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Original Article

The emergent neurosurgical outcome of spontaneous intracranial hemorrhage in patients with chronic liver disease

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Abstract

Objectives: The influence of chronic liver disease (CLD) on emergent neurosurgical outcomes in patients with spontaneous intracerebral hemorrhage (ICH) remains unclear. CLD is usually associated with coagulopathy and thrombocytopenia, which contribute to a high rebleeding rate and poor prognosis after surgery. This study aimed to confirm the outcomes of spontaneous intracranial hemorrhage in patients with CLD after emergent neurosurgery. **Materials and Methods:** We reviewed the medical records of all patients with spontaneous ICH from February 2017 to February 2018 at the Buddhist Tzu Chi Hospital, Hualien, Taiwan. This study was approved by the Review Ethical Committee/Institutional Board Review of Hualien Buddhist Tzu Chi Hospital (IRB111-051-B). Patients with aneurysmal subarachnoid hemorrhage, tumors, arteriovenous malformations, and those younger than 18 years were excluded. Duplicate electrode medical records were also removed. **Results:** Among the 117 enrolled patients, 29 had CLD and 88 did not. There were no significant differences in essential characteristics, comorbidities, biochemical profile, Glasgow coma scale (GCS) score at admission, or ICH sites. The length of hospital stay (LOS) and length of intensive care unit stay (LOICUS) are significantly longer in the CLD group (LOS: 20.8 vs. 13.5 days, $P = 0.012$; LOICUS: 11 vs. 5 days, $P = 0.007$). There was no significant difference in the mortality rate between the groups (31.8% vs. 28.4%, $P = 0.655$). The Wilcoxon rank-sum test for liver and coagulation profiles between survivors and the deceased revealed significant differences in the international normalized ratio ($P = 0.02$), including low platelet counts ($P = 0.03$) between survivors and the deceased. A multivariate analysis of mortality found that every 1 mL increase in ICH at admission increased the mortality rate by 3.9%, and every reduction in GCS at admission increased the mortality rate by 30.7%. In our subgroup analysis, we found that the length of ICU stay and LOS are significantly longer in patients with CLD who underwent emergent neurosurgery: 17.7 ± 9.9 days versus 7.59 ± 6.68 days, $P = 0.002$, and 27.1 ± 7.3 days versus 16.36 ± 9.08 days, $P = 0.003$, respectively. **Conclusions:** From our study's perspective, emergent neurosurgery is encouraged. However, there were more prolonged ICU and hospital stays. The mortality rate of patients with CLD who underwent emergent neurosurgery was not higher than that of patients without CLD.

Keywords: *Chronic liver disease, Emergent neurosurgery, Intracranial hemorrhage*

Introduction

Spontaneous intracranial hemorrhage (ICH) accounts for approximately one-fifth of all types of stroke and is a major global health problem with different expressions worldwide but with a significant impact in different countries [1,2]. Evidence has shown that the presence of coagulopathy resulting from chronic liver diseases (CLDs), such as liver cirrhosis, alcoholic liver disease, and viral hepatitis, could theoretically predispose to bleeding and precipitate the severity of ICH [3-5]. Extensive lobar hemorrhages or hematomas may lead to life-threatening cerebral or brainstem herniation, which may require life-saving emergency surgical evacuation [6]. CLDs are well-documented as the primary mortality factors for trauma, laparotomy, and cardiothoracic surgery [7]; however, there is

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a lack of studies on the outcomes of emergent neurosurgical procedures. One retrospective study by Chen *et al*. found that patients with liver cirrhosis had rebleeding and mortality rates as high as 63.2% after emergent neurosurgery for traumatic brain injury [8]. However, a study of a population suffering from spontaneous ICH who underwent emergent neurosurgical procedures remains desired. Hence, our study focused on the emergent neurosurgical outcomes of spontaneous intracranial hemorrhage in patients with CLD to fill this knowledge gap.

Materials and Methods

We reviewed the medical records of all patients with spontaneous ICH from February 2017 to February 2018 at the Buddhist Tzu Chi Hospital, Hualien, Taiwan. This study was approved by the Review Ethical Committee/Institutional Board Review of Hualien Buddhist Tzu Chi Hospital (IRB111-051-B). Patients with aneurysmal subarachnoid hemorrhage, tumors, arteriovenous malformations, and those younger than 18 years were excluded. We collected a database on each patient's characteristics, including age, sex, biochemistry profile including aspartate aminotransferase, alanine aminotransferase (ALT), creatinine, bilirubin, albumin, prothrombin time, international normalized ratio (INR), platelet count, hepatitis B virus, and hepatitis C virus (HCV). The Glasgow coma scale (GCS) was used to evaluate neurological status and severity on admission. The ICH site was classified, and once ICH involved more than two regions, the location was determined as the location where the hematoma was largest on computed tomography. ICH volume was calculated based on the first CT scan using the following formula: volume = $(A \times B \times C)/2$ (cm^3). A is the maximum diameter in centimeters, and B is another maximum diameter 90° angle to A in centimeters. C is the total number of 2.5-mm axial slices. The primary outcomes of this study were overall mortality and length of intensive care unit stay (LOICUS). The secondary outcomes were the length of hospital stay (LOS) and hematoma volume. Student's *t*-test is used for the analysis of independent continuous variables and Chi-square test is used for the analysis of independent categorical variables. Wilcoxon rank-sum test is used for nonparametric statistics. All statistical calculations were performed using SPSS version 25.0, and statistical significance was set at $P < 0.05$.

Results

Essential demographic characteristics [Table 1] among the 117 enrolled patients included the following: 29 patients had CLD and 88 patients did not and 96% of the CLD cases were diagnosed with hepatic viruses, 62% with hepatitis B, 24% with hepatitis C, and 10% with both. There were no significant differences in the baseline characteristics, comorbidities, coagulation profile at admission, or liver profile at admission. The most common ICH site was the putamen, followed by the thalamus, subcortex, and cerebellum, similar to CLD and non-CLD (P = 0.388). In addition, there was no statistically significant difference in the GCS score under 12 (P = 0.68), and the ICH volume in the CLD group was calculated as 28.64 ± 25.81 mL, compared with

Table 1: Essential demographic characteristics (*n*=117)

	CLD (*n*=29)	Non-CLD (*n*=88)	*P*
Age, medium (Q1-Q3)	63 (47-79)	65 (41-79)	0.688
Sex, male (%)	14 (48.3)	50 (56.8)	0.423
Comorbidity (%)			
Hypertension	20 (69.0)	51 (57.6)	0.292
Diabetes mellitus	4 (13.8)	27 (30.7)	0.074
HBV	18 (62.0)	0 (0.0)	-
HCV	7 (24.0)	0 (0.0)	-
HBV + HCV	3 (10.0)	0 (0.0)	-
Other liver disease	1 (4.0)	0 (0.0)	-
GCS <12 at admission (%)	17 (58.6)	40 (45.6)	0.68
Coagulation profile at admission			
Platelet count (10^3)	201±15.4	197±8.9	0.83
PT (s)	14.2±1.90	11.6±0.46	0.072
INR	1.36±0.17	1.43±0.32	0.795
Liver profile at admission			
AST, units/L	61.2±22.8	43.6±5.58	0.292
ALT, units/L	31.1±4.79	45.4±9.91	0.416
Total bilirubin, mg/dL	1.28±0.24	1.23±0.27	0.924
ICH volume at admission (mL)	28.64±25.81	23.05±21.11	0.478
ICH site (%)			
Putamen	11 (29.3)	26 (29.5)	0.388
Thalamus	6 (20.7)	13 (14.8)	
Subcortex	4 (13.8)	35 (39.8)	
Cerebellum	0 (0.0)	7 (8.0)	
Brainstem	4 (13.8)	5 (5.7)	
Intraventricular	4 (13.8)	2 (2.2)	
Length of ICU stay (day)	11	5	0.007**
Length of hospital stay (day)	20.8	13.5	0.012**
Mortality (%)	7 (31.8)	25 (28.4)	0.655

**P<0.05 is considered statistically significant. ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CLD: Chronic liver disease, HBV: Hepatitis B virus, HCV: Hepatitis C virus, ICH: Intracranial hemorrhage, ICU: Intensive care unit, PT, Prothrombin time

the non-CLD group calculated at 23.05 ± 21.11 mL, which was not statistically different (P = 0.478). Nevertheless, the LOS and LOICUS were significantly longer in the CLD group (LOS: 20.8 vs. 13.5 days, P = 0.012; LOICUS: 11 vs. 5 days, P = 0.007). There was no significant difference in the mortality rate between the groups (31.8% vs. 28.4%, P = 0.655). In search of predictors for mortality, we performed the Wilcoxon rank-sum test for the liver profile of ALT, coagulation profile of platelet counts, and INR between survival and death [Table 2] and logistic regression for age, sex, hypertension, diabetes mellitus, ICH volume at admission, and GCS at admission [Table 3]. We noted significant differences in the INR (P = 0.02) and low platelet counts (P = 0.03) between survivors and the deceased. Multivariate analysis of mortality found that every 1 mL increase in ICH at admission increased the mortality rate by 3.9%, and every reduction in GCS at admission increased the mortality rate by 30.7%.

In our subgroup analysis of patients who underwent emergent neurosurgery [Table 4], we found that the length of ICU stay and LOS are significantly longer in patients with CLD who underwent emergent neurosurgery: 17.7 ± 9.9 days versus 7.59 ± 6.68 days, P = 0.002, and 27.1 ± 7.3 days versus 16.36 ± 9.08 days, P = 0.003, respectively. There was no significant difference between mortality rates; however, mortality rates in patients with CLD were three times lower than those in patients without CLD (10% vs. 36.2%, P = 0.132).

Discussion

Spontaneous ICH is life-threatening and sometimes overlooked due to the similarities of neurological deficits caused by hepatic encephalopathy [9]. Most cirrhotic patients who developed spontaneous ICH were sent to the emergency room for resuscitation and admitted to the neurosurgery wards for surgical intervention [7].

Neurosurgeons intuitively believe that patients with a history of CLD have a high risk of bleeding, which may be attributed to decreased platelet count and function, decreased levels of clotting factors, fibrinogen abnormality, and Vitamin K deficiency [8,10,11]. The most significant concern for emergent neurosurgery is whether the procedure causes secondary hemorrhage and worsens the patient's outcome than nonperformance of the procedure [12]. Our preliminary study showed consistent results in that there were statistically significant differences in the INR (P = 0.02) and low platelet counts (P = 0.03) between survivors and deceased patients, which indicates that increasing values at admission correlate with higher mortality rates. Accordingly, platelet, Vitamin K, and fresh-frozen plasma transfusions are advised to decrease the risk of coagulopathy before surgery [13,14]. We hope that preoperative prophylactic management can reduce surgical complications and postoperative re-bleeding rates.

Table 2: Biochemistry profile between survivors and the deceased

	Survivor (n=86)	Deceased (n=31)	P
ALT (Q1-Q3)	24.5 (15-51.25)	20 (13.5-40)	0.42
Platelet count (Q1-Q3)	192.5 (154.5-239.25)	199 (151.5-236)	0.03**
INR (Q1-Q3)	1.01 (0.98-1.05)	1.03 (0.98-1.11)	0.01**

**P<0.05 is considered statistically significant. Wilcoxon rank-sum test is used for nonparametric statistics. ALT: Alanine aminotransferase, INR: International normalized ratio

Table 3: Logistic regression for prediction of mortality

	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Age	0.997 (0.966-1.029)	0.834	0.969 (0.925-1.015)	0.183
Sex, male	0.813 (0.322-2.05)	0.661	0.548 (0.144-2.085)	0.553
HTN	1.375 (0.512-3.691)	0.527	1.249 (0.341-4.569)	0.742
DM	1.899 (0.658-5.483)	0.236	1.337 (0.328-5.446)	0.692
ICH volume at admission	1.035 (1.012-1.059)	0.003**	1.039 (1.014-1.065)	0.002**
GCS at admission	0.709 (0.612-0.822)	<0.001**	0.693 (0.567-0.847)	<0.001**

**P<0.05 is considered statistically significant. CI: Confidence interval, DM: Diabetes mellitus, GCS: Glasgow coma scale, HTN: Hypertension, ICH: Intracranial hemorrhage, OR: Odds ratio

Table 4: Patients underwent emergent neurosurgery (n=32)

	CLD (n=10)	Non-CLD (n=22)	P
GCS on admission	10.6±3.77	9.59±4.40	0.536
Volume of ICH (mL)	39.43±32.17	27.36±18.59	0.295
Length of ICU stay (day)	17.7±9.9	7.59±6.68	0.002**
Length of hospital stay (day)	27.1±7.3	16.36±9.08	0.003**
Mortality (%)	10	36.3	0.132

**P<0.05 is considered statistically significant. CLD: Chronic liver disease, GCS: Glasgow coma scale, ICH: Intracranial hemorrhage, ICU: Intensive care unit

Patients with CLD have a longer ICU stay and length of hospital stay, regardless of whether they undergo emergent neurosurgery. In our hospital's experience and published literature, difficulty in ventilator weaning and ventilator-associated pneumonia are reasons for extended intensive care unit stay [15]. Moreover, patients with alcoholic liver disease may have longer hospital stays because of alcohol withdrawal syndrome [16]. Previous studies [Table 5] reported a high mortality rate in patients with CLD who underwent emergent neurosurgical procedures [7,8,11]. Our study focuses on patients without a history of cancer, showing the least mortality rate. Moreover, we believe that we are the first study to compare the outcome of patients with and without the CLD who underwent emergent neurosurgery. There was no significant difference in the volume of ICH and GCS scores at admission and the overall mortality rate between patients with and without CLD. However, multivariate analysis of mortality found that every 1 mL increase in ICH at admission increased the mortality rate by 3.9%, and every reduction of GCS at admission increased the mortality rate by 30.7%. Paradoxically, in our subgroup analysis, we found that the mortality rate of patients with CLD who underwent emergency neurosurgery was three times lower than that of patients without CLD. Although there was no statistically significant difference, it may encourage neurosurgeons not to hesitate in the decision-making of life-saving neurosurgical procedures for patients with CLD.

Limitation

This was a single-center study. We retrospectively collected information from electronic medical records. Hence, the study might underestimate the number of patients with CLD due to errors in ICD codes or misdiagnosis. In addition, our study was limited by the annual records and number of patients of interest.

Conclusion

From our study's perspective, emergent neurosurgery is encouraged. However, there were more prolonged ICU and hospital stays. The mortality rate of patients with CLD who underwent emergent neurosurgery was not higher than that of the patients without CLD.

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Conflicts of interest

There are no conflicts of interest.

Table 5: Comparison of mortality rate with literature of emergent neurosurgery

Author	Year	Patients (*n*)	Reason for surgery	Etiology of CLD	Mortality rate (%)
Huang *et al*. [11]	2008	36	SICH	Viral hepatitis alcoholic cirrhosis HCC	47
Chen *et al*. [8]	2012	44	SICH	Viral hepatitis alcoholic cirrhosis HCC	22.7
Chang *et al*. (This study)	2022	32	SICH	Viral hepatitis alcoholic cirrhosis	10

CLD: Chronic liver disease, HCC: Hepatocellular carcinoma, SICH: Spontaneous intracranial hemorrhage

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