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Chapter

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

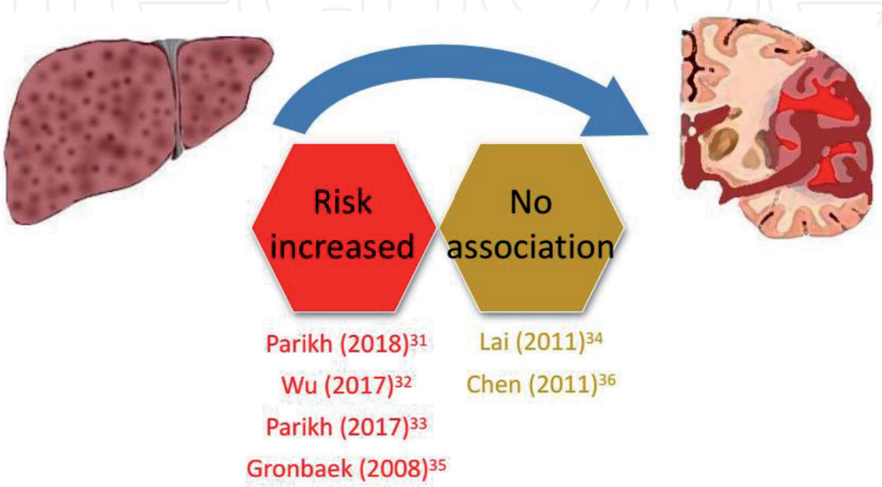

Figure 1.
The association between liver cirrhosis and hemorrhagic stroke.

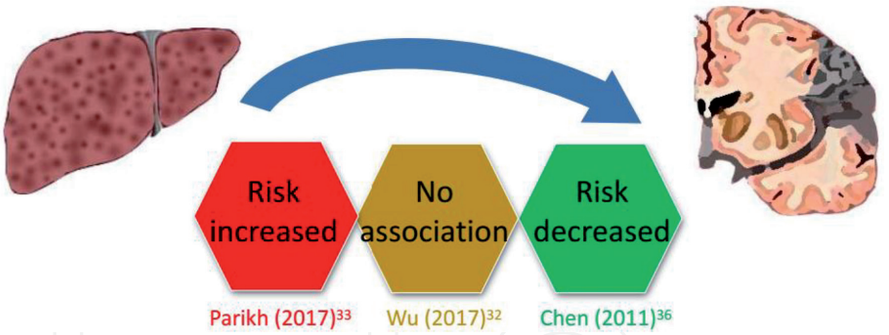

Figure 2.
The association between liver cirrhosis and ischemic stroke.

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.

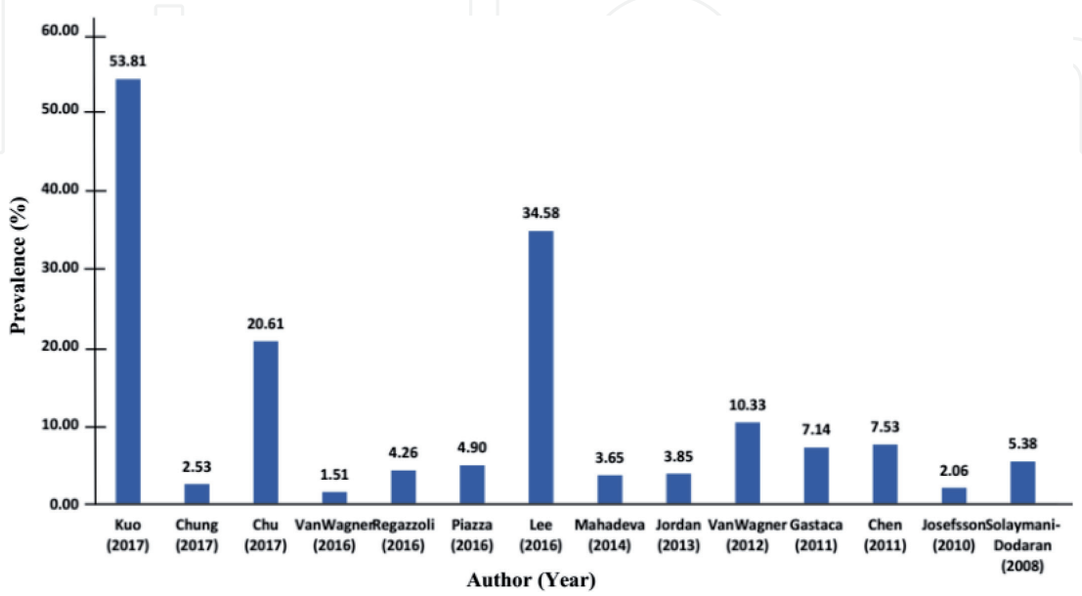

Figure 3.
The prevalence of stroke in liver cirrhosis.

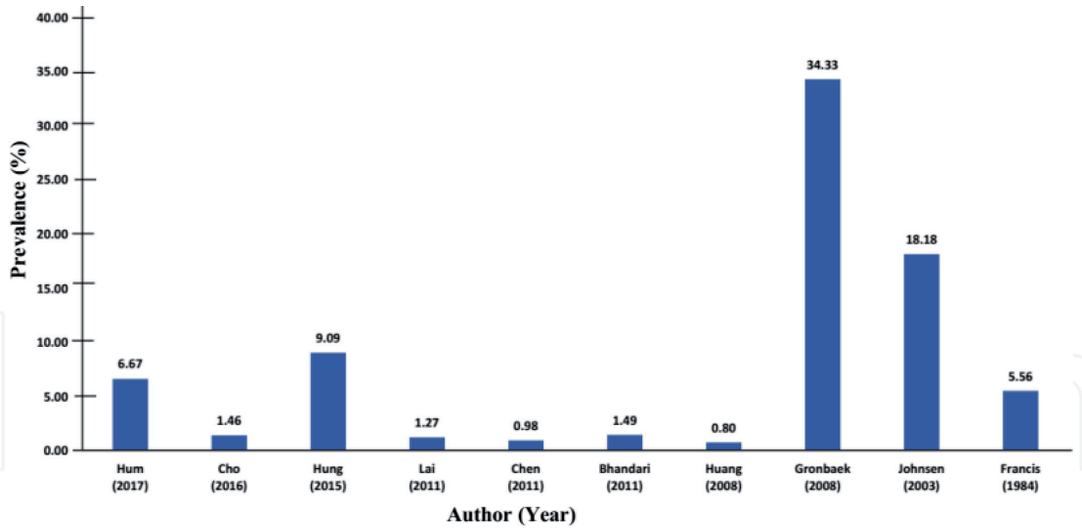

Figure 4.
The prevalence of hemorrhagic stroke in liver cirrhosis.

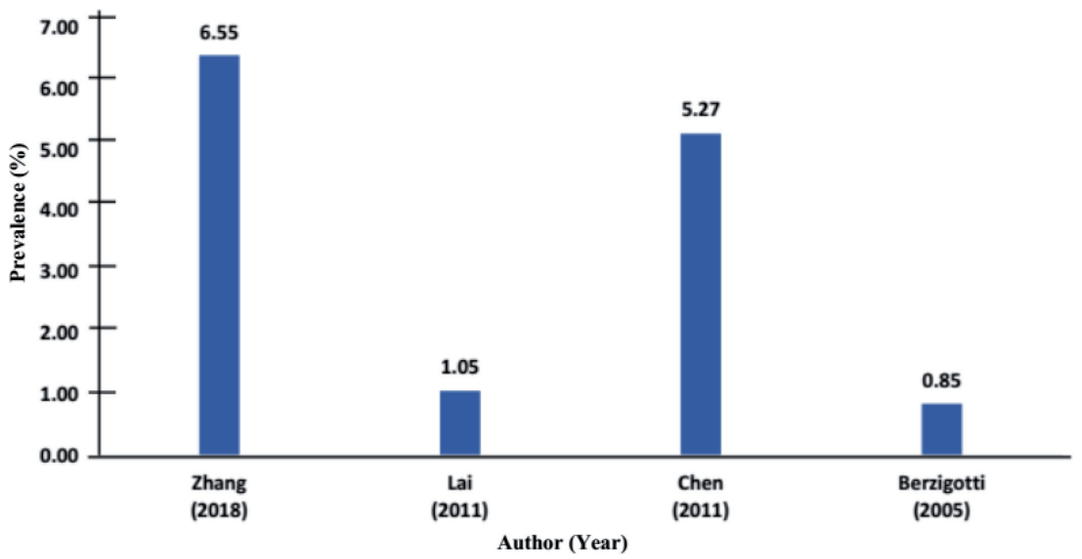

Figure 5.
The prevalence of ischemic stroke in liver cirrhosis.

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 gastroesophageal 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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References

[1] GBD. 2015 mortality and causes of death collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: A systematic analysis for the global burden of disease study 2015. Lancet. 2016;**388**:1459-1544

[2] Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke. 2013;**44**:2064-2089

[3] Freedman B, Potpara TS, Lip GY. Stroke prevention in atrial fibrillation. Lancet. 2016;**388**:806-817

[4] O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): A case-control study. Lancet. 2016;**388**:761-775

[5] Kim JS. Stroke in Asia: A global disaster. International Journal of Stroke. 2014;**9**:856-857

[6] Kumar S, Selim MH, Caplan LR. Medical complications after stroke. Lancet Neurology. 2010;**9**:105-118

[7] Hackett ML, Kohler S, O'Brien JT, Mead GE. Neuropsychiatric outcomes of stroke. Lancet Neurology. 2014;**13**:525-534

[8] Gresham GE, Fitzpatrick TE, Wolf PA, McNamara PM, Kannel WB, Dawber TR. Residual disability in survivors of stroke—the Framingham study. The New England Journal of Medicine. 1975;**293**:954-956

[9] O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): A case-control study. Lancet. 2010;**376**:112-123

[10] Qi X, Qiu J, De Stefano V, Shao X, Sun R, Guo X. Development of acute ischemic stroke in two patients with acute upper gastrointestinal bleeding. AME Medical Journal. 2017;**2**:24

[11] Qi X, De Stefano V, Shao X, Guo X. Thrombocytosis in a patient with upper gastrointestinal bleeding. Intractable & Rare Diseases Research. 2017;**6**:69-71

[12] Qi X, Wang J, Yu X, De Stefano V, Li H, Wu C, et al. Hemocoagulase might not control but worsen gastrointestinal bleeding in an elderly patient with type II respiratory failure. Translational Gastroenterology and Hepatology. 2017;**2**:71

[13] Nelamangala-Ramakrishnaiah VP, Chellappa V, Goneppanavar M. Blood transfusion strategy in cirrhotic patients with active upper GI bleeding. AME Medical Journal. 2019;**4**:1. Available from: http://amj.amegroups.com/article/view/4768/html

[14] Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet. 2014;**383**:1749-1761

[15] Schuppan D, Afdhal NH. Liver cirrhosis. Lancet. 2008;**371**:838-851

[16] Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the global burden of disease study 2010. Lancet. 2012;**380**:2095-2128

[17] Mokdad AA, Lopez AD, Shahraz S, Lozano R, Mokdad AH, Stanaway J,

et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: A systematic analysis. BMC Medicine. 2014;**12**:145

[18] Ge PS, Runyon BA. Treatment of patients with cirrhosis. The New England Journal of Medicine. 2016;**375**:767-777

[19] Selmi C, Bowlus CL, Gershwin ME, Coppel RL. Primary biliary cirrhosis. Lancet. 2011;**377**:1600-1609

[20] Henriksen JH, Fuglsang S, Bendtsen F, Moller S. Arterial hypertension in cirrhosis: Arterial compliance, volume distribution, and central haemodynamics. Gut. 2006;**55**:380-387

[21] Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. The New England Journal of Medicine. 2010;**362**:823-832

[22] Gines P, Cardenas A, Arroyo V, Rodes J. Management of cirrhosis and ascites. The New England Journal of Medicine. 2004;**350**:1646-1654

[23] Moller S, Henriksen JH. Cardiovascular complications of cirrhosis. Gut. 2008;**57**:268-278

[24] Shawcross D, Jalan R. Dispelling myths in the treatment of hepatic encephalopathy. Lancet. 2005;**365**:431-433

[25] Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018;**391**:1301-1314

[26] Maluccio M, Covey A. Recent progress in understanding, diagnosing, and treating hepatocellular carcinoma. CA: A Cancer Journal for Clinicians. 2012;**62**:394-399

[27] Qi X, Han G, Fan D. Management of portal vein thrombosis in liver cirrhosis. Nature Reviews. Gastroenterology & Hepatology. 2014;**11**:435-446

[28] Qi X, Ren W, Guo X, Fan D. Epidemiology of venous thromboembolism in patients with liver diseases: A systematic review and meta-analysis. Internal and Emergency Medicine. 2015;**10**:205-217

[29] Garcia-Tsao G, Bosch J. Varices and variceal hemorrhage in cirrhosis: A new view of an old problem. Clinical Gastroenterology and Hepatology. 2015;**13**:2109-2117

[30] Sogaard KK, Horvath-Puho E, Gronbaek H, Jepsen P, Vilstrup H, Sorensen HT. Risk of venous thromboembolism in patients with liver disease: A nationwide population-based case-control study. The American Journal of Gastroenterology. 2009;**104**:96-101

[31] Parikh NS, Merkler AE, Jesudian A, Kamel H. Liver cirrhosis is associated with an increased risk of aneurysmal subarachnoid hemorrhage. Stroke. 2018;**49**:ATP171

[32] Wu HY, Lin CS, Yeh CC, Hu CJ, Shih CC, Cherng YG, et al. Cirrhosis patients' stroke risks and adverse outcomes: Two nationwide studies. Atherosclerosis. 2017;**263**:29-35

[33] Parikh NS, Navi BB, Schneider Y, Jesudian A, Kamel H. Association between cirrhosis and stroke in a nationally representative cohort. JAMA Neurology. 2017;**74**:927-932

[34] Lai CH, Cheng PY, Chen YY. Liver cirrhosis and risk of intracerebral hemorrhage: A 9-year follow-up study. Stroke. 2011;**42**:2615-2617

[35] Gronbaek H, Johnsen SP, Jepsen P, Gislum M, Vilstrup H, Tage-Jensen U, et al. Liver cirrhosis, other liver diseases, and risk of hospitalisation for intracerebral haemorrhage: A Danish population-based case-control study. BMC Gastroenterology. 2008;**8**:16

[36] Chen YH, Chen KY, Lin HC. Non-alcoholic cirrhosis and the risk of stroke: A 5-year follow-up study. Liver International. 2011;**31**:354-360

[37] Solaymani-Dodaran M, Aithal GP, Card T, West J. Risk of cardiovascular and cerebrovascular events in primary biliary cirrhosis: A population-based cohort study. The American Journal of Gastroenterology. 2008;**103**:2784-2788

[38] Kuo L, Chao TF, Liu CJ, Lin YJ, Chang SL, Lo LW, et al. Liver cirrhosis in patients with atrial fibrillation: Would oral anticoagulation have a net clinical benefit for stroke prevention? Journal of the American Heart Association. 2017;**6**:e005307

[39] Chung MS, Kim HS, Lim YS, Jeon SB, Kim SO, Kim HJ, et al. Clinical impact of preoperative brain MR angiography and MR imaging in candidates for liver transplantation: A propensity score-matching study in a single institution. European Radiology. 2017;**27**:3532-3541

[40] Chu LM, Liu CC, Yeh CC, Chang YC, Hu CJ, Shih CC, et al. Increased diabetes risk and interaction with social and medical events in patients upon stroke: Two nationwide studies. Atherosclerosis. 2017;**265**:87-92

[41] VanWagner LB, Serper M, Kang R, Levitsky J, Hohmann S, Abecassis M, et al. Factors associated with major adverse cardiovascular events after liver transplantation among a national sample. American Journal of Transplantation. 2016;**16**:2684-2694

[42] Regazzoli D, Latib A, Montorfano M, Tanaka A, Jabbour R, Chieffo A, et al. Acute and medium-term outcomes of transcatheter aortic valve implantation in patients with cirrhosis. Giornale Italiano di Cardiologia. 2016;**17**:e14

[43] Piazza NA, Singal AK. Frequency of cardiovascular events and effect on survival in liver transplant recipients for cirrhosis due to alcoholic or nonalcoholic steatohepatitis. Experimental and Clinical Transplantation. 2016;**14**:79-85

[44] Lee SJ, Uhm JS, Kim JY, Pak HN, Lee MH, Joung B. The safety and efficacy of vitamin K antagonist in patients with atrial fibrillation and liver cirrhosis. International Journal of Cardiology. 2015;**180**:185-191

[45] Mahadeva S, Kadhim O. Morbidity and mortality differences between cryptogenic and non-cryptogenic cirrhosis: A retrospective cohort study. Journal of Gastroenterology and Hepatology. 2014;**29**:189-190

[46] Jordan C, Pilch N, Taber D, Meadows H, Fleming J, Mardis A, et al. Liver transplant for NASH: We need to spare the nephron. American Journal of Transplantation. 2013;**13**:72

[47] Vanwagner LB, Bhave M, Te HS, Feinglass J, Alvarez L, Rinella ME. Patients transplanted for nonalcoholic steatohepatitis are at increased risk for postoperative cardiovascular events. Hepatology. 2012;**56**:1741-1750

[48] Gastaca M, Agüero F, Montejo M, Rimola A, Miralles P, Lozano R, et al. Retransplantation in HIV-infected patients after liver transplantation: A prospective cohort study. American Journal of Transplantation. 2011;**11**:277

[49] Josefsson A, Fu M, Bjornsson E, Olausson M, Kalaitzakis E. The use of beta-blockers in patients with liver cirrhosis undergoing liver transplantation. Gastroenterology. 2010;**138**:S821

[50] Hum J, Shatzel JJ, Jou JH, Deloughery TG. The efficacy and safety of direct oral anticoagulants vs traditional anticoagulants in cirrhosis.

European Journal of Haematology. 2017;**98**:393-397

[51] Cho J, Choi SM, Yu SJ, Park YS, Lee CH, Lee SM, et al. Bleeding complications in critically ill patients with liver cirrhosis. The Korean Journal of Internal Medicine. 2016;**31**:288-295

[52] Hung TH, Hsieh YH, Tseng KC, Tseng CW, Lee HF, Tsai CC, et al. High mortality in cirrhotic patients following hemorrhagic stroke. Journal of Clinical Neuroscience. 2015;**22**:995-997

[53] Bhandari BM, Kumar S, Latimer DC, Sass DA, Rothstein K. A head CT is unnecessary in the initial evaluation of hepatic encephalopathy in patients with cirrhosis. Gastroenterology. 2011;**140**:S903

[54] Huang HH, Lin HH, Shih YL, Chen PJ, Chang WK, Chu HC, et al. Spontaneous intracranial hemorrhage in cirrhotic patients. Clinical Neurology and Neurosurgery. 2008;**110**:253-258

[55] Johnsen SP, Pedersen L, Friis S, Blot WJ, McLaughlin JK, Olsen Jø H, et al. Nonaspirin nonsteroidal anti-inflammatory drugs and risk of hospitalization for intracerebral hemorrhage: A population-based case-control study. Stroke. 2003;**34**:387-391

[56] Francis RB Jr, Feinstein DI. Clinical significance of accelerated fibrinolysis in liver disease. Haemostasis. 1984;**14**:460-465

[57] Zhang X, Qi X, Yoshida E, Méndez-Sánchez N, Hou F, Deng H, et al. Ischemic stroke in liver cirrhosis: Epidemiology, risk factors, and in-hospital outcomes. European Journal of Gastroenterology & Hepatology. 2018;**30**:233-240

[58] Berzigotti A, Bonfiglioli A, Muscari A, Bianchi G, Libassi S, Bernardi M, et al. Reduced prevalence of ischemic events and abnormal supraortic flow patterns in patients with liver cirrhosis. Liver International. 2005;**25**(2):331-336

[59] Choi J, Kim J, Shim JH, Kim M, Nam GB. Risks versus benefits of anticoagulation for atrial fibrillation in cirrhotic patients. Journal of Cardiovascular Pharmacology. 2017;**70**:255-262

[60] Jairath V, Burroughs A. Anticoagulation in patients with liver cirrhosis: Complication or therapeutic opportunity? Gut. 2013;**62**:479-482

[61] Lisman T, Leebeek FW, de Groot PG. Haemostatic abnormalities in patients with liver disease. Journal of Hepatology. 2002;**37**:280-287

[62] Drolz A, Horvatits T, Roedl K, Rutter K, Staufer K, Kneidinger N, et al. Coagulation parameters and major bleeding in critically ill patients with cirrhosis. Hepatology. 2016;**64**:556-568

[63] Everett LA, Cleuren AC, Khoriaty RN, Ginsburg D. Murine coagulation factor VIII is synthesized in endothelial cells. Blood. 2014;**123**:3697-3705

[64] Tripodi A, Primignani M, Chantarangkul V, Dell'Era A, Clerici M, de Franchis R, et al. An imbalance of pro- vs anti-coagulation factors in plasma from patients with cirrhosis. Gastroenterology. 2009;**137**:2105-2111

[65] Peck-Radosavljevic M. Thrombocytopenia in liver disease. Canadian Journal of Gastroenterology. 2000;**14**(Suppl D):60d-66d

[66] Yongxiang W, Zongfang L, Guowei L, Zongzheng J, Xi C, Tao W. Effects of splenomegaly and splenic macrophage activity in hypersplenism due to cirrhosis. The American Journal of Medicine. 2002;**113**:428-431

[67] Moore KP, Aithal GP. Guidelines on the management of ascites in cirrhosis. Gut. 2006;**55**(Suppl 6):vi1-v12

[68] Hsu SJ, Huang HC. Management of ascites in patients with liver cirrhosis: Recent evidence and controversies. Journal of the Chinese Medical Association. 2013;**76**:123-130

[69] Iwakiri Y, Groszmann RJ. The hyperdynamic circulation of chronic liver diseases: From the patient to the molecule. Hepatology. 2006;**43**:S121-S131

[70] Arroyo V, Gines P. Mechanism of sodium retention and ascites formation in cirrhosis. Journal of Hepatology. 1993;**17**(Suppl 2):S24-S28

[71] Zhao J, Qi X, Hou F, Ning Z, Zhang X, Deng H, et al. Prevalence, risk factors and in-hospital outcomes of QTc interval prolongation in liver cirrhosis. The American Journal of the Medical Sciences. 2016;**352**:285-295

[72] Zhao J, Li S, Ren L, Guo X, Qi X. Pro-brain natriuretic peptide and troponin T-hypersensitivity levels correlate with the severity of liver dysfunction in liver cirrhosis. The American Journal of the Medical Sciences. 2017;**354**:131-139

[73] Anstee QM, Mantovani A, Tilg H, Targher G. Risk of cardiomyopathy and cardiac arrhythmias in patients with nonalcoholic fatty liver disease. Nature Reviews. Gastroenterology & Hepatology. 2018;**15**:425-439

[74] Hickman IJ, Macdonald GA. Impact of diabetes on the severity of liver disease. The American Journal of Medicine. 2007;**120**:829-834

[75] Junker AE, Gluud LL, Holst JJ, Knop FK, Vilsboll T. Influence of gastrointestinal factors on glucose metabolism in patients with cirrhosis. Journal of Gastroenterology and Hepatology. 2015;**30**:1522-1528

[76] Deschenes M, Somberg KA. Effect of transjugular intrahepatic portosystemic shunt (TIPS) on glycemic control in cirrhotic patients with diabetes mellitus. The American Journal of Gastroenterology. 1998;**93**:483

[77] Petrides AS. Hepatogenic diabetes: Pathophysiology, therapeutic options and prognosis. Zeitschrift für Gastroenterologie. 1999;(Suppl 1):15-21

[78] Nderitu P, Bosco C, Garmo H, Holmberg L, Malmstrom H, Hammar N, et al. The association between individual metabolic syndrome components, primary liver cancer and cirrhosis: A study in the Swedish AMORIS cohort. International Journal of Cancer. 2017;**141**:1148-1160

[79] Sierra-Johnson J, Somers VK, Kuniyoshi FH, Garza CA, Isley WL, Gami AS, et al. Comparison of apolipoprotein-B/apolipoprotein-AI in subjects with versus without the metabolic syndrome. The American Journal of Cardiology. 2006;**98**:1369-1373