肝硬化與頭部外傷後顱內出血的關聯性

蔡鎔阡[1]、許建清[2]、彭巧珍[3]、林正耀[3]、*黃建程[3]

[1]台南新樓醫院急診科、[2]南臺科技大學生物與食品科技系、[3]南臺科技大學高齡福祉服務系

*chienchenghuang@stust.edu.tw

摘要

肝硬化導致的凝血功能異常可能會增加頭部外傷後顱內出血的機會，然而肝硬化病人發生頭部外傷後進行電腦斷層檢查的適應症尚未清楚。我們以台灣健保資料庫來進行這一個以全國人口為基礎的研究，比較肝硬化與無肝硬化病人頭部外傷後顱內出血的風險，以供決定是否需要降低肝硬化病人頭部外傷後進行頭部電腦斷層檢查的閥值。我們共收錄了 10,087 位病人(917 位肝硬化；9,170 位無肝硬化)，以條件邏輯回歸的方式來比較二群病人頭部外傷後顱內出血的風險。結果發現共有 223 個病人發生顱內出血，其中肝硬化病人有 21 位(2.3%)，無肝硬化病人有 202 位(2.2%)。條件邏輯回歸顯示肝硬化病人比起無肝硬化病人，並無較高的顱內出血風險(odds ratio [OR]: 1.0; 95% confidence interval [CI]: 0.7–1.6)。二組在立即顱內出血(OR: 1.1; 95% CI: 0.7–1.9)與延遲性顱內出血 (OR: 0.9; 95% CI: 0.4–2.1)的比較上也無明顯差別。我們的結論是肝硬化並不會增加頭部外傷後顱內出血的風險，可能的原因是肝硬化同時減少了促凝血和抗凝血因子所造成的平衡。因此，肝硬化病人發生頭部外傷並不需要降低進行電腦斷層檢查的閥值。

關鍵詞：電腦斷層、頭部外傷、顱內出血、肝硬化

Association between Liver Cirrhosis and Risk of Intracranial Hemorrhage after Head Injury

Jung–Chien Tsai[1], Chien–Chin Hsu[2], Ciao–Jhen Peng[3], Cheng–Yao Lin[3], *Chien–Cheng Huang[3]

[1]Department of Emergency Medicine, Sin–Lau Hospital

[2]Department of Biotechnology and Food Technology, Southern Taiwan University of Science and Technology

[3]Department of Senior Services, Southern Taiwan University of Science and Technology

Abstract

Coagulopathy in liver cirrhosis (LC) might increase the risk of intracranial hemorrhage (ICH) after a head injury (HI). However, the indications of head computed tomography (CT) in patients with LC do not evidently support this interrelation. We compared the risk of ICH between patients with and without LC to determine whether we should lower the threshold of head CT in patients with LC after HI. We did a nationwide population–based study using Taiwan's National Health Insurance Research Database. We identified 10,087 patients with HI (917 cases of LC; 9,170 randomly selected controls without LC). Conditional logistic regression was used to measure the post–HI association between LC and ICH. Two hundred twenty–three (2.2%) patients had post–HI ICH: among them, there were 21 (2.3%) patients with LC and there were 202 (2.2%) controls. Conditional logistic regression showed that patients with LC had no greater risk of ICH (odds ratio [OR]: 1.0; 95% confidence interval [CI]: 0.7–1.6) than did controls. There were also no significant differences in the subgroup analyses of immediate ICH (OR: 1.1; 95% CI: 0.7–1.9) and delayed ICH (OR: 0.9; 95% CI: 0.4–2.1). LC did not increase the post–HI risk of ICH. The restored balance of hemostasis provided by the concomitant reduction of procoagulant and anticoagulant factors might explain this. Therefore, lowering the threshold of head CT in patients with LC seems unnecessary.

Keywords: Computed Tomography, Head Injury, Intracranial Hemorrhage, Liver Cirrhosis.

Received: Jan. 21, 2019; first revised: Apr. 3, 2019; second revised: May 24, 2019; accepted: Oct. 2019.

Corresponding author: C.–C. Huang, Department of Senior Services, Southern Taiwan University of Science and Technology, Tainan 71005, Taiwan.

I. Introduction

Head injury (HI) is a major public health and socioeconomic problem throughout the world [1–4]. It is estimated that 7.7 million people in Europe who have had an HI have disabilities [5]. In the US, where the financial burden of HI has been estimated at over US$60 billion per year [6], approximately 5.3 million people are living with a HI–related disability [7].

In the Emergency Department (ED), up to 15% of patients with HI and a Glasgow Coma Scale score of 15 had intracranial hemorrhage (ICH) on head computed tomography (CT) [8–11]. Therefore, the biggest challenge ED physicians is identifying which patients with HI have an acute ICH [12]. The widespread use of head CT has greatly helped physicians to better manage patients with HI [12]. In the New Orleans [8] and Canadian CT Clinical Decision Rules [9], head CT is recommended for patients who are alcohol dependent, on a chronic anticoagulant regimen, or have known coagulopathy. However, the indication for head CT in patients with liver cirrhosis (LC), a disease with higher risk for hematologic complications because of coagulation disorders and thrombocytopenia [13], is not clear. Physicians always face the question: *Do we need to lower the threshold of head CT in patients with LC?* Therefore, we did a nationwide population–based study to determine the risk of ICH after HI in patients with LC. We hypothesized that LC increases the ICH risk in patients after HI because of coagulopathy.

II. Methods

1. Data sources

The National Health Insurance Research Database (NHIRD) was released by Taiwan's National Health Insurance (NHI) Program, begun in 1995, covers nearly 100% of the country's legal residents, released the National Health Insurance Research Database (NHIRD) [14]. We used the Longitudinal Health Insurance Database 2000 (LHID2000), a data subset derived from the NHIRD; it contains all claims data of one million (4.34% of the total population) beneficiaries drawn randomly in 2000. There are no significant differences in age, gender, or healthcare costs between the LHID2000 dataset and all NHI enrollees. The LHID2000 contains encrypted patient identification numbers, basic socioeconomic data, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD–9–CM) diagnosis codes, prescribed drugs, procedures, and dates of clinic visit, admission, and discharge [14]. All of the costs of LC, HI, and ICH are covered by NHI.

2. Selection of Cases and Controls

We identified patients diagnosed with HI (ICD–9–CM codes 850, 852, 853, 854, 959.0, 959.01, 959.09) between 2002 and 2008 for this longitudinal study (Figure 1). The Cases Group (with LC [LCPos]) were patients diagnosed with LC before their HI, which was confirmed if the dataset indicated that they had any one of these ICD–9 codes: 571.2, 571.5, or 571.6. The Control Group (without LC [LCNeg]) were patients not diagnosed with LC before their HI. The cases and controls were then matched (1:10 ratio) by age, gender, and index year. As with the cases, we assigned the first use of medical care during the index year as the index date for controls.

We linked to the diagnostic codes through the ambulatory and inpatient care claims of the LHID2000 dataset. We included baseline comorbidities that may have presented before the index date were diabetes mellitus (DM) (ICD–9–CM code 250), hypertension (HTN) (ICD–9–CM codes 401–405), congestive heart failure (CHF) (ICD–9–CM code 428), stroke (ICD–9–CM codes 430–438), and cancer (ICD–9–CM codes 140–208). We counted these comorbidities if they occurred either in the inpatient setting or in 3 or more ambulatory care claims coded before the index date.

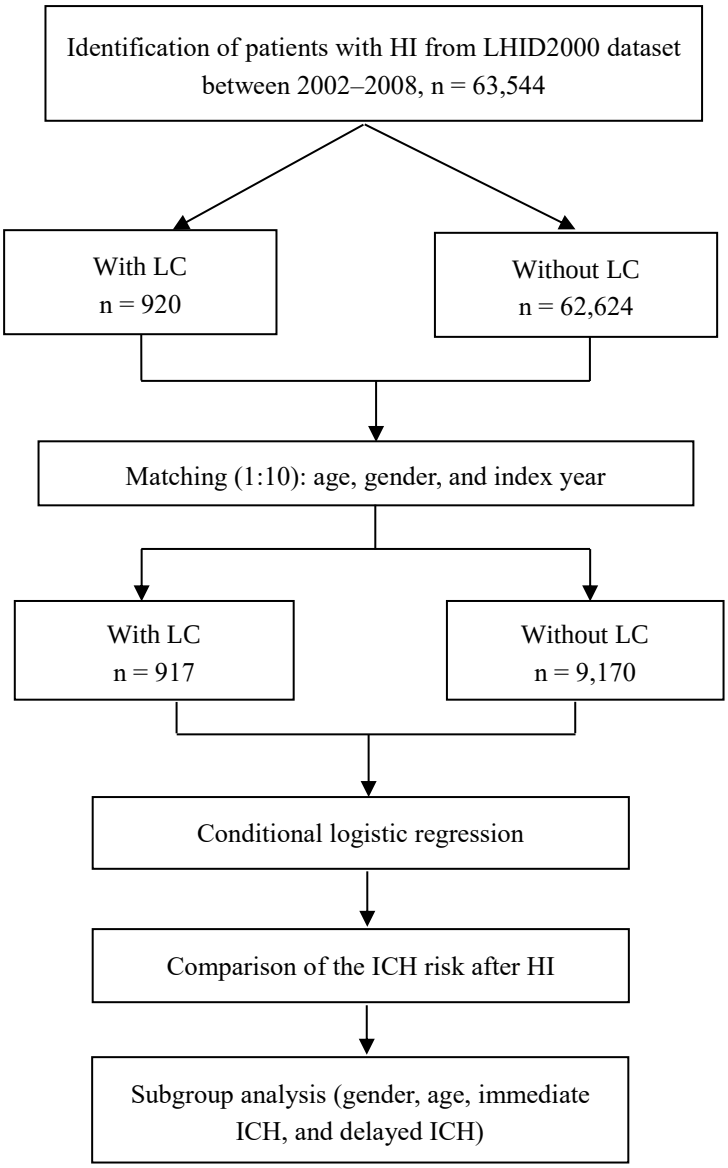

Fig.1 Flowchart of the study. LC, liver cirrhosis; ICH, intracranial hemorrhage.

3. Primary outcome measurements

We compared the ICH risk after HI between patients with and without LC. ICH was the primary outcome measure that included medical codes for (i) immediate ICH after HI (ICD–9–CM codes: 850, 852, 853, 854); and (ii) delayed ICH within 7 days of HI (ICD–9–CM codes: 850, 852, 853, 854, 430, 431, 432, 432.1, 432.9). By definition, all patients had not been previously diagnosed with ICH.

4. Stratification and subgroup analysis

We also stratified the data by gender, age, and subgroup analysis for immediate ICH and delayed ICH to evaluate the association between LC and the risk for ICH risk patients with HI. Elderly was defined as ≥ 65 years old.

5. Ethic statement

We conducted this study according to the Declaration of Helsinki. It was approved by the Institutional Review

Board (IRB) at Chi–Mei Medical Center (IRB number: 10502–E01), which waived the need for informed patient consents because the dataset used in this study consists of deidentified, nationwide, secondary data released to the public for research. The waiver does not affect the rights and welfare of the patients.

6. Statistical analysis

We used Pearson $\chi 2$ tests for categorical variables and Student's t tests for continuous variables to evaluate the significance of the differences in demographic characteristics and comorbidities between the patients with and without LC. We used conditional logistic regression to evaluate the association of LC and ICH after HI. We did not adjust for age and gender because both were matched in the recruitment process and comorbidities, and because they were not considered confounding factors in the literature. We used SAS 9.3.1 for Windows (SAS Institute, Cary, NC, USA) for all analyses. Significance was set at $P < 0.05$ (two–tailed).

III. Results

We identified 10,087 HI^{Pos} patients (LC^{Pos}: 917; LC^{Neg}: 9,170) between 2002–2008 (Figure 1 and Table 1). Both groups had a mean age of 58.3 ± 16.0 years and male predominance (71.2%). LC^{Pos} patients had significantly higher incidences of DM, HTN, CHF, stroke, and cancer than did LC^{Neg} patients.

There was no significant difference in the ICH risk after HI in the overall analysis (OR: 1.0; 95% CI: 0.7–1.6) or after stratifications based on gender and age (Table 2). In the subgroup analysis, there was no significant difference in the immediate (OR: 1.1; 95% CI: 0.7–1.9) (Table 3) or delayed ICH risk (OR: 0.9; 95% CI: 0.4–2.1) (Table 4) after HI. The ICH risk after HI was not significantly different between the LC^{Pos} and the LC^{Neg} elderly (Tables 2–4).

Table 1. Demographic characteristics of total patients with head injury

Characteristic	With LC	Without LC	*P*–value
Number of patients	917	9170	
Age (years)	58.3 ± 16.0	58.3 ± 16.0	> 0.99
0–64	582 (63.5)	5,823 (63.5)	0.98
≥ 65	335 (36.5)	3,347 (36.5)	
Gender			
Male	653 (71.2)	6,350 (71.2)	> 0.99
Female	264 (28.8)	2,640 (28.8)	
Comorbidities			
DM	232 (25.3)	1,262 (13.8)	< 0.01
HTN	295 (32.2)	2,581 (28.2)	0.01
CHF	39 (4.3)	237 (2.6)	< 0.01
Stroke	117 (12.8)	916 (10.0)	< 0.01
Cancer	106 (11.6)	295 (3.2)	< 0.01

Data are n (%) or means ± standard deviation. LC, liver cirrhosis; DM, diabetes mellitus; HTN, hypertension; CHF, congestive heart failure.

Table 2. Comparison of the risk of intracranial hemorrhage after head injury between patients with and without LC.

Outcome	With LC	Without LC	OR	*P*–value
Overall				
Yes, n (%)	21 (2.3)	202 (2.2)	1.0 (0.7–1.6)	0.86
No, n (%)	896 (97.7)	8968 (97.8)	1.0	
Gender				
Male				
Yes, n (%)	15 (2.3)	153 (2.3)	1.0 (0.6–1.7)	0.94
No, n (%)	638 (97.7)	6377 (97.7)	1.0	
Female				
Yes, n (%)	6 (2.3)	49 (1.9)	1.2 (0.5–2. 9)	0.64
No, n (%)	258 (97.7)	2591 (98.1)	1.0	
Age				
Non–elderly (0 < 65 years)				
Yes, n (%)	16 (2.8)	121 (2.1)	1.3 (0.8–2.3)	0.29
No, n (%)	566 (97.3)	5702 (97.9)	1.0	
Elderly (≥ 65 years)				
Yes, n (%)	5 (1.5)	81 (2.4)	0.6 (0.3–1.5)	0.29
No, n (%)	330 (98.5)	3266 (97.6)	1.0	

Data are presented as n (%). Conditional logistical regression was used. LC, liver cirrhosis; OR, odds ratio.

Table 3. Comparison of the risk of immediate intracranial hemorrhage after head injury between patients with LC and patients without LC

Outcome	With LC	Without LC	OR	*P*–value
Overall				
Yes, n (%)	15 (1.6)	135 (1.5)	1.1 (0.7–1.9)	0.70
No, n (%)	902 (98.4)	9035 (98.5)	1.0	
Gender				
Male				
Yes, n (%)	10 (1.5)	99 (1.5)	1.0 (0.5–2.0)	0.98
No, n (%)	643 (98.5)	6431 (98.5)	1.0	
Female				
Yes, n (%)	5 (1.9)	36 (1.4)	1.4 (0.5–3.6)	0.49
No, n (%)	259 (98.1)	2604 (98.6)	1.0	
Age				
Non–elderly (0 < 65 years)				
Yes, n (%)	11 (1.9)	81 (1.4)	1.4 (0.7–2.6)	0.34
No, n (%)	571 (98.1)	5742 (98.6)	1.0	
Elderly (≥ 65 years)				
Yes, n (%)	4 (1.2)	54 (1.6)	0.7 (0.3–2.1)	0.56
No, n (%)	331 (98.8)	3293 (98.4)	1.0	

Data are n (%). Conditional logistical regression was used. LC, liver cirrhosis; OR, odds ratio.

Table 4. Comparison of the risk of delayed intracranial hemorrhage after head injury between patients with LC and patients without LC.

Outcome	With LC	Without LC	OR	*P*–value
Overall				
Yes, n (%)	6 (0.7)	67 (0.7)	0.9 (0.4–2.1)	0.80
No, n (%)	911 (99.4)	9103 (99.3	1.0	
Gender				
Male				
Yes, n (%)	5 (0.8)	54 (0.8)	0.9 (0.4–2.3)	0.87
No, n (%)	648 (99.2)	6476 (99.2)	1.0	
Female				
Yes, n (%)	1 (0.4)	13 (0.5)	0.8 (0.1–5.9)	0.80
No, n (%)	263 (99.6)	2627 (99.5)	1.0	
Age				
Non–elderly (0 < 65 years)				
Yes, n (%)	5 (0.9)	40 (0.7)	1.3 (0.5–3.2)	0.64
No, n (%)	577 (99.1)	5783 (99.3)	1.0	
Elderly (≥ 65 years)				
Yes, n (%)	1 (0.3)	27 (0.8)	0.4 (0.1–2.7)	0.33
No, n (%)	334 (99.7)	3320 (99.2)	1.0	

Data are n (%). Conditional logistical regression was used. LC, liver cirrhosis; OR, odds ratio.

IV. Discussion

This is the first study to report the associations between LC and ICH risk after HI. Based on a nationwide population–based study design with a large sample, we found that LC did not increase the ICH risk after HI, regardless of gender, age, and subgroup analysis of immediate ICH and delayed ICH. These findings suggest that lowering the threshold for a head CT in patients with LC after HI may be not necessary. In addition, in elderly patients with LC, a population more sensitive to ICH, the criteria for head CT need not be different from those of the general population. This result is valuable for helping supplement deficiency in previous guidelines for managing HI in the patients with LC and reducing medical costs by decreasing the rate of unnecessary head CTs examination, especially in the elderly.

The possible explanation for no increased ICH risk in patients with LC is the balance between concomitant reduction of procoagulant and anticoagulant factors [15]. That is also the reason why patients with LC are not protected from arterial and venous thrombosis [15]. This may be explained by two findings in other studies: (1) There was a procoagulant imbalance in patients with LC because of the resistance to thrombomodulin [16–23]; and (2) There was a compensation for thrombocytopenia in patients with LC due to the increased levels of the adhesive protein, von Willebrand factor [15]. An animal study reported that platelet activation played an important role in the immune–mediated progression of liver disease [15]. In some situations, the risk for thrombosis may be higher than the risk of bleeding [15]. The bleeding tendency in end–stage LC should not be explained by hypocoagulability; however, underlying conditions that favor hemorrhage, such as hemodynamic alterations subsequent to portal hypertension, endothelial dysfunction, bacterial infections, and renal failure, might be more important [23–28].

The restored balance of hemostasis also explains that coagulation studies (i.e., measuring prothrombin time and activated partial–thromboplastin time) are not good indices for a head CT in patients with LC because they are also poorly correlated with bleeding events such as a liver biopsy or other potentially hemorrhagic procedures [29,30], gastrointestinal bleeding, and the prototype of hemorrhagic events in patients with end–stage liver disease [31,32]. For example, a prothrombin–time test does not accurately indicate the coagulation and the risk of hemorrhage because it only measures the procoagulant drivers (i.e., thrombin generated in plasma) [15]. The thrombin inhibited by the anticoagulant drivers is not measured [15]. Despite the decreased coagulation factors, it is generally believed that thrombin generation is maintained in patients with LC and platelet counts above 60,000/ml, because of a simultaneous decrease in coagulation inhibitors (i.e., protein C, protein S, and antithrombin) [15].

In spontaneous ICH, other studies [33] have reported controversial results about the effect of LC. A Danish population–based case–control study reported that patients with alcoholic or non–alcoholic liver cirrhosis and non–cirrhotic alcoholic liver disease had a substantially increased risk for spontaneous ICH [33]. However, another nationwide population–based cohort study in Taiwan reported that LC did not increase the incidence rate of spontaneous ICH after a 9–year follow–up [34].

This study has some limitations. First, there was no information on the severity and classification of LC, ICH, and HI; therefore, we were unable to evaluate the severity and classification association between them. Second, some drugs that affect coagulation, such as warfarin, aspirin, and clopidogrel, were not investigated; therefore, we were unable to adjust for these variables as confounding factors in this study. Additional studies on this topic are warranted. Finally, despite our database being nationwide, our findings may not be generalizable to other nations.

V. Conclusions

This is the first nationwide population–based study to clarify that patients with LC had no higher a risk for ICH after HI than did patients without LC. The restored balance of hemostasis afforded by the concomitant reduction of procoagulant and anticoagulant factors might play the major role. Therefore, it may be not necessary for physicians to lower the threshold for head CT in patients with LC after HI. However, the effect of severity and classification of LC, ICH, and HI needs additional studies to clarify this question.

References

[1] F. Khan, I. Baguley, and I. D. Cameron. (2003). 4: Rehabilitation after traumatic brain injury. *Medical Journal of Australia, 178*(6), 290–295.

[2] A. I. Maas, N. Stocchetti, and R. Bullock. (2008). Moderate and severe traumatic brain injury in adults. *The Lancet Neurology, 7*(8), 728–741.

[3] J. Ghajar. (2000). Traumatic brain injury. *The Lancet, 356*(9233), 923–929.

[4] T. B. Cole. (2004). Global road safety crisis remedy sought: 1.2 million killed, 50 million injured annually. *JAMA, 291*(21), 2531–2532. DOI: 10.1001/jama.291.21.2531

[5] F. Tagliaferri, C. Compagnone, M. Korsic, F. Servadei, and J. Kraus. (2006). A systematic review of brain injury epidemiology in Europe. *Acta Neurochirurgica (Wien), 148*(3), 255–268.

[6] D. Thurman. (2001). The epidemiology and economics of head trauma. In: L. P. Miler, and R. L. Hayes. (Eds.) *Head trauma: basic, preclinical, and clinical directions* (pp.1193–1202). New York, NY: Wiley-Liss.

[7] J. A. Langlois and R. W. Sattin. (2005). Traumatic brain injury in the United States: research and programs of the Centers for Disease Control and Prevention (CDC). *The Journal of Head Trauma Rehabilitation, 20*(3), 187–188. DOI: 10.1097/00001199-200505000-00001

[8] M. J. Haydel, C. A. Preston, T. J. Mills, S. Luber, E. Blaudeau, and P. M. DeBlieux. (2000). Indications for computed tomography in patients with minor head injury. *The New England Journal of Medicine, 343*(2), 100–105.

[9] I. G. Stiell, C. M. Clement, B. H. Rowe, M. J. Schull, R. Brison, D. Cass, …G. A. Wells. (2005). Comparison of the Canadian CT Head Rule and the New Orleans Criteria in patients with minor head injury. *JAMA, 294*(12), 1511–1518. DOI: 10.1001/jama.294.12.1511

[10] M. Smits, D. W. Dippel, G. G. de Haan, H. M. Dekker, P. E. Vos, D. R. Kool, …M. G. Hunink.(2005). External validation of the Canadian CT Head Rule and the New Orleans Criteria for CT scanning in patients with minor head injury. *JAMA, 294*(12), 1519–1525.

[11] L. R. Mack, S. B. Chan, J. C. Silva, and T. M. Hogan. (2003). The use of head computed tomography in elderly patients sustaining minor head trauma. *The Journal of Emergency Medicine, 24*(2), 157–162. DOI: 10.1016/s0736-4679(02)00714-x

[12] A. S. Jagoda, J. J. Bazarian, J. Jr. Bruns, S. V. Cantrill, A. D. Gean, P. K. Howard, …R. R. Whitson. (2008). Clinical policy: neuroimaging and decisionmaking in adult mild brain injury in the acute setting. *Annals of Emergency Medicine, 52*(6), 714–748.

[13] A. Pluta, K. Gutkowski, and M. Hartleb. (2010). Coagulopathy in liver diseases. *Advances in Medical Science, 55*(1), 16 –21.

[14] National Health Insurance Administration, Ministry of Health and Welfare, Taiwan, R.O.C. (2014). *2014-2015 National Health Insurance Annual Report*. Retrieved from: https://www.nhi.gov.tw/Resource/webdata/28140_1_National%20Health%20Insurance%20in%20Taiwan%202014-2015%20(bilingual).pdf

[15] A. Tripodi and P. M. Mannucci. (2011). The coagulopathy of chronic liver disease. *The New England Journal of Medicine, 365*(2), 147–156. DOI: 10.1056/NEJMra1011170

[16] A. Tripodi, M. Primignani, V. Chantarangkul, A. Dell'Era, M. Clerici, R. de Franchis, M. Colombo, and P. M. Mannucci. (2009). An imbalance of pro– vs anti–coagulation factors in plasma from patients with cirrhosis. *Gastroenterology, 137*(6), 2105–2111.

[17] A. Tripodi, M. Primignani, L. Lemma, V. Chantarangkul, A. Dell'Era, F. Iannuzzi, A. Aghemo, and P. M. Mannucci. (2010). Detection of the imbalance of procoagulant versus anticoagulant factors in cirrhosis by a simple laboratory method. *Hepatology, 52*(1), 249–255.

[18] T. Saleh, F. Matta, F. Alali, and P. D. Stein. (2011). Venous thromboembolism with chronic liver disease. *The American Journal of Medicine, 124*(1), 64–68.

[19] T. Lisman, K. Bakhtiari, I. T. Pereboom, H. G. Hendriks, J. C. Meijers, and R. J. Porte. (2010). Normal to increased thrombin generation in patients undergoing liver transplantation despite prolonged conventional coagulation tests. *Journal of Hepatology, 52*(3), 355–361.

[20] A. Gatt, A. Riddell, V. Calvaruso, E. G. Tuddenham, M. Makris, and A. K. Burroughs. (2010).

Enhanced thrombin generation in patients with cirrhosis–induced coagulopathy. *Journal of Thrombosis and Haemostasis, 8*(9), 1994–2000.

[21] B. Delahousse, V. Labat–Debelleix, L. Decalonne, L. d'Alteroche, J. M. Perarnau, and Y. Gruel. (2010). Comparative study of coagulation and thrombin generation in the portal and jugular plasma of patients with cirrhosis. *Thrombosis and Haemostasis, 104*(4), 741–749.

[22] J. L. Kujovich. (2015). Coagulopathy in liver disease: a balancing act. *Hematology, ASH Education Program, 2015*(1), 243–249.

[23] N. M. Intagliata, J. P. E. Davis, and S. H. Caldwell. (2018). Coagulation pathways, hemostasis, and thrombosis in liver failure. *Seminars in Respiratory and Critical Care Medicine, 39*(5), 598–608.

[24] S. H. Caldwell, M. Hoffman, T. Lisman, B. K. Macik, P. G. Northup, K. R. Reddy, … A. J. Sanyal. (2006). Coagulation disorders and hemostasis in liver disease: pathophysiology and critical assessment of current management. *Hepatology, 44*(4), 1039–1046.

[25] G. Garcia–Tsao and J. Bosch. (2010). Management of varices and variceal hemorrhage in cirrhosis. *The New England Journal of Medicine, 362*(9), 823–32. [Erratum, *The New England Journal of Medicine, 364*, 490.]

[26] P. Montalto, J. Vlachogiannakos, D. J. Cox, S. Pastacaldi, D. Patch, and A. K. Burroughs. (2002). Bacterial infection in cirrhosis impairs coagulation by a heparin effect: a prospective study. *Journal of Hepatology, 37*(4), 463–470.

[27] R. de Franchis. (2010). Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *Journal of Hepatology, 53*(4), 762–768. DOI: 10.1016/j.jhep.2010.06.004

[28] M. Noris and G. Remuzzi. (1999). Uremic bleeding: closing the circle after 30 years of controversies? *Blood, 94*(8), 2569–2574.

[29] B. Terjung, I. Lemnitzer, F. L. Dumoulin, W. Effenberger, H. H. Brackmann, T. Sauerbruch, and U. Spengler. (2003). Bleeding complications after percutaneous liver biopsy: an analysis of risk factors. *Digestion, 67*(3), 138–145.

[30] J. B. Segal and W. H. Dzik. (2005). Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence–based review. *Transfusion, 45*(9), 1413–1425.

[31] A. L. Boks, E. J. Brommer, S. W. Schalm, and H. H. van Vliet. (1986). Hemostasis and fibrinolysis in severe liver failure and their relation to hemorrhage. *Hepatology, 6*(1), 79–86.

[32] E. C. Vieira da Rocha, E. A. D'Amico, S. H. Caldwell, T. R. Flores da Rocha, C. S. Soares E Silva, V. Dos Santos Bomfim, …A. Q. Farias.(2009). A prospective study of conventional and expanded coagulation indices in predicting ulcer bleeding after variceal band ligation. *Clinical Gastroenterology and Hepatology, 7*(9), 988–993. DOI: 10.1016/j.cgh.2009.04.019

[33] H. Grønbaek, S. P. Johnsen, P. Jepsen, M. Gislum, H. Vilstrup, U. Tage–Jensen, and H. T. Sørensen. (2008). Liver cirrhosis, other liver diseases, and risk of hospitalisation for intracerebral haemorrhage: a Danish population–based case–control study. *BMC Gastroenterology, 8*, 16. DOI:10.1186/1471-230X-8-16

[34] C. H. Lai, P. Y. Cheng, and Y. Y. Chen. (2011). Liver cirrhosis and risk of intracerebral hemorrhage: a 9–year follow–up study. *Stroke, 42*(9), 2615–2617.