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# Risk of Cerebral Aneurysm Rupture After Liver Transplantation: Development and Validation of a Hemorrhagic Stroke Scoring Model

Minwoo Kim ,<sup>1</sup> Jae Hyun Kim ,<sup>1</sup> Wonhyoung Park ,<sup>1</sup> Jung Cheol Park ,<sup>1</sup> Jae Sung Ahn ,<sup>1</sup> Byung Duk Kwun ,<sup>1</sup> Sung-Gyu Lee ,<sup>2</sup> Shin Hwang ,<sup>2</sup> Moinay Kim ,<sup>1</sup> and Seungjoo Lee <sup>1</sup>

<sup>1</sup>Department of Neurosurgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

<sup>2</sup>Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Asan Medical Centre, University of Ulsan College of Medicine, Seoul, Korea

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Address for Correspondence:

Seungjoo Lee, MD, PhD

Department of Neurosurgery, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.  
Email: changhill@gmail.com

Moinay Kim, MD, PhD

Department of Neurosurgery, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.  
Email: aussie84@naver.com

\*Minwoo Kim and Moinay Kim contributed equally as first authors

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ORCID iDs

Minwoo Kim

<https://orcid.org/0000-0001-7980-9870>

Jae Hyun Kim

<https://orcid.org/0000-0002-2278-8615>

## ABSTRACT






**Background:** Liver transplantation (LT) patients appear to be more prone to neurological events compared to individuals undergoing other types of solid-organ transplantation. The aims of the present study were to analyze the prevalence of unruptured intracranial aneurysms (UIAs) in patients undergoing liver transplantation (LT) and to examine the perioperative occurrence of subarachnoid hemorrhage (SAH). Also, it intended to systematically identify the risk factors of SAH and hemorrhagic stroke (HS) within a year after LT and to develop a scoring system which involves distinct clinical features of LT patients.

**Methods:** Patients who underwent LT from January 2012 to March 2022 were analyzed. All included patients underwent neurovascular imaging within 6 months before LT. We conducted an analysis of prevalence and radiological features of UIA and SAH. The clinical factors that may have an impact on HS within one year of LT were also reviewed.

**Results:** Total of 3,487 patients were enrolled in our study after applying inclusion and exclusion criteria. The prevalence of UIA was 5.4%. The incidence of SAH and HS within one year following LT was 0.5% and 1.6%, respectively. We developed a scoring system based on multivariable analysis to predict the HS within 1-year after LT. The variables were a poor admission mental status, the diagnosis of UIA, serum ammonia levels, and Model for End-stage Liver Disease (MELD) scores. Our model showed good discrimination among the development (C index, 0.727; 95% confidence interval [CI], 0.635–0.820) and validation (C index, 0.719; 95% CI, 0.598–0.801) cohorts.

**Conclusion:** The incidence of UIA and SAH was very low in LT patients. A poor admission mental status, diagnosis of UIA, serum ammonia levels, and MELD scores were significantly associated with the risk of HS within one year after LT. Our scoring system showed a good discrimination to predict the HS in LT patients.

**Keywords:** Aneurysm; Intracerebral Hemorrhage; Stroke; Subarachnoid Hemorrhage; Liver Transplantation; Scoring System

Wonhyoung Park   
<https://orcid.org/0000-0002-9977-0595>  
 Jung Cheol Park   
<https://orcid.org/0000-0001-6677-455X>  
 Jae Sung Ahn   
<https://orcid.org/0000-0002-6586-5668>  
 Byung Duk Kwun   
<https://orcid.org/0000-0001-7290-2087>  
 Sung-Gyu Lee   
<https://orcid.org/0000-0001-9161-3491>  
 Shin Hwang   
<https://orcid.org/0000-0002-9045-2531>  
 Moinay Kim   
<https://orcid.org/0000-0002-6443-7098>  
 Seungjoo Lee   
<https://orcid.org/0000-0003-0641-3917>

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### Disclosure

The authors have no potential conflicts of interest to disclose.

### Data Availability Statement

All relevant data generated or analyzed during this study are included in this article and its supplementary data. Further enquires can be directed to the corresponding author.

### Author Contributions

Conceptualization: Kim JH, Park W, Park JC, Ahn JS, Kwun BD, Lee SG, Hwang S, Kim M<sup>1</sup>, Lee S. Data curation: Kim M<sup>2</sup>, Kim JH, Park W, Park JC, Ahn JS, Kwun BD, Lee SG, Hwang S, Kim M<sup>1</sup>, Lee S. Formal analysis: Kim M<sup>2</sup>, Kim JH, Park W, Kim M<sup>1</sup>, Lee S. Funding acquisition: Kim M<sup>1</sup>, Lee S. Investigation: Kim M<sup>2</sup>, Hwang S, Kim M<sup>1</sup>, Lee S. Methodology: Kim M<sup>2</sup>, Kim M<sup>1</sup>, Lee S. Project administration: Kim M<sup>2</sup>, Kim M<sup>1</sup>. Resources: Kim M<sup>2</sup>, Kim M<sup>1</sup>. Software: Kim M<sup>2</sup>, Kim M<sup>1</sup>. Supervision: Kim M<sup>1</sup>. Validation: Kim M<sup>1</sup>. Visualization: Kim M<sup>1</sup>. Writing - original draft: Kim M<sup>1</sup>. Writing - review & editing: Park W, Park JC, Ahn JS, Kwun BD, Lee SG, Hwang S, Kim M<sup>1</sup>, Lee S.

Kim M<sup>1</sup>, Moinay Kim; Kim M<sup>2</sup>, Minwoo Kim.

## INTRODUCTION

Liver transplantation (LT) is the standard of care for acute and chronic end-stage liver disease,<sup>1</sup> representing a pivotal therapeutic approach in contemporary medical practice. With an ever-increasing number of patients undergoing transplantation<sup>2</sup> and remarkable improvements in early post-transplant survival rates,<sup>3</sup> the imperative of comprehensive and vigilant long-term management of transplant recipients has become apparent.

Following LT, patients may experience neurologic complications such as cerebral hemorrhage, infarct, encephalopathy, and other related conditions during the perioperative period.<sup>4,5</sup> These neurological events have been reported in a substantial proportion of LT recipients, with prevalence rates ranging from 15% to 71%.<sup>6,7</sup> Notably, LT patients appear to be more prone to neurological events compared to individuals undergoing other types of solid-organ transplantation.<sup>8</sup> The etiology of these neurologic complication is multifactorial and can be attributed, in part, to the fragile preoperative clinical condition of LT recipients. Factors such as malnutrition, coagulopathy, multi-organ dysfunction, and pre-LT encephalopathy contribute to the increased vulnerability of patients to post-LT neurologic issues.<sup>9</sup>

Patients undergoing LT surgery typically belong to the elderly demographic and often present with concurrent medical conditions, including hypertension, smoking history, and atherosclerosis,<sup>1</sup> all of which are well-established risk factors for the development of unruptured intracranial aneurysms (UIAs).<sup>10</sup> Additionally, these patients commonly exhibit endothelial cell dysfunction and systemic inflammatory responses,<sup>11</sup> which might significantly influence the growth and rupture potential of UIAs.<sup>12</sup> Moreover, perioperative hypertensive episodes and coagulopathy are frequent occurrences in LT surgery,<sup>13</sup> further heightening the likelihood of UIA occurrence and rupture in this specific patient population.

The management of patients with UIA during the perioperative period for LT poses a significant challenge. The specific characteristics of patients with end-stage liver disease (ESLD), such as reduced coagulation factors, compromised brain blood flow autoregulation, and heightened vascular inflammatory status, pose a formidable risk in combination with the inherent hemodynamic instability and potential for massive bleeding after LT.<sup>14,15</sup> Furthermore, during the postoperative period after LT, the restoration of normal pathophysiology, which may involve an elevation in blood pressure, can also contribute to an increased risk of aneurysm rupture.<sup>16</sup> Indeed, the occurrence of hemorrhagic stroke (HS) after LT is a matter of significant interest. The reported frequency of HS in this context ranges from 1% to 3%, with higher Model for End-stage Liver Disease (MELD) scores and a history of stroke identified as reported risk factors for this complication.<sup>17</sup> Nevertheless, despite these plausible associations, a comprehensive understanding of the actual prevalence and rupture risk of UIAs and HS in patients undergoing LT surgery remains elusive, with no existing studies to guide the optimal management of UIAs in this specific context. Despite the recognition of potential risks, the prevalence of UIA in LT recipients remains poorly defined. There is limited available data on the perioperative risk of subarachnoid hemorrhage (SAH) resulting from the rupture of UIA and the occurrence of HS in patients undergoing LT.

Therefore, our objective was to investigate the prevalence of UIAs in patients undergoing LT to examine the perioperative occurrence of SAH. Also, we intended to systematically identify the risk factors of SAH and HS within a year after LT and to develop a scoring system which involves distinct clinical features of LT patients that is also simple, precise and readily

adoptable in most institutions. Furthermore, we investigated data of LT patients to validate our scoring system from different cohorts to examine its generalizability and reliability.

## METHODS

### Study design and participants

#### *Derivation cohorts*

The derivation cohort was retrospectively collected from a tertiary medical center, Asan Medical Center (AMC), in Seoul, Korea. Data of recipients who underwent LT from January 2012 to March 2020 were collected via a computerized data recording system (Asan Biomedical Research Program, Seoul, Korea). All included patients underwent neurovascular imaging within 6 months before LT, utilizing computed tomography angiography (CTA), magnetic resonance angiography (MRA), or digital subtraction angiography (DSA). The analysis of UIA prevalence encompassed patients meeting the inclusion criteria after applying the aforementioned exclusion criteria. Specifically, patients with saccular UIAs were identified for inclusion in the study, while those with dissecting aneurysms and fusiform aneurysms were excluded due to the distinct pathophysiological characteristics associated with these types of aneurysms.

#### *Validation cohorts*

We involved validation cohorts in our study to verify the compatibility and efficiency of our scoring system. Validation samples were retrospectively collected from the same institution as validation cohort between April 2020 and May 2022.

### Data collection and definitions

The related data were obtained from the medical records by a physician and trained research nurse. In this study, the following candidate factors were analyzed: 1) age; 2) sex; 3) comorbidities: hypertension and diabetes; 4) cause of liver cirrhosis (LC): viral, alcoholic, biliary, autoimmune, toxic; 5) diagnosis of hepatocellular carcinoma (HCC); 6) smoking; and 7) admission mental status.

### Unruptured intracranial aneurysm and other vascular malformations evaluation

In our institution, all patients underwent brain angiography as part of the routine preoperative evaluation before LT. The diagnosis of an UIA was made if intracranial saccular or broad-based aneurysms were diagnosed using CTA, MRA or DSA. In cases where multiple imaging modalities were employed, the results from DSA were prioritized, followed by CTA and MRA results. UIA characteristics were assessed through the examination of formal radiologic reports by our institution's board-certified neuroradiologists. The treatment decisions for UIAs were at the discretion of the attending neurovascular surgeon. However, patients who had previously undergone surgical treatment for UIA before LT were excluded from the study unless residual unruptured aneurysms were detected. In cases where patients had multiple aneurysms, the largest UIA size was utilized for the per-patient analysis.

The following characteristics of UIA were collected: size; locations (anterior cerebral artery, basilar artery, internal carotid artery, middle cerebral artery, posterior cerebral artery, vertebral artery, and posterior inferior cerebellar artery), multiple or complex (giant, pseudoaneurysm, dissecting, infectious) aneurysms. The rupture risk of UIA was evaluated using UCAS<sup>18</sup> and PHASES<sup>19</sup> scores. Modified Fisher grade<sup>20</sup> was used to evaluate the

distribution and pattern of SAH. Treatment modalities including clipping, coil embolization with or without stent for the aneurysm were also analyzed.

Vascular malformations such as arteriovenous malformation (AVM) and cavernous malformation (CM) are significant factors contributing to the development of HS. Additionally, previous report has emphasized that the prevalence of these vascular malformations is notably high among patients with liver cirrhosis LC.<sup>21</sup> Hence, we conducted an analysis of the prevalence of AVM and CM in liver LT patients to examine the likelihood of developing HS.

### Assessment and follow-up

The fundamental management of SAH and HS including blood pressure control, intracranial pressure monitoring and other relevant interventions, was conducted in accordance with established standard guidelines.<sup>22,23</sup> The primary objective of this study was to investigate the incidence of aneurysmal SAH occurring within one year following LT. In this context, aneurysmal SAH specifically referred to subarachnoid bleeding that was confirmed using radiological methods and attributed to the rupture of an aneurysm. Cases of SAH resulting from traumatic events, thrombocytopenia, or coagulopathy were excluded from the analysis. The secondary objective focused on HS observed at the one-year time point. HS encompassed a comprehensive category comprising intracerebral hemorrhage (ICH), intraventricular hemorrhage (IVH), SAH as well as non-traumatic subdural or epidural hematomas. The study cohort underwent continuous monitoring for a duration of one year.

### Statistical analysis

In analysis of categorical variables including underlying medical conditions and neurovascular status evaluation, statistical tests such as Pearson's  $\chi^2$  test and Fisher's exact test were performed. And these variables were represented in terms of percentages or frequencies. In addition, continuous variables including laboratory findings, were statistically analyzed based on their distribution patterns, performing either the independent Student's *t*-test or the Wilcoxon rank-sum test. For single independent variables, univariate logistic regression was utilized, while for multiple independent variables, multivariate logistic regression was utilized. This comprehensive analysis aimed to investigate the risk factors influencing HS following liver transplantation. Statistical analysis results were obtained using SPSS (version 29; IBM Corp., Armonk, NY, USA), SAS 9.4 (SAS Institute, Cary, NC, USA) and R software (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria, [www.R-project.org](http://www.R-project.org)) in association with packages 'rms' and 'pROC'. *P* value less than 0.05 was designed to suggest the statistical significance. The precision of the estimates was assessed with 95% confidence interval (CI).

### Optimization of scoring system

The establishment of a scoring system model for the prediction of HS occurrences in post LT patients was executed through an analysis of the development cohort. Within this cohort, candidate predictors were meticulously chosen from a comprehensive set of variables, employing a multivariable Cox-proportional hazards model with backward elimination. To address missing data points, a single imputation approach was employed, specifically utilizing the Markov chain Monte Carlo method. Subsequently, univariate and multivariate logistic regression analyses were conducted to evaluate the impact of individual or multiple variables, as well as their combined effects. These analyses aimed to elucidate the risk factors associated with HS incidents following LT in the developmental cohort of patients.

### Grading with the scoring system

The risk score was computed as the weighted sum of specific predictors, with the weights determined as the integer values resulting from dividing the regression coefficients by the coefficient associated with the reference predictor. Additionally, a constant value denoted as 'B' (with a value of 0.481) was introduced, signifying the incremental effect size per 10 points increase in the MELD score.

The estimation of the 1-year risk of HS event was computed using the Cox regression equation as follows:  $\text{Risk Estimate} = 1 - S_0(1)^{\exp(B \times \text{Risk Score})}$ . Here, ' $S_0(1)$ ' represents the baseline survival function at 1 year, which has a value of 0.995. This value corresponds to the probability of being free from a HS event when all covariates are set to their reference values. The 'B' in the equation stands for the constant value mentioned earlier, specifically 0.481, and the 'Risk Score' signifies the weighted sum of predictors based on the model's coefficients. The equation provides an estimate of the risk of experiencing a HS event within 1 year for a given set of predictor values.

### Validation of the scoring system

To validate the proportional hazards assumption, we conducted Schoenfeld residual testing. Additionally, we utilized log-minus-log survival plots for visual inspection, aiming to identify any deviations from this assumption. The discrimination capability of the risk score was evaluated using the Harrell C-index and the area under the time-dependent receiver operating characteristic (AUROC) curve specifically at the 1-year mark. To assess the calibration performance of the risk score, we employed calibration curves. These curves allow us to compare the predicted values with the observed estimates at the 1-year time point. To ensure the robustness of our findings, we also conducted these discrimination and calibration assessments in a separate validation set, providing validation for the model's performance.

### Ethics statement

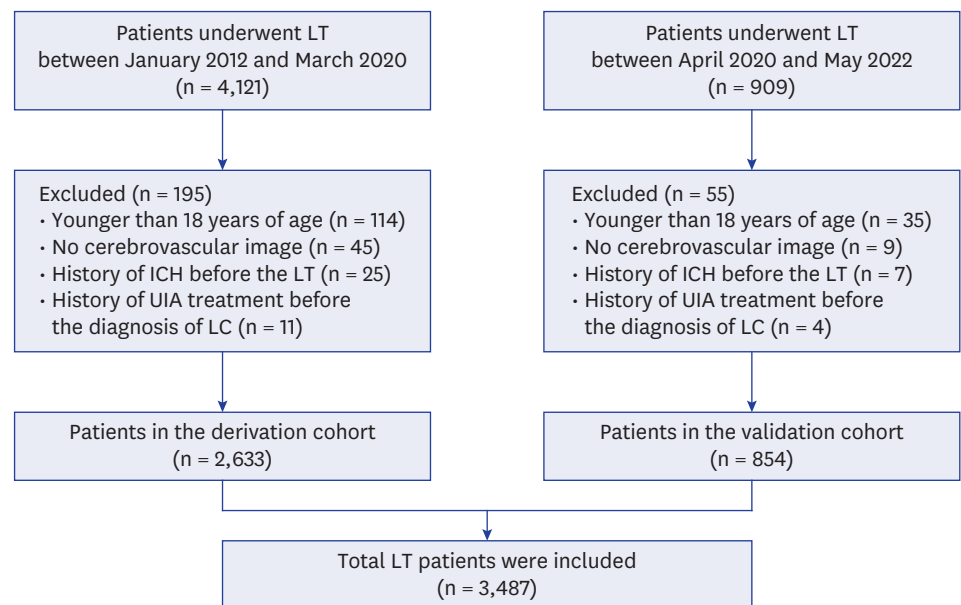
This study protocol was reviewed and approved by Institutional Review Board (IRB) of Asan Medical Center, Korea (Approval number: 2021-0261) and patient consent was waived by the board. The data supporting the findings of this study are available from the corresponding author upon reasonable request.

## RESULTS

### Characteristics of study patients

We screened 5,030 LT patients who admitted to our institution between January 2012 and May 2022. Patients younger than 18 years of age ( $n = 149$ ), no cerebrovascular radiological images obtained ( $n = 54$ ) and those with preoperative intracranial hemorrhage detected during the preoperative evaluation ( $n = 32$ ) were excluded from the study. In the risk analysis for SAH, individuals with UIAs identified at the time of LT were included in the study. However, patients who had undergone pre-LT treatment for UIA ( $n = 15$ ) were excluded from the analysis. On the other hand, patients with residual aneurysms following previous treatment for UIA ( $n = 5$ ) were included in the study population. Finally, 3,487 patients were enrolled in our study after applying inclusion and exclusion criteria, including 2,633 patients from the development cohort and 854 patients from the validation cohort (Fig. 1).





**Fig. 1.** Enrollment and follow-up for study patients.

LT = liver transplantation, ICH = intracerebral hemorrhage, UIA = unruptured intracranial aneurysm, LC = liver cirrhosis.

The mean age for development and validation groups were  $54.23 \pm 8.48$  and  $55.39 \pm 10.09$  years, respectively. The male gender predominated in both groups (73.11% vs. 69.2%). Comorbidities such hypertension (81.62% vs. 78.1%) and diabetes (74.67% vs. 69.91%) were prevalent in both study groups. Viral cirrhosis (62.93% vs. 49.2%) emerged as the predominant etiological factor for LC in both cohorts, followed by alcoholic cirrhosis (22.8% vs. 29%). Roughly half of the patients in both groups received a diagnosis of HCC (50.1% vs. 54.2%). The majority of patients presented with alertness upon admission (93.4% vs. 90.9%). The results are summarized in **Table 1**.

### Characteristics of UIA and vascular malformations

In our study, a total of 190 intracranial aneurysms were diagnosed. The development cohort included 138 UIAs and 1 ruptured case, while the validation cohort consisted of 51 UIAs. Multiple UIAs were observed in 18 patients (12.9%) in the development and 7 patients (13.7%) in the validation cohort. The internal carotid artery was the most common location for aneurysms in both cohorts. The majority of patients in both groups did not require treatment before LT (95.7% vs. 98%). In the development cohort, 6 patients underwent treatment for UIAs before LT, whereas only 1 patient did so in the validation cohort. The prevalence of AVM or CM was 12 (8.6%) and 7 (13.7%) in the development and validation cohorts, respectively (**Table 2**).

### Primary and secondary outcomes

In our study cohort, within 1 year following LT, only 1 patient experienced an aneurysmal rupture leading to SAH, representing an incidence of 0.5% (1/190) in terms of proportions. This patient underwent coil embolization with a stent for the treatment of the ruptured aneurysm (**Supplementary Fig. 1**). Furthermore, the incidence of HS within one-year post-LT was determined to be 1.6% (55/3,487). Among these cases, ICH or IVH were identified as the predominant causative factors for HS (**Supplementary Table 1**).

**Table 1.** Patient characteristics

Characteristics	Development (n = 2,633, 75.5)	Validation (n = 854, 24.5)	Total (N = 3,487)
Age, yr	54.23 ± 8.48	55.39 ± 10.09	54.52 ± 8.91
Sex (male)	1,925 (73.1)	591 (69.2)	2,516
Comorbidity			
Hypertension	2,149 (81.6)	667 (78.1)	2,816
Diabetes	1,966 (74.7)	597 (69.9)	2,563
Smoking	213 (8.1)	89 (10.4)	302
BMI, kg/m <sup>2</sup>	23.80 ± 3.50	23.87 ± 3.81	23.81 ± 3.58
Etiology of cirrhosis			
Viral cirrhosis	1,657 (62.9)	420 (49.2)	2,077
Alcoholic	600 (22.8)	248 (29)	848
Biliary	12 (0.5)	3 (0.4)	15
Autoimmune	92 (3.5)	55 (6.4)	147
Toxic	46 (1.7)	10 (1.2)	56
Other	226 (8.6)	118 (13.8)	344
HCC	1,320 (50.1)	463 (54.2)	1,783
Admission mental status			
Alert	2,459 (93.4)	776 (90.9)	3,235
Drowsy	73 (2.8)	22 (2.6)	95
Stupor	66 (2.5)	30 (3.5)	96
Unresponsive	35 (1.3)	26 (3)	61
Admission laboratory tests			
Platelet, $\mu$ L	76.53 ± 49.99	79.94 ± 56.20	77.36 ± 51.59
aPTT, sec	36.72 ± 17.93	36.06 ± 15.80	36.56 ± 17.43
PT, INR	1.87 ± 4.92	1.60 ± 2.09	1.80 ± 4.40
AST, U/L	81.43 ± 503.91	65.64 ± 199.50	77.56 ± 448.89
ALT, U/L	58.50 ± 350.80	44.05 ± 209.45	54.96 ± 322.00
CRP, mg/dL	0.79 ± 3.09	1.09 ± 2.37	0.86 ± 2.93
Sodium, mEq/L	138.43 ± 5.18	137.80 ± 4.89	138.28 ± 5.11
Bilirubin, mg/dL	16.79 ± 12.32	20.59 ± 16.756	17.72 ± 13.64
Albumin, g/dL	3.14 ± 0.57	3.09 ± 0.61	3.13 ± 0.58
Ammonia pre-LT, $\mu$ /dL	24.89 ± 25.97	54.38 ± 34.97	32.11 ± 31.13
Ammonia post-LT, $\mu$ /dL	18.08 ± 10.22	27.74 ± 12.50	20.45 ± 11.59
MELD score	14.99 ± 8.32	16.45 ± 9.95	15.35 ± 8.77
MELD-Na score	16.24 ± 8.70	17.78 ± 10.02	16.62 ± 9.07
CTP score	8.01 ± 2.30	8.35 ± 2.54	8.09 ± 2.37

Values are presented as mean ± standard deviation or number (%).

BMI = body mass index, HCC = hepatocellular carcinoma, aPTT = activated partial thromboplastin time, PT = prothrombin time, INR = international normalized ratio, AST = aspartate aminotransferase, ALT = alanine aminotransferase, CRP = c-reactive protein, MELD = Model for End-stage Liver Disease, CTP = child-Turcotte-Pugh.

### Development of a scoring model

We conducted an analysis of multiple factors to identify the clinical variables that have an impact on HS in post-LT patients. The independent risk factors from the multivariate analyses were scaled for the hazard ratio using the relative weighting method to evaluate the risk of HS. In the multivariate analysis, a poor admission mental status (i.e., stupor or unresponsiveness), pre-operative diagnosis of UIA or vascular malformation (AVM or CM), MELD score, and serum ammonia levels exhibited significant associations with HS within one year after LT (**Table 3**). These four variables were then incorporated into a clinical prediction tool with associated point values, as the estimate value for alert or drowsiness on the admission was converted to 0 as reference value, and other worst mental status was assigned 2 points. The diagnosis of UIA or vascular malformations prior to LT was assigned 2 points and 0 if absent. MELD score of 1–15 was assigned 0 point, whereas score 16–30 and greater or equal to 31 were assigned as 1 and 2 points, respectively. Serum ammonia levels lower or equal to 35 was assigned as 0 point and greater than 35 was assigned as 1 point.

**Table 2.** Characteristics of intracranial aneurysms

Characteristics of intracranial aneurysm	Development (n = 139)	Validation (n = 51)	Total (N = 190)
Multiple <sup>a</sup>	18 (12.9)	7 (13.7)	25 (13.2)
Complex			
Giant	0 (0.0)	0 (0.0)	0 (0.0)
Pseudoaneurysm	0 (0.0)	0 (0.0)	0 (0.0)
Dissecting	1 (0.7)	0 (0.0)	1 (0.5)
Infectious	0 (0.0)	0 (0.0)	0 (0.0)
Location <sup>b</sup>			
Anterior cerebral artery	29 (20.9)	11 (21.6)	40 (21.1)
Basilar artery	7 (5.0)	0 (0.0)	7 (3.7)
Internal carotid artery <sup>c</sup>	65 (46.8)	28 (54.9)	105 (55.3)
Posterior cerebral artery	18 (12.9)	5 (9.8)	23 (12.1)
Middle cerebral artery	28 (20.1)	11 (21.6)	43 (22.6)
Vertebral artery or posterior inferior cerebellar artery	3 (2.2)	0 (0.0)	3 (1.6)
Treatment prior to LT			
No	133 (95.7)	50 (98.0)	183 (96.3)
Craniotomy and clipping	1 (0.7)	0 (0.0)	1 (0.5)
Coil embolization without stent	4 (2.9)	0 (0.0)	4 (2.1)
Coil embolization with stent	1 (0.7)	1 (2.0)	2 (1.1)
Rupture (i.e., causing SAH)			
Before LT	0 (0.0)	0 (0.0)	0 (0.0)
After LT	1 (0.7)	0 (0.0)	1 (0.5)
Vascular malformations (AVM or CM)	12 (8.6)	7 (13.7)	19 (10.0)

Values are presented as number (%).

LT = liver transplantation, SAH = subarachnoid hemorrhage, AVM = arteriovenous malformation, CM = cavernous malformation.

<sup>a</sup>Denotes more than two aneurysms.

<sup>b</sup>Multiple selections were available for multiple aneurysms.

<sup>c</sup>Involves clinoidal, ophthalmic or communicating segment origin aneurysm.

These scores were summed to determine the HS prediction score of outcome and hence the scoring system ranged from 0 to 7 (**Table 4**).

### Risk group stratification and estimates for HS

After development of the scoring system, we stratified into two risk group grades based on total scoring system: low risk, 0–2 points; and high risk, 3–7 points. According to our scoring system, estimates of HS increases as the total score increases; when the point was scored 0 and 2, the estimates of HS were 0.5%, 0.8%, and 1.3% respectively. When the point was 7, the estimates of HS was 13.6%. According to this risk group stratification, the development cohort of 2,633 cases was categorized as follows: 2,343 (89.0%) as low risk, and 290 (11.0%) as high risk. Generally, when the score was lower, the estimate of HS was low. Conversely, the estimates of HS were much higher when the score was high. Similar findings were observed in the validation cohort. (**Table 5**, **Supplementary Fig. 2**).

### Assessment of scoring system

To assess the performance of our scoring system, we adopted C-index to evaluate the model's discrimination and AUROC for the calibration of the model. Our model showed good discrimination among development (C index, 0.727; 95% CI, 0.635–0.820) and validation (C index, 0.719; 95% CI, 0.598–0.801) cohorts (**Table 6**). The AUROC curves of prediction for the scoring system in the development and validation cohorts are also illustrated (**Fig. 2**).



**Table 3.** Univariate and multivariate analyses associated with hemorrhagic stroke from the development cohort

Variables	Univariate analyses		Multivariate analyses		
	HR (95% CI)	P value	Estimate	HR (95% CI)	P value
Sex (female)	1.012 (0.490–2.090)	0.975			
Hypertension	0.871 (0.363–2.088)	0.757			
Diabetes	1.271 (0.628–2.572)	0.505			
BMI	0.924 (0.838–1.018)	0.110			
Etiology of cirrhosis					
Viral cirrhosis	1	0.325			
Alcoholic	2.198 (1.067–4.527)	0.033			
Biliary	Infinite	0.987			
Autoimmune	1.069 (0.142–8.032)	0.948			
Toxic	2.124 (0.283–15.959)	0.464			
Other	2.289 (0.844–6.207)	0.104			
HCC	0.425 (0.210–0.860)	0.017			
Smoking	1.355 (0.480–3.825)	0.566			
Mental status					0.046
Alert or drowsy	1			1	
Stupor or unresponsive	6.224 (2.733–14.175)	0.000	1.032	2.806 (1.020–7.718)	
Preop aneurysm (–)					
Preop aneurysm or vascular malformations (+)	3.303 (1.378–7.920)	0.007	1.271	3.563 (1.480–8.579)	0.005
Platelet	0.997 (0.989–1.004)	0.385			
aPTT	1.017 (1.009–1.025)	0.000			
PT, INR	0.999 (0.930–1.073)	0.978			
< 1.7	1	< 0.001			
1.7–2.3	2.804 (1.260–6.243)	0.012			
> 2.3	5.141 (2.372–11.139)	0.000			
AST	0.999 (0.995–1.003)	0.679			
ALT	0.997 (0.988–1.006)	0.482			
CRP	1.013 (0.949–1.0801)	0.703			
Sodium	0.973 (0.919–1.031)	0.354			
Ammonia pre-LT	1.010 (1.001–1.018)	0.025	0.006	1.006 (0.998–1.014)	0.122
Ammonia post-LT	1.008 (0.979–1.038)	0.597			
MELD score	1.066 (1.035–1.099)	0.000	0.048	1.049 (1.014–1.086)	0.006
1–15	1	< 0.001			
16–30	4.169 (2.051–8.473)	< 0.001			
≥ 31	3.170 (1.022–9.829)	0.046			
CTP score					
A 5–6	1	0.002			
B 7–9	2.837 (0.934–8.620)	0.066			
C 10–15	6.158 (2.095–18.104)	0.001			

HR = hazard ratio, CI = confidence interval, BMI = body mass index, HCC = hepatocellular carcinoma, aPTT = activated partial thromboplastin time, PT = prothrombin time, INR = international normalized ratio, AST = aspartate aminotransferase, ALT = alanine aminotransferase, CRP = C-reactive protein, LT = liver transplantation, MELD = Model for End-stage Liver Disease, CTP = child-Turcotte-Pugh.

## DISCUSSION

We exclusively analyzed 3,487 LT patients and revealed significant findings regarding the prevalence and incidence of UIAs, vascular malformations and their association with post-LT outcomes. The feasibility of our analysis stems from the extensive experience of our institution (AMC, Seoul, Korea), which has conducted more than 8,000 LT cases over the past 30 years. Our study has determined a UIA prevalence rate of 5.4% (190/3,487) among the LT patient population. Furthermore, we observed a 1-year incidence of SAH following LT in those individuals harboring UIAs, which was notably low at 0.6%. Notably, these figures stand in contrast to the higher prevalence rates reported in the general population, typically ranging between 0.95% to 1.4%.<sup>19,24</sup> Our analysis identified several key risk factors for the occurrence of postoperative 1-year HS; admission mental status, presence of UIA or vascular malformations, MELD scores, and serum ammonia levels. These findings not only

**Table 4.** Development of scoring system for prediction of hemorrhagic stroke within one year after liver transplantation

Parameters	Reference value	$\beta^a$	$\beta(W - W_{REF})^b$	Points <sup>c</sup>
Admission mental status				
Alert or drowsy	0 ( $W_{REF}$ )		0	0
Stupor or unresponsive	1	1.032	1.032	2
Pre-op radiologic diagnosis				
UIA or vascular malformations <sup>d</sup> (-)	0 ( $W_{REF}$ )		0	0
UIA or vascular malformations (+)	1	1.271	1.271	2
MELD score		0.048		
1–15	8.2 ( $W_{REF}$ )		0	0
16–30	14.5		0.303	1
≥ 31	29.4		1.019	2
Ammonia		0.006		
≤ 35	13.8 ( $W_{REF}$ )		0	0
> 35	65		0.322	1
Total				7

UIA = unruptured intracranial aneurysm, MELD = Model for End-stage Liver Disease.

<sup>a</sup>Parameter estimate; <sup>b</sup>Constant for the scoring system; <sup>c</sup>Points =  $\beta(W - W_{REF})/\beta$ .

<sup>d</sup>Vascular malformations denote arteriovenous malformation or cavernous malformation.

**Table 5.** Risk group stratification and estimates of HS from the study cohorts

Risk group	Points	Estimate of 1-year HS risk	Development group		Validation group	
			No. of patients	HS incidence	No. of patients	HS incidence
Low	0	0.0050	820	5	100	1
	1	0.0081	854	7	256	1
	2	0.0131	669	8	280	7
High	3	0.0212	166	6	130	6
	4	0.0340	88	5	39	3
	5	0.0544	33	4	45	2
	6	0.0866	3	0	0	0
	7	0.1362	0	0	4	0
Total			2,633	35	854	20

HS = hemorrhagic stroke.

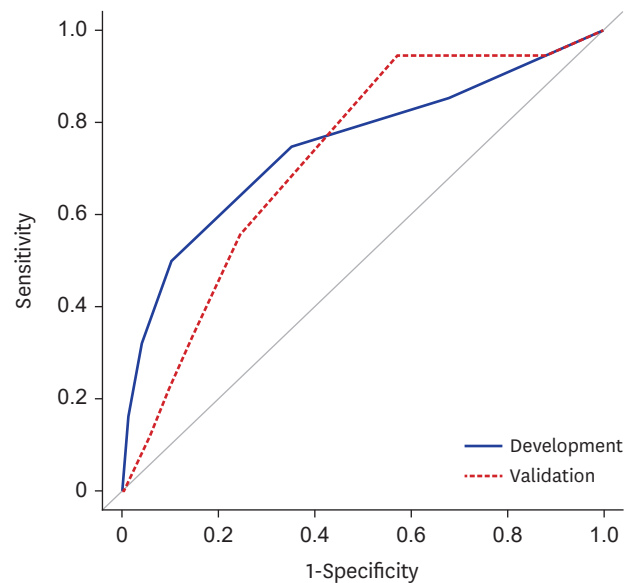
**Table 6.** Assessment of scoring system

Cohorts	C index	SE	95% CI	AUC at 1 year	95% CI
Development	0.727	0.047	0.635–0.820	0.767	0.629–0.847
Validation	0.719	0.052	0.598–0.801	0.740	0.606–0.813

C index = Concordance index, SE = standard error, CI = confidence interval, AUC = area under the curve.

shed light on the comparatively lower incidence of SAH in LT recipients with UIAs but also emphasize the importance of considering specific clinical factors, such as MELD scores and hematological parameters, in assessing the risk of postoperative HS in this unique patient population. To our knowledge, this is the first study to address the scoring system of LT patients preoperatively, using various parameters to predict postoperative HS in a relatively large development and validation cohorts and confirmed its clinical value.

The diagnosis of UIA in the context of preoperative evaluations for LT presents a substantial dilemma for both patients and healthcare professionals. While the occurrence of aneurysm rupture subsequent to LT represents a dire and life-threatening complication associated with a high mortality rate, a growing body of evidence underscores the relatively low risk of rupture in UIAs while simultaneously highlighting the considerable morbidity linked with preventive surgical intervention.<sup>21,25</sup> This confluence of factors complicates the decision-making process regarding the optimal management of affected patients. Furthermore, the presence of cirrhosis-related complications, such as coagulopathy and hyperammonemia introduces additional layers of complexity into the perioperative management of cirrhotic



**Fig. 2.** Area under the receiver-operating characteristic curve of prediction for the scoring system in the development and validation cohorts.

patients awaiting LT. Hence, we exclusively developed and validated a predictive model designed to assess the risk of HS in patients undergoing LT, which is characterized by its simplicity, reliability, and reproducibility, rendering it applicable across a broad institution.

The distinctive attributes of ESLD, which entail inflammatory pathological alterations within the vascular wall,<sup>25</sup> significantly compromise the structural integrity of the cerebral arterial wall. Additional mechanisms, such as endothelial cell dysfunction<sup>26</sup> and alterations in the levels of cellular adhesion molecules responsible for mediating leukocyte adhesion to the vascular endothelium,<sup>27</sup> also play a contributory role in the genesis and subsequent rupture of these aneurysms. Consequently, this process contributes to the formation of cerebral aneurysms, thereby yielding a heightened prevalence of UIAs in this specific patient cohort compared to the general population. Future studies are warranted at the molecular and genetic levels to elucidate the nature of vascular malformations in LT patients.

Our study unveiled a significant discovery: a considerably higher prevalence of vascular malformations among LT recipients when compared to the general population, which is known to have a prevalence of less than 1%.<sup>28</sup> The etiology of these vascular malformations remains unknown. Nonetheless, a sequence of initial thrombogenic, inflammatory, mechanical, or ischemic insults has been observed to lead to the pro-angiogenic state required for the development of these vascular malformations.<sup>29</sup> Also hepatopathy may play a pivotal role in this process, given its common etiological association with peripheral systemic AVMs. Chronic venous hypertension resulting from hepatopathy can induce tissue hypoxia, thereby contributing to angiogenesis. This notion finds support in documented cases of spontaneous AVM regression following living-donor LT.<sup>30</sup>

Interestingly, our observations revealed that the risk of SAH did not exhibit a higher incidence in patients with LC when compared to the general population. Prior literature had posited LC as an independent risk factor for aneurysmal SAH, citing factors such as coagulopathy, liver fibrosis-related small vessel disease, abnormal systemic vascular tone,

and vascular malformation as potential contributors to this elevated risk.<sup>15,16,31</sup> Furthermore, LT is distinguished by its intricate hemodynamic shifts, encompassing phenomena like postreperfusion syndrome, as well as complications such as porto-pulmonary hypertension and hepatopulmonary syndrome,<sup>32</sup> all of which have the potential to precipitate cardiovascular instability and could theoretically augment the risk of aneurysm rupture. Intriguingly, our findings are in consonance with previous investigations conducted within our institutions,<sup>21,25</sup> which have consistently indicated that the risk of aneurysm rupture does not experience an appreciable increase in LT patients within the initial one-year post-LT. This discovery aligns with investigations into the impact of pregnancy or childbirth on the risk of UIA rupture, which has raised concerns regarding the potential influence of labor pains and the physiological increase in circulatory volume. A study utilizing data from the US National Inpatient Sample spanning from 1988 to 2009, for instance, reported no discernible heightened association between pregnancy or childbirth and the risk of UIA rupture.<sup>33</sup> Similarly, in a nationwide Swedish cohort study conducted between 1987 and 1995, the highest one-year incidence rate of SAH during delivery was a mere 0.31%.<sup>34</sup>

The inclusion of the MELD score as a risk factor for HS within our predictive model aligns with previous research findings, as documented in earlier studies.<sup>35,36</sup> Cirrhosis-associated abnormalities in hemostasis and coagulation, stemming from reduced platelet count and function, diminished levels of clotting factors, and vitamin K deficiency, may collectively contribute to an elevated predisposition toward bleeding events.<sup>37</sup> This heightened propensity for bleeding incidents may consequently increase the risk of HS. Furthermore, impaired cerebral autoregulation, a phenomenon associated with the severity of cirrhosis, may further exacerbate the susceptibility to HS.<sup>38</sup>

The association between serum ammonia levels and HS is unclear. Several studies have indicated a correlation between hyperammonemia and decreased platelet levels.<sup>39,40</sup> Ammonia is a well-established neurotoxin implicated in the onset of hepatic encephalopathy, a condition often characterized by prolonged prothrombin time, activated partial thromboplastin time, and international normalized ratio values.<sup>41,42</sup> Consequently, there may exist plausible connections between ammonia levels and the development of HS. Given that elevated ammonia levels can weaken immune function, exacerbate hepatocyte damage, and impede liver recovery,<sup>43</sup> it is conceivable that HS may be more susceptible to development under such circumstances. Furthermore, hyperammonemia can lead to reduced consciousness by inducing astrocytic swelling, tissue edema, and neuronal toxicity in cerebral tissues.<sup>44</sup>

The retrospective nature conducted in a single institution represents a limitation. Referral bias cannot be excluded, given that our institution is one of the most prolific centers for LT worldwide. Despite our inclusion of a substantial population comprising 3,487 patients, the detection of SAHs remained infrequent due to the relatively uncommon presence of UIAs and the rarity of UIA rupture. Consequently, we cannot definitively discount the possibility of a greater actual rupture risk than what has been indicated by our study. Nevertheless, the fact that LT can be safely performed without introducing an additional risk of UIA rupture adds value to our study. It is important to acknowledge that our study was conducted at a single center and primarily involved Korean patient populations. Consequently, caution should be exercised when extrapolating these findings to centers with dissimilar patient profiles. However, given that the reported UIA rupture rates in Korea are purportedly higher than those in other countries, with the exception of Japan and Finland<sup>10,45</sup> it is unlikely that the

risk of perioperative UIA rupture would be disproportionately elevated in other countries. Regardless of these limitations, our study included a comparatively large sample size to develop a prediction model which was also validated from separate cohorts to show its generalizability and efficiency. Also, other strength is that even though all cases underwent LT in the present study, the parameters related to scoring system can be evaluated before the surgery. Hence, the application of our model to anticipate clinical outcome is not solely relying on the surgical factors and hence be also recommended to LC patients whom are not candidate for the surgery.

In conclusion, our proposed prediction model for assessing the risk of HS within one year following LT relies on readily accessible patient characteristics, including mental status, the presence of UIA, MELD scores, and ammonia levels. It is acknowledged that a simplistic scoring system, as presented in our study, may not comprehensively capture all the multifaceted factors associated with a complex condition such as LC. Nevertheless, our prediction model may assist physicians in assessing the risk of UIA rupture and HS in LT patients.

## SUPPLEMENTARY MATERIALS

### Supplementary Table 1

Incidence of hemorrhagic stroke within one year after liver transplantation

### Supplementary Fig. 1

Post liver transplant patient with SAH. A 50-year-old female underwent cadaveric liver transplantation due to acute alcoholic hepatitis. (A, B) On post-operative day 61, she showed decreased consciousness and a computed tomography scan revealed a SAH resulting from the rupture of a left posterior communicating artery aneurysm. (C, D) Emergency coil embolization was performed to prevent rebleeding. The ruptured aneurysm was not observed on the pre-liver transplant brain imaging. According to transfemoral catheter angiography, the ruptured aneurysm appeared to be an infectious aneurysm. Despite best medical support, she expired due to the SAH.

### Supplementary Fig. 2

The predicted 1-year risk of HS based on the scoring system. The one-year cumulative incidence of HS after liver transplantation, as determined by our scoring system, assessed in both the development and validation cohorts. The development groups have been stratified based on our scoring system, ranging from 0 to 7 (A), and categorized as low vs. high (scores 0–2 vs. 3–7) (B). The scoring system has been adapted for use with the validation cohort. The validation groups have been stratified based on our scoring system, ranging from 0 to 7 (C), and categorized as low vs. high (scores 0–2 vs. 3–7) (D).

## REFERENCES

1. Oliveira CP, Stefano JT, Alvares-da-Silva MR. Cardiovascular risk, atherosclerosis and metabolic syndrome after liver transplantation: a mini review. *Expert Rev Gastroenterol Hepatol* 2013;7(4):361-4. [PUBMED](#) | [CROSSREF](#)
2. Ahn C, Koo TY, Jeong JC, Kim M, Yang J, Lee J, et al. Initial report of the Korean Organ Transplant Registry: the first report of national kidney transplantation data. *Transplant Proc* 2014;46(2):425-30. [PUBMED](#) | [CROSSREF](#)

3. Wang JH, Skeans MA, Israni AK. Current status of kidney transplant outcomes: dying to survive. *Adv Chronic Kidney Dis* 2016;23(5):281-6. [PUBMED](#) | [CROSSREF](#)
4. Vizzini G, Asaro M, Miraglia R, Gruttadauria S, Fili D, D'Antoni A, et al. Changing picture of central nervous system complications in liver transplant recipients. *Liver Transpl* 2011;17(11):1279-85. [PUBMED](#) | [CROSSREF](#)
5. Saner FH, Sotiropoulos GC, Gu Y, Paul A, Radtke A, Gensicke J, et al. Severe neurological events following liver transplantation. *Arch Med Res* 2007;38(1):75-9. [PUBMED](#) | [CROSSREF](#)
6. Kim BS, Lee SG, Hwang S, Park KM, Kim KH, Ahn CS, et al. Neurologic complications in adult living donor liver transplant recipients. *Clin Transplant* 2007;21(4):544-7. [PUBMED](#) | [CROSSREF](#)
7. Bronster DJ, Emre S, Boccagni P, Sheiner PA, Schwartz ME, Miller CM. Central nervous system complications in liver transplant recipients--incidence, timing, and long-term follow-up. *Clin Transplant* 2000;14(1):1-7. [PUBMED](#) | [CROSSREF](#)
8. Senzolo M, Ferronato C, Burra P. Neurologic complications after solid organ transplantation. *Transpl Int* 2009;22(3):269-78. [PUBMED](#) | [CROSSREF](#)
9. Kumar SS, Mashour GA, Picton P. Neurologic considerations and complications related to liver transplantation. *Anesthesiology* 2018;128(5):1008-14. [PUBMED](#) | [CROSSREF](#)
10. Thompson BG, Brown RD Jr, Amin-Hanjani S, Broderick JP, Cockroft KM, Connolly ES Jr, et al. Guidelines for the management of patients with unruptured intracranial aneurysms: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2015;46(8):2368-400. [PUBMED](#) | [CROSSREF](#)
11. Mesquita GL, Yokoyama AP, de Souza CM, Kutner JM, de Almeida MD, Vaz CO, et al. Role of microvesicles as markers of inflammation and adverse clinical outcomes in orthotopic liver transplantation. *J Liver Transpl* 2023;9:100138. [CROSSREF](#)
12. Chalouhi N, Ali MS, Jabbour PM, Tjoumakaris SI, Gonzalez LF, Rosenwasser RH, et al. Biology of intracranial aneurysms: role of inflammation. *J Cereb Blood Flow Metab* 2012;32(9):1659-76. [PUBMED](#) | [CROSSREF](#)
13. Moreno R, Berenguer M. Post-liver transplantation medical complications. *Ann Hepatol* 2006;5(2):77-85. [PUBMED](#) | [CROSSREF](#)
14. Parikh NS, Navi BB, Schneider Y, Jesudian A, Kamel H. Association between cirrhosis and stroke in a nationally representative cohort. *JAMA Neurol* 2017;74(8):927-32. [PUBMED](#) | [CROSSREF](#)
15. Parikh NS, Merkler AE, Jesudian A, Kamel H. Association between cirrhosis and aneurysmal subarachnoid hemorrhage. *Ann Clin Transl Neurol* 2018;6(1):27-32. [PUBMED](#) | [CROSSREF](#)
16. Cebal JR, Mut F, Weir J, Putman CM. Association of hemodynamic characteristics and cerebral aneurysm rupture. *AJNR Am J Neuroradiol* 2011;32(2):264-70. [PUBMED](#) | [CROSSREF](#)
17. Weiss N, Thabut D. Neurological complications occurring after liver transplantation: role of risk factors, hepatic encephalopathy, and acute (on chronic) brain injury. *Liver Transpl* 2019;25(3):469-87. [PUBMED](#) | [CROSSREF](#)
18. UCAS Japan Investigators, Morita A, Kirino T, Hashi K, Aoki N, Fukuhara S, et al. The natural course of unruptured cerebral aneurysms in a Japanese cohort. *N Engl J Med* 2012;366(26):2474-82. [PUBMED](#) | [CROSSREF](#)
19. Greving JP, Wermer MJ, Brown RD Jr, Morita A, Juvela S, Yonekura M, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. *Lancet Neurol* 2014;13(1):59-66. [PUBMED](#) | [CROSSREF](#)
20. Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly ES Jr, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. *Neurosurgery* 2006;59(1):21-7. [PUBMED](#) | [CROSSREF](#)
21. Chung Y, Lee S, Park JC, Ahn JS, Moon EJ, Park JW, et al. Prevalence of cerebrovascular diseases that can cause hemorrhagic stroke in liver transplantation recipients: a 6-year comparative study with 24,681 healthy adults. *Neurol Sci* 2021;42(7):2753-61. [PUBMED](#) | [CROSSREF](#)
22. Hoh BL, Ko NU, Amin-Hanjani S, Chou SH, Cruz-Flores S, Dangayach NS, et al. 2023 Guideline for the management of patients with aneurysmal subarachnoid hemorrhage: a guideline from the American Heart Association/American Stroke Association. *Stroke* 2023;54(7):e314-70. [PUBMED](#) | [CROSSREF](#)
23. Greenberg SM, Ziai WC, Cordonnier C, Dowlatshahi D, Francis B, Goldstein JN, et al. 2022 Guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American Heart Association/American Stroke Association. *Stroke* 2022;53(7):e282-361. [PUBMED](#) | [CROSSREF](#)
24. Kim T, Lee H, Ahn S, Kwon OK, Bang JS, Hwang G, et al. Incidence and risk factors of intracranial aneurysm: a national cohort study in Korea. *Int J Stroke* 2016;11(8):917-27. [PUBMED](#) | [CROSSREF](#)



25. Kwon HM, Jun IG, Kim KS, Moon YJ, Huh IY, Lee J, et al. Rupture risk of intracranial aneurysm and prediction of hemorrhagic stroke after liver transplant. *Brain Sci* 2021;11(4):445. [PUBMED](#) | [CROSSREF](#)
26. Targher G, Bertolini L, Scala L, Zoppini G, Zenari L, Falezza G. Non-alcoholic hepatic steatosis and its relation to increased plasma biomarkers of inflammation and endothelial dysfunction in non-diabetic men. Role of visceral adipose tissue. *Diabet Med* 2005;22(10):1354-8. [PUBMED](#) | [CROSSREF](#)
27. Raevens S, Coulon S, Van Steenkiste C, Colman R, Verhelst X, Van Vlierberghe H, et al. Role of angiogenic factors/cell adhesion markers in serum of cirrhotic patients with hepatopulmonary syndrome. *Liver Int* 2015;35(5):1499-507. [PUBMED](#) | [CROSSREF](#)
28. Kim T, Kwon OK, Bang JS, Lee H, Kim JE, Kang HS, et al. Epidemiology of ruptured brain arteriovenous malformation: a national cohort study in Korea. *J Neurosurg* 2018;130:1965-70. [PUBMED](#) | [CROSSREF](#)
29. Gondar R, El Rahal A, Kulcsár Z, Schaller K, Momjian S. Spontaneous appearance of de novo intracranial arteriovenous malformation in hepatic cirrhosis. *Neurochirurgie* 2019;65(6):393-6. [PUBMED](#) | [CROSSREF](#)
30. Shimoda Y, Kuroda S, Kashiwazaki D, Asano T, Yamashita K, Taniguchi M, et al. Spontaneous disappearance of intracranial arteriovenous malformation after living-donor liver transplantation: a case report. *No Shinkei Geka* 2011;39(6):589-94. [PUBMED](#)
31. Kim YD, Song D, Heo JH, Kim SU, Kim BK, Park JY, et al. Relationship between cerebral microbleeds and liver stiffness determined by transient elastography. *PLoS One* 2015;10(9):e0139227. [PUBMED](#) | [CROSSREF](#)
32. Kang Y, Elia E. Anesthesia management of liver transplantation. In: Doria C, editor. *Contemporary Liver Transplantation*. Cham, Switzerland: Springer Nature; 2017, 143-87.
33. Kim YW, Neal D, Hoh BL. Cerebral aneurysms in pregnancy and delivery: pregnancy and delivery do not increase the risk of aneurysm rupture. *Neurosurgery* 2013;72(2):143-9. [PUBMED](#) | [CROSSREF](#)
34. Salonen Ros H, Lichtenstein P, Belloc R, Petersson G, Cnattingius S. Increased risks of circulatory diseases in late pregnancy and puerperium. *Epidemiology* 2001;12(4):456-60. [PUBMED](#) | [CROSSREF](#)
35. Zhang Y, Li L, Jia L, Chong W, Hai Y, Lunsford LD, et al. Association of chronic liver disease and mortality in patients with aneurysmal subarachnoid hemorrhage. *Stroke* 2021;52(10):e614-7. [PUBMED](#) | [CROSSREF](#)
36. Lagman C, Nagasawa DT, Sheppard JP, Jacky Chen CH, Nguyen T, Prashant GN, et al. End-stage liver disease in patients with intracranial hemorrhage is associated with increased mortality: a cohort study. *World Neurosurg* 2018;113:e320-7. [PUBMED](#) | [CROSSREF](#)
37. Prelipcean CC, Fierbinteanu-Braticevici C, Drug VL, Lăcătușu C, Mihai B, Mihai C. Liver cirrhosis--procoagulant stasis. *Rev Med Chir Soc Med Nat Iasi* 2011;115(3):678-85. [PUBMED](#)
38. Strauss GI, Hansen BA, Herzog T, Larsen FS. Cerebral autoregulation in patients with end-stage liver disease. *Eur J Gastroenterol Hepatol* 2000;12(7):767-71. [PUBMED](#) | [CROSSREF](#)
39. Djambou-Nganjeu H. Hepatic encephalopathy in liver cirrhosis. *J Transl Int Med* 2017;5(1):64-7. [PUBMED](#) | [CROSSREF](#)
40. Koch DG, Speiser JL, Durkalski V, Fontana RJ, Davern T, McGuire B, et al. The natural history of severe acute liver injury. *Am J Gastroenterol* 2017;112(9):1389-96. [PUBMED](#) | [CROSSREF](#)
41. Pan C, Xu LJ, Zhou R, Zhou W, Huang JR. Multivariate analysis of hepatic encephalopathy occurrence in patients with liver failure. *Chung Hua Kan Tsang Ping Tsa Chih* 2012;20(6):434-7. [PUBMED](#) | [CROSSREF](#)
42. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001;33(2):464-70. [PUBMED](#) | [CROSSREF](#)
43. Shalimar , Sheikh MF, Mookerjee RP, Agarwal B, Acharya SK, Jalan R. Prognostic role of ammonia in patients with cirrhosis. *Hepatology* 2019;70(3):982-94. [PUBMED](#) | [CROSSREF](#)
44. Back A, Tupper KY, Bai T, Chiranand P, Goldenberg FD, Frank JI, et al. Ammonia-induced brain swelling and neurotoxicity in an organotypic slice model. *Neurol Res* 2011;33(10):1100-8. [PUBMED](#) | [CROSSREF](#)
45. Byoun HS, Huh W, Oh CW, Bang JS, Hwang G, Kwon OK. Natural history of unruptured intracranial aneurysms: a retrospective single center analysis. *J Korean Neurosurg Soc* 2016;59(1):11-6. [PUBMED](#) | [CROSSREF](#)