (**Figures 1 and 2**).

5. Incidence/prevalence of stroke in liver cirrhosis

Regardless of the type of stroke, the prevalence of stroke was from 2.06 to 53.81% [36–49] (**Figure 3**). Several subgroup populations should be further reported.

First, the prevalence of hemorrhagic stroke in liver cirrhosis seemed to be higher than that of ischemic stroke. The prevalence of hemorrhagic stroke was from 0.80 to 34.33% [34–36, 50–56] (**Figure 4**).

The prevalence of ischemic stroke was from 0.85 to 6.55% [34, 36, 57, 58] (**Figure 5**).

Second, the annual incidence of ischemic stroke in cirrhotic patients with atrial fibrillation was 1.2% [59]. The prevalence of stroke in cirrhotic patients with atrial fibrillation was 53.81 and 34.58% in the studies by Kuo [38] and Lee [44], respectively. This figure is significantly higher than that reported by studies including unclassified cirrhotic patients without atrial fibrillation.

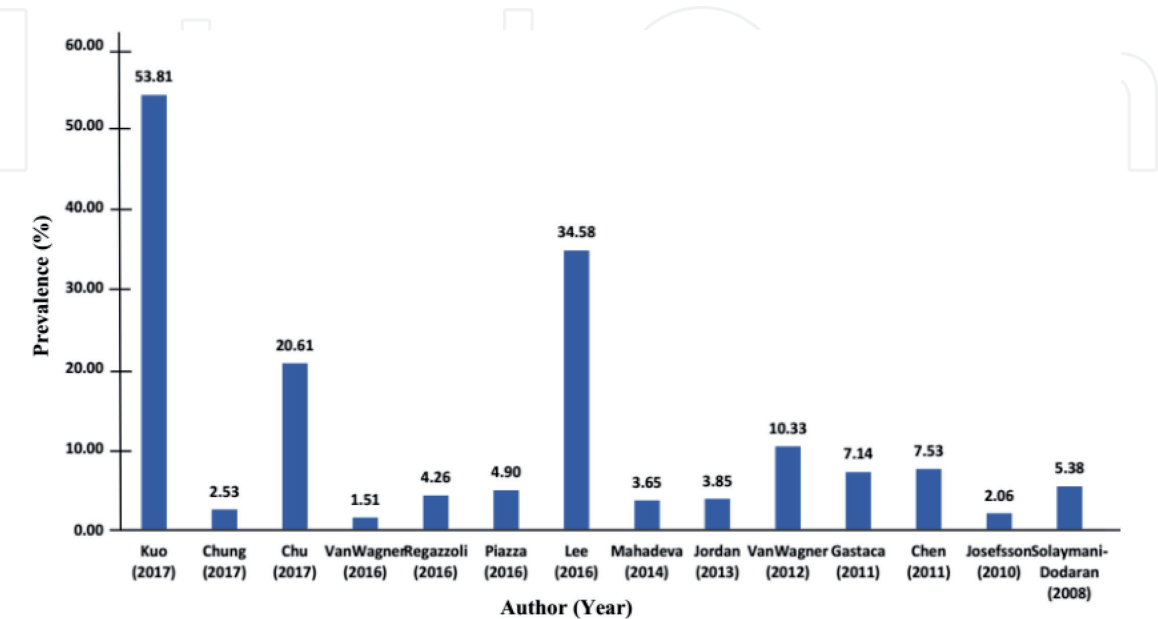


Figure 3.
The prevalence of stroke in liver cirrhosis.

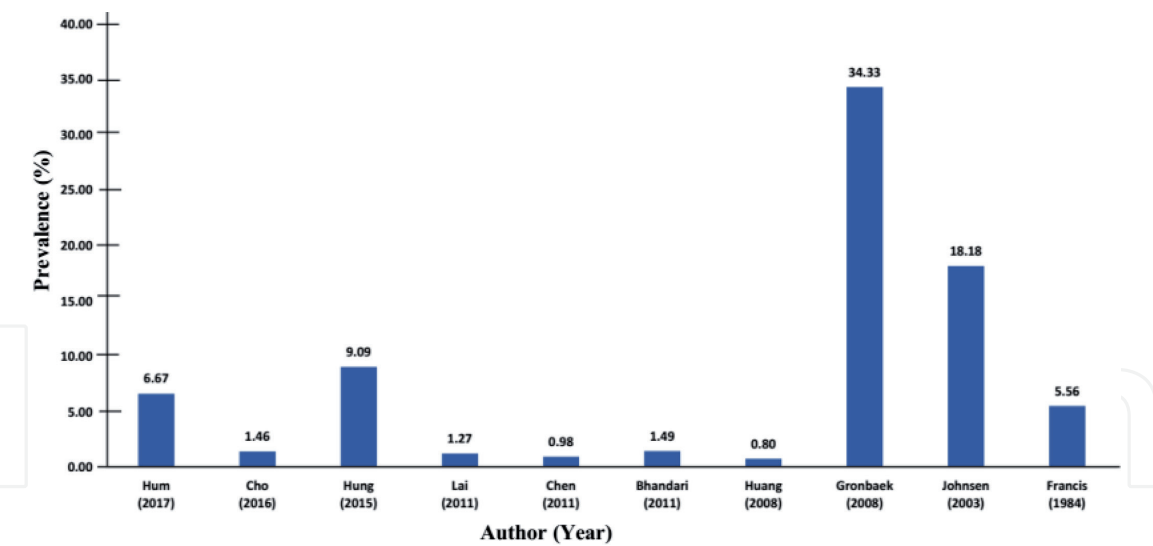


Figure 4.
The prevalence of hemorrhagic stroke in liver cirrhosis.

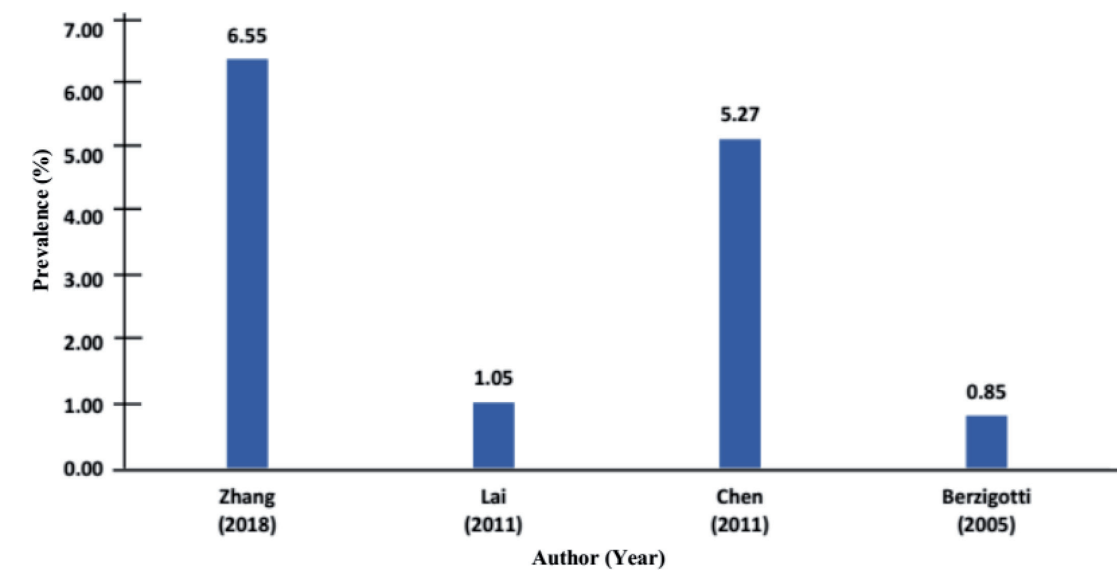


Figure 5.
The prevalence of ischemic stroke in liver cirrhosis.

Third, the annual incidence of aneurysmal subarachnoid hemorrhage (SAH) in cirrhotic patients was 0.11% [31].

6. Potential mechanisms for the association between stroke and liver cirrhosis

There are several potential mechanisms for explaining the association between stroke and liver cirrhosis.

6.1 Coagulopathy

Coagulation and anticoagulation factors maintain a dynamic balance to prevent from the development of thrombosis and hemorrhage in healthy population [60]. By comparison, coagulopathy is frequently observed in cirrhotic patients [61] due to an imbalance between coagulation and anticoagulation factors [62]. First, clotting factors are often decreased in cirrhotic patients [63] and in parallel to the

progression of liver disease [64]. Second, the mean lifetime of platelet is shortened and thrombopoietin production is decreased [65]. Thrombocytopenia is also caused by hypersplenism, antiplatelet autoantibodies, toxic effects of excessive alcohol intake, and treatment with interferon [65, 66]. Third, a hypercoagulable status has been recognized in advanced cirrhosis due to increased levels of factor VIII and decreased levels of protein C [64]. Therefore, both hemorrhage and thrombosis can develop in cirrhotic patients.

6.2 Hypoperfusion

Hypoperfusion is often observed in liver cirrhosis. First, ascites is a common clinical sign in cirrhotic patients due to liver dysfunction and portal hypertension [67], in which lots of capillary fluids leak into abdominal cavity. Second, serum albumin level is often decreased in liver cirrhosis, which can decrease intravascular osmotic pressure [68]. Third, massive gastrointestinal bleeding secondary to gastro-esophageal variceal rupture is a common complication of liver cirrhosis, leading to the hypoperfusion of various organs [21]. Fourth, there is a hyperdynamic circulation status in cirrhotic patients, which is characterized by arterial hypotension, high cardiac output, and low peripheral vascular resistance [69, 70].

6.3 Cardiac diseases

Cirrhotic patients often present with cirrhotic cardiomyopathy defined as cardiac systolic and/or diastolic dysfunction in the absence of previous history of heart disease [23]. Additionally, cardiac arrhythmias, especially atrial fibrillation, have been increasingly recognized in patients with chronic liver diseases [71, 72]. A nationwide population-based study suggests an increased risk of atrial fibrillation development in cirrhosis [73].

6.4 Diabetes

Up to 70% of cirrhotic patients develop diabetes or impaired glucose tolerance [74]. Evidence also suggests an association of hepatogeneous diabetes with higher portal pressure and increased risk of hepatocellular carcinoma, hepatic encephalopathy, and mortality in cirrhosis [75]. Several potential mechanisms of hepatogeneous diabetes include [1] reduced insulin clearance and hyperinsulinemia [76], [2] beta cell failure and reduced insulin secretion [77], and [3] increased secretion from alpha cells and hyperglucagonemia [75].

6.5 Dyslipidemia

Liver plays a key role in the synthesis, decomposition, and digestion of lipids, and dyslipidemia is found in patients with impaired liver function. Triglycerides, the ratio of triglycerides to high-density lipoprotein, and the ratio of apolipoprotein B to apolipoprotein A1 increase in cirrhotic patients [78, 79].

7. Conclusions

Patients with liver cirrhosis might have an increased risk of stroke probably due to their concomitant high-risk factors, such as coagulopathy, hypoperfusion, cardiac diseases, diabetes, and dyslipidemia. Once a patient was diagnosed with liver cirrhosis, the management of stroke should be initiated.

Abbreviations

Apo	apolipoprotein
HBV	hepatitis B virus
HCV	hepatitis C virus
NASH	nonalcoholic steatohepatitis
SAH	subarachnoid hemorrhage

Author contributions

Kexin Zheng: reviewed the literature and drafted the manuscript. Xiaozhong Guo, Xinhong Wang: gave critical comments. Xingshun Qi: conceived the work and drafted and revised the manuscript. All authors have made an intellectual contribution to the manuscript and approved the submission.

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