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Incidence and Risk Factors of Intracranial Hemorrhage in Liver Transplant Recipients

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Abstract

Background—Intracranial hemorrhage after liver transplantation is an infrequently reported complication but one which can have devastating consequences.

Methods—We performed a retrospective cross-sectional analysis of all liver transplants performed between January 2010 and June 2015 at a single high-volume institution using a prospectively maintained electronic database and query of the electronic medical record. Cases of intracranial hemorrhage were adjudicated as either spontaneous intraparenchymal (IPH) or extra-axial (EAH) hemorrhages. Patients with confirmed intracranial hemorrhage were compared with all other liver transplant recipients. Risk factors were identified by univariate analysis and logistic regression models for IPH and EAH.

Results—Thirty-one (5.2%) of 595 liver transplant recipients developed an intracranial hemorrhage within 12 months of transplantation, 15 IPH and 16 EAH. The majority of intracranial hemorrhages were diagnosed within 1 month of transplantation. Eight (26%) intracranial hemorrhage patients died during hospitalization. Fourteen (45%) intracranial hemorrhage patients died within 1 year of transplantation and 1-year mortality was greater than in patients without

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intracranial hemorrhage (11.2%, $p<0.01$). Female sex (adjusted OR 3.291; 95% CI 1.092–9.924, $p=0.034$), higher pretransplant bilirubin (adjusted OR 1.037; 95% CI 1.006–1.070; $p=0.020$), and greater increase in pre to posttransplant systolic blood pressure (adjusted OR 1.029; 95% CI 1.006–1.052, $p=0.012$) were associated with posttransplant IPH. Lower pretransplant serum fibrinogen level (adjusted OR 0.988; 95% CI 0.979–0.998, $p=0.017$) was associated with posttransplant EAH.

Conclusion—Postoperative blood pressure control and pretransplant fibrinogen levels may be modifiable risk factors for preventing posttransplant intracranial hemorrhage.

Introduction

Intracranial hemorrhage following liver transplant is a potentially devastating complication. The overall incidence is ill defined, and there are limited reports in the literature concerning etiology and risk factors (1, 2). In the general population, intracranial hemorrhage may occur in association with coagulopathy, acute hypertension, or chronic hypertension (3–6). In particular, control of systolic hypertension has been central in efforts to reduce the incidence of intraparenchymal hemorrhage (IPH) and manage IPH when it occurs (7, 8). Based on these observations, we hypothesized that similar risk-factors may be associated with posttransplant intracranial hemorrhage and represent potentially modifiable targets for clinical intervention.

In this study, we sought to define the overall incidence of intracranial hemorrhage within 12 months following transplant among all patients undergoing liver transplantation during a 66-month period at a high-volume center. We sought to identify demographic and clinical variables associated with 2 classes of posttransplant intracranial hemorrhage, spontaneous intraparenchymal hemorrhage (IPH) and extra-axial hemorrhage (EAH), which includes both subdural hemorrhage and subarachnoid hemorrhage.

Methods

Data were extracted on all patients who underwent liver transplantation from January 1st, 2010 through June 30th, 2015. Transplantation data, including clinical events following transplant, were prospectively recorded in an electronic database. The occurrence of any form of intracranial hemorrhage was a clinical event specifically recorded in this database. Query of the database was used to identify those patients diagnosed with an intracranial hemorrhage within a 12-month period following liver transplant. Laboratory, medication administration, and blood pressure data were extracted from the electronic medical record by the Northwestern Medicine Enterprise Data Warehouse (EDW) analytics team. Neuro-imaging studies from each identified case of intracranial hemorrhage were reviewed by board certified radiologists and a board-certified attending neurologist with expertise in neurologic critical care and intracranial hemorrhage. Hemorrhages were adjudicated to either of 2 categories based on the anatomical origin of the hemorrhage: intraparenchymal or extra-axial. IPH originates within the substance of the brain while EAH originates intracranially but outside of the brain tissue itself. Extra-axial hemorrhages included subdural and subarachnoid hemorrhages; no epidural hemorrhages were identified in this cohort. We categorized intracranial hemorrhages into IPH and EAH and analyzed them

separately because they likely have different causative mechanisms and, in the general population, have unique risk factors (6, 9). Hemorrhage characteristics on initial diagnostic neuro-imaging studies were recorded and included: location, IPH volume, EAH thickness (thin versus thick [≥ 10 mm greatest thickness]), and the occurrence of radiographic brain herniation (uncal, central, tonsillar, or subfalcine herniation) or severe brain compression (brain tissue distortion requiring emergent surgical or medical intervention). The presenting neurologic symptoms, indications for neuro-imaging, and patient outcomes at hospital discharge were extracted by chart review. Intracranial hemorrhages determined to be chronic at the time of transplantation (eg chronic subdural hemorrhages) or lesions not representing primary hemorrhages (eg intracranial cavernous malformations, acute ischemic strokes with hemorrhagic transformation, intracranial device related hemorrhages) were excluded from analysis. We also excluded patients undergoing repeat liver transplantation.

Data on intraoperative blood product transfusion and thromboelastography were not electronically recorded prior to 2012 and, therefore, were not available for analysis in this study. Our intraoperative approach to transfusion involves administering packed red blood cells to maintain a hemoglobin goal level of 10 g/dL. Transfusion of platelets and plasma-derived products is avoided prior to graft arterial reperfusion in order to minimize the risk of hepatic artery thrombosis. Thromboelastography is used to guide intra-operative management of clotting and fibrinolysis status and aminocaproic acid is used to treat elevated fibrinolytic activity. Heparin infusion may be used when a relative hypercoagulable state is suspected; our protocol provides a recommended heparin dose guided by international normalized ratio (200 units/hour for INR $\leq$ 1.5 and 100 units/hour for INR 1.6–1.7). Of note, due to depressed production of antithrombin, Protein C, and Protein S during cirrhosis, the INR may be more reflective of the degree of liver disease than bleeding tendency in cirrhosis and it is even possible for cirrhotic patients with elevated INR to be hypercoagulable by thromboelastography (10). For each patient, we identified whether heparin infusion or aminocaproic acid was used during transplantation.

Patients with confirmed intracranial hemorrhage were compared with all other liver transplant recipients (controls). Baseline patient characteristics and demographic data including pretransplant Model for End-Stage Liver Disease (MELD) score, living versus deceased donor status, and intra-operative data were extracted from the transplant database. Pretransplant and posttransplant laboratory variables and systolic blood pressure values were extracted from the hospital electronic medical record by computerized query. The most deranged laboratory values according to clinical significance (for example the lowest platelet and fibrinogen level, the highest International Normalized Ratio) and highest systolic blood pressure (SBP) in the 24-hour period prior to transplant were selected to represent the pretransplant period. The most deranged laboratory values and highest SBP in the 96-hour period after transplant were selected to represent the posttransplant period. The 96-hour time period was selected for analysis because this represented the duration after transplant in which each patient who ultimately had an intracranial hemorrhage was still hospitalized and receiving regular blood pressure monitoring and laboratory studies. Using blood pressure values from the pretransplant and posttransplant periods, we calculated the change in SBP between the time periods.

Continuous variables are reported as mean (standard deviation) or median (interquartile range). Categorical variables are reported as proportions. Comparisons of continuous variables between groups (controls, IPH, and EAH) were made using one-way ANOVA test for normally distributed variables and Kruskal-Wallis test for nonnormally distributed variables. Groups were compared pairwise using either one-way ANOVA or Kruskal-Wallis post hoc tests adjusted for multiple comparisons. Post hoc Tukey's honest significant difference tests were used for normally distributed variables and post hoc Bonferroni adjusted multiple comparison tests were used for nonnormally distributed variables. Categorical variables were compared between each group of intracranial hemorrhage and controls by Fisher's exact test. Separate logistic regression models for IPH and EAH were built to identify variables independently associated with each type of hemorrhage. Variables with univariate $p < 0.15$ between cases and controls were assessed for model inclusion. In the case of the MELD score, we assessed the individual component variables for model inclusion. The final parsimoniously adjusted models were created using the backward stepwise approach with a removal criterion of probability of F-to-remove 0.1. This approach ensured an adequate number of events per variable to meet published recommendations for robust logistic models (11). We considered $p < 0.05$ to be significant.

Statistical analysis was performed using SPSS v.23 (IBM, Armonk, NY). The Northwestern University Institutional Review Board approved this study.

Results

The study cohort included 595 liver transplant recipients (378 male, 56.5 (11.0) years, 24 acute liver failure, MELD at the time of transplant 24 [14–35]). Within 1 year of liver transplant, 31 (5.2%) patients developed an intracranial hemorrhage, 15 IPH and 16 EAH. Two cases of chronic subdural hematoma, 1 case of acute ischemic stroke with hemorrhagic transformation, and 1 case of chronic cavernous malformation were excluded from analysis. Invasive intracranial pressure monitors were used in 2 patients prior to liver transplantation; intracranial hemorrhage was not observed on neuro-imaging in these patients. Diagnosis of IPH occurred a median of 16 (5–33) days posttransplant and diagnosis of EAH occurred a median of 9 (4–16) days posttransplant. In 14 IPH and 13 EAH cases either acute onset of neurologic symptoms or prior neuro-imaging confirmed that hemorrhage onset occurred posttransplantation. In the remaining 4 cases (1 IPH and 3 EAH) neuro-imaging was performed because of prolonged depressed mental status following transplantation and the possibility of intra-operative hemorrhage onset could not be excluded. Table 1 summarizes the indications for neuro-imaging and the initial neurologic symptoms of the intracranial hemorrhage patients. Table 2 summarizes the radiographic hemorrhage characteristics. Neuro-imaging within 1 year of transplantation was acquired in 124 (22%) control patients at a median of 8 (3–36) days. Among controls, the most frequent indications for neuro-imaging were: fall, headache, and altered mental status.

Neurosurgical and neurocritical care consultations were obtained in each hemorrhage case. Repeat neuroimaging to evaluate hemorrhage evolution was obtained in 30 patients. One patient died of brain herniation before repeat neuro-imaging. Three EAH and 4 IPH patients had cerebrovascular imaging. Brain MRI was obtained in 11 EAH and 8 IPH patients. An

underlying structural lesion as the cause of hemorrhage was not identified in any case. No patient with intracranial hemorrhage had bacteremia or fungemia prior to or at the time of hemorrhage diagnosis. Platelet infusion was given in 3 EAH and 3 IPH cases in response to platelet count below 100 thousand/ μ L. Coagulation factors were given in 5 EAH and 1 IPH case in response to INR > 1.7. Craniectomy with hematoma evacuation was performed in 2 EAH patients. One IPH patient had a decompressive hemicraniectomy and 1 IPH patient had a decompressive hemicraniectomy with hematoma evacuation.

Eight (26%) of patients who developed intracranial hemorrhage died during hospitalization. Intracranial hemorrhage that progressed to brain herniation contributed to death in six (19%) of these patients. Fourteen (45%) of patients who developed intracranial hemorrhage were discharged to home or acute rehabilitation; of these, 4 had disabling hemiparesis or aphasia at discharge and 10 had minimal residual symptoms attributable to the hemorrhage. Among the nine (29%) patients discharged to a skilled nursing or long-term acute care facility, 2 were bed-bound and 3 were not independently mobile due to neurologic injury. Among those who had neurosurgical intervention, 1 patient was discharged to acute rehabilitation with hemiparesis and moderate aphasia, 1 patient was discharged to a long-term acute care hospital in persistent coma, and 2 patients died in hospital with palliative care after several weeks of persistent coma. At 1 year after transplant, 63 (11.2%) controls, 8 (53%) IPH, and 6 (37.5%) EAH patients had died. Compared to controls, both types of intracranial hemorrhage had a significantly higher 1-year mortality ($p < 0.01$). Among the cases of EAH, 2 of the 6 deaths occurred within 30 days of hemorrhage diagnosis. Among the cases of IPH, 5 of the 8 deaths occurred within 30 days of hemorrhage diagnosis.

Table 3 summarizes patient demographic, clinical, pre and posttransplant SBP, and pretransplant laboratory data for control, IPH, and EAH patients with p-values between hemorrhage groups and controls. Posttransplant platelet count between controls and EAH patients (43 [32–63] versus 36 [20–47] thousand/ μ L, $p = 0.079$) was the only posttransplant laboratory measure that suggested a difference between groups ($p < 0.15$). There was a trend towards more frequent aminocaproic acid use during transplantation in EAH patients than in controls (13% versus 3.4%, $p = 0.11$). However, there was no difference in pretransplant fibrinogen level between those who received aminocaproic acid and those who did not ($p = 0.65$).

IPH was associated with female sex (adjusted OR 3.291; 95% CI 1.092–9.924, $p = 0.034$), higher pretransplant serum total bilirubin level (adjusted OR 1.037; 95% CI 1.006–1.070; $p = 0.020$), and greater increase in pre to posttransplant SBP (adjusted OR 1.029; 95% CI 1.006–1.052, $p = 0.012$). Pretransplant INR and pretransplant systolic blood pressure did not meet criteria for inclusion in the final IPH model. An increase in pre to posttransplant SBP of 28 or more mmHg was 80% sensitive and 53% specific for IPH. EAH was associated with lower pretransplant serum fibrinogen level (adjusted OR 0.988; 95% CI 0.979–0.998, $p = 0.017$). Intra-operative aminocaproic acid, pretransplant and posttransplant platelet count did not meet criteria to remain in the final model. Pretransplant serum fibrinogen level lower than 148 mg/dL was 81% sensitive and 53% specific for EAH.

Discussion

The overall incidence of intracranial hemorrhage within 12 months of liver transplant in this cohort was 5.2%. This incidence is similar to that reported by Wang et al (5 IPH out of 75 [6.7%] patients) and Wijdicks et al (8 IPH out of 207 [3.9%] patients). Patients with intracranial hemorrhage had greater 1-year mortality compared to controls, with a 30-day and 1-year mortality of 33.3% and 53.3% for IPH and 12.5% and 37.5% for EAH, respectively. Female sex, higher pretransplant serum bilirubin level, and greater increase in SBP between pretransplant to posttransplant levels were associated with IPH. Lower pretransplant serum fibrinogen level was associated with EAH.

While our study was not designed to elucidate the physiologic mechanisms leading to intracranial hemorrhage after liver transplantation, we identified mechanistically plausible associations. IPH associated with cerebral hyperperfusion and acute systemic hypertension has been described in the posterior reversible encephalopathy syndrome (PRES), eclampsia, and after carotid stenting and carotid endarterectomy(5, 12). In these conditions, the magnitude of acute change in blood pressure and the extent to which cerebral blood flow regulation (cerebral autoregulation) is impaired seems to correlate to symptoms better than absolute blood pressure(5). In our cohort, the average SBP increased from normotension pretransplant to stage 1 hypertension posttransplant(7) while those who had IPH experienced a significantly greater increase in SBP. Others have also reported an increase in blood pressure within 24 hours of liver transplantation. Liver transplantation eventually results in correction of portal hypertension and reversal of the pathophysiological mechanisms that lead to hyperdynamic circulation in cirrhotics (13). However, this process may take up to 12 months to achieve (14–16). Cerebral autoregulation impairments that have been described in association with cirrhosis may further complement our findings. Studies have suggested that impaired cerebral autoregulation is associated with lower blood pressure and more severe Child-Pugh scores in patients with cirrhosis (17, 18). These observations raise the possibility that the IPH patients in our cohort, who had significantly lower pretransplant blood pressures and higher serum bilirubin, may also have had more impaired cerebral autoregulation. The combination of chronically impaired cerebral autoregulation and increased cerebral blood flow after transplantation could place patients with large increases in blood pressure at risk for cerebral hyperperfusion and IPH. Alternatively, cirrhosis may have masked some patients' comorbid predisposition to hypertension, which subsequently manifested after transplantation and contributed to the risk of future IPH. The observed association between systolic blood pressure changes and IPH in our study could also merely represent an epiphenomenon rather than a causal mechanism.

In our patients with EAH, the association with low pretransplant fibrinogen is mechanistically plausible as it may have contributed to inadequate clot formation in the immediate posttransplant period. In this setting, subdural or subarachnoid hemorrhages may have resulted from even innocuous trauma. Once formed these hemorrhages are prone to expansion and potential symptomatic presentation (9).

Mitigating the intracranial hemorrhage risk factors identified in this study might seem intuitive but caution is warranted. For example, EAH may be difficult to predict because

these lesions are highly related to trauma. Keeping fibrinogen levels artificially elevated in all patients before liver transplantation might inappropriately expose patients to the risks and complications of treatment in order to avoid the uncommon EAH. In fact, some have advocated that providing treatments merely to correct abnormal coagulation studies should be avoided since it exposes patients to risks including acute lung injury, infection and thrombosis (19, 20). In terms of increased blood pressure and risk of posttransplant IPH, it may be more reasonable for the clinician to recognize and address relative posttransplant hypertension on an individual patient basis than enforce a standard blood pressure range for all patients. Our data suggest that it may be reasonable for the clinician to evaluate the risks and benefits of instituting blood pressure interventions when the increase in pretransplantation to posttransplantation SBP exceeds 28 mmHg.

There are a number of limitations to our study. This study represents a single center experience and it is unclear if it can be generalized to other transplant centers. Furthermore, the incidence of intracranial hemorrhage was rather low and therefore the number of cases relatively modest. However, our series represents more cases of IPH, 15, than the combined number of cases, 13, from the 2 previously published series on the topic (1, 2). We also describe EAH in the posttransplant population, which to our knowledge has not previously been studied. While intracranial hemorrhage is a potentially devastating complication of liver transplantation, the infrequent occurrence represents a challenge to studying this disease. Future research into the mechanisms of and interventions for posttransplantation intracranial hemorrhage might benefit from the collection of mechanistically plausible variables in a national database.

Like the series by Wang et al and Wijdicks et al, we found univariate data to suggest a relationship between intracranial hemorrhage, thrombocytopenia, and coagulation measures. However, these variables did not remain significant in regression models. Unfortunately, intraoperative transfusion and thromboelastography data were not available for analysis in the entire cohort since these data were only consistently recorded after January 2012. We were unable to confirm the association between intraoperative transfusion requirements and risk of intracranial hemorrhage suggested by Wang et al. We also found no data to support an association between posttransplant intracranial hemorrhage and bacteremia as suggested by Wijdicks et al. It should also be noted that not every patient in our cohort had neurologic imaging after liver transplantation. Therefore, it is possible that some patients in the control group had asymptomatic intracranial hemorrhages.

Conclusion

The overall incidence of postoperative intracranial hemorrhage within 12 months of liver transplantation in this cohort was 5.2% and was associated with worse 1-year posttransplant mortality. Regardless of whether intracranial hemorrhage occurred, systolic hypertension shortly after liver transplantation appeared to be common. Female sex, higher pretransplant total serum bilirubin level, and greater change in SBP from baseline after transplant were associated with IPH. Lower pretransplant fibrinogen level was associated with EAH. While these associations may inform the clinician regarding a potentially disastrous complication,

an individualized approach with specific attention to the potential adverse effects of intervention is warranted.

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Table 1

Indications for neuro-imaging and initial neurologic symptoms in patients with intracranial hemorrhage

Intraparenchymal Hemorrhage	
Imaging indication and initial symptoms	n (%)
Acute fixed/dilated pupil and unresponsive	3 (20%)
Acute altered mental status	5 (33%)
Acute hemiparesis	3 (20%)
Acute hemiparesis and aphasia	1 (7%)
Acute hemiparesis and seizure	1 (7%)
Prolonged depressed mental status after transplantation ^I	2 (13%)
Extra-axial Hemorrhage	
Imaging indication and initial symptoms	n (%)
Acute fixed/dilated pupil and unresponsive	1 (6%)
Acute, transient unresponsiveness	1 (6%)
Acute altered mental status	3 (19%)
Acute altered mental status and fall	2 (13%)
Acute altered mental status and convulsive seizure	2 (13%)
Acute hemiparesis	2 (13%)
Acute hemiparesis and headache	1 (6%)
“Particularly” hypocoagulable intra-operatively, received aminocaproic acid	1 (6%)
Prolonged depressed mental status after transplantation ^I	3 (19%)

^IOne IPH and 1 EAH patient had prior posttransplantation neuro-imaging that confirmed hemorrhage onset was after transplantation.

Table 2

Radiographic hemorrhage characteristics on initial diagnostic neuro-imaging

Intraparenchymal Hemorrhage	
Hematoma Volume	
Minimum, maximum	<1 mL (multifocal), 108 mL
Median (IQR)	4 mL (1 mL – 12.5 mL)
Multifocal	4 (27%)
Brain herniation or severe brain compression ¹	5 (33%)
MRI consistent with posterior reversible encephalopathy syndrome	2 (13%)
Extra-axial Hemorrhage	
Hemorrhage type	
Subdural only	13 (81%)
Subarachnoid only	1 (6%)
Subdural and Subarachnoid	2 (13%)
Thick Hemorrhage (≥ 10 mm) ²	2 (13%)
Multifocal	5 (31%)
Brain herniation or severe brain compression	2 (13%)
MRI consistent with posterior reversible encephalopathy syndrome	1 (6%)

¹One additional patient experienced subsequent expansion of a basal ganglia hemorrhage that resulted in brain herniation.

²One additional patient experienced subsequent subdural hemorrhage expansion to >10 mm with resulting brain herniation.

IQR=interquartile range, mL=milliliter, MRI=magnetic resonance imaging

Table 3

Demographic, clinical, and pretransplant laboratory data.

Variable	Control Group (n=564)	Intraparenchymal Hemorrhage (n=15)	p-value versus control [*]	Extra-Axial Hemorrhage (n=16)	p-value versus control [*]
Age (years)	56.6 (10.9)	56.3 (14.0)	1.0	56.1 (11.0)	0.98
Male	365 (64.7%)	5 (33.3%)	0.025	8 (50.0%)	0.29
Body Mass Index (kg/m ²)	28.2 (24.4–33.4)	26.2 (24.4–31.8)	1.0	26.8 (22.4–29.9)	0.46
Acute Liver Failure	23 (4.1%)	1 (6.7%)	0.47	0 (0.0%)	1.0
Etiology of Cirrhosis					
Alcoholic	119 (21.1%)	1 (6.7%)		5 (31.3%)	
Hepatitis B	23 (4.1%)	1 (6.7%)		0 (0.0%)	
Hepatitis C	184 (32.6%)	2 (13.3%)		4 (25.0%)	
Steatosis	56 (9.9%)	2 (13.3%)		3 (18.8%)	
Polycystic Liver/Kidney Disease [†]	1 (0.2%)	0 (0%)		0 (0%)	
Other	158 (28.0%)	8 (53.3%)		4 (25.0%)	
Living Donor Transplant	80 (14.2%)	1 (6.7%)	0.71	2 (12.5%)	1.0
Simultaneous Liver Kidney Transplant	101 (17.9%)	5 (33.3%)	0.17	2 (12.5%)	0.75
Heparin Infusion During Liver Transplantation	469 (83.2%)	14 (93.3%)	0.49	14 (87.5%)	1.0
Aminocaproic Acid Treatment During Liver Transplantation	19 (3.4%)	1 (7%)	0.41	2 (13%)	0.11
Use of vasopressors within 96 hours posttransplantation.	42 (7.4%)	0 (0%)	0.62	0 (0%)	0.62
MELD score	23 (14–35)	35 (26–41)	0.030	26 (22–31)	0.46
Pretransplant Systolic Blood Pressure (mmHg)	120 (23)	104 (14)	0.018	116 (29)	0.77
Posttransplant Systolic Blood Pressure (mmHg)	144 (25)	146 (26)	0.93	140 (14)	0.85
Pre to Posttransplant Systolic Blood Pressure Difference (mmHg)	23 (28)	42 (20)	0.026	22 (31)	1.0

Variable	Control Group (n=564)	Intraparenchymal Hemorrhage (n=15)	p-value versus control*	Extra-Axial Hemorrhage (n=16)	p-value versus control*
Pretransplant Total Bilirubin (mg/dL, reference 0.2–1.2 mg/dL)	5.7 (2.1–16.7)	19.6 (9.8–28.7)	0.011	9.9 (3.6–19.7)	0.88
Pretransplant Creatinine (mg/dL, reference 0.6–1.2 mg/dL)	1.15 (0.80–1.97)	1.09 (1.06–1.55)	1.0	0.96 (0.71–2.69)	1.0
Pretransplant Fibrinogen (mg/dL, reference 150–400 mg/dL)	153 (108–217)	125 (99–150)	0.62	100 (87–146)	0.022
Pretransplant Hemoglobin (g/dL, reference 13.5–17.5 [male], 12.0–15.5 [female])	9.1 (7.9–11.0)	7.9 (7.6–8.8)	0.15	8.4 (7.5–10.2)	0.38
Pretransplant INR (reference <1.3)	1.8 (1.4–2.5)	2.4 (2.1–3.1)	0.042	2.0 (1.6–3.0)	0.43
Pretransplant partial thromboplastin time (seconds, reference 25–35 seconds)	40.3 (33.9–50.7)	49.0 (35.6–66.5)	0.15	45.2 (36.2–62.6)	0.45
Pretransplant platelet count (thousand/ μ L, reference 150–400 thousand/ μ L)	60 (42–93)	55 (34–69)	1.0	45 (29–69)	0.083

* Post hoc Tukey's honest significant difference tests were used for normally distributed variables and post hoc Bonferroni adjusted multiple comparison tests were used for nonnormally distributed variables. Categorical variables were compared between each group of intracranial hemorrhage and controls by Fisher's exact test.

/ Polycystic liver/kidney disease patients have an increased risk of intracranial aneurysms. Diagnostic evaluation for polycystic liver/kidney disease in this patient was performed 6 years prior to transplantation at another institution. Records from the pretransplantation evaluation state no intracranial aneurysm was discovered during the patient's diagnostic evaluation for polycystic liver/kidney disease.

dL=deciliter, INR=international normalized ratio, MELD=model for end-state liver disease, mg=milligrams, mmHg=millimeters of mercury, μ L=microliters