HEPATOLOGY

HEPATOLOGY, VOL. 67, NO. 5, 2018

Bleeding Complications in Acute Liver Failure

R. Todd Stravitz,[1] Caitlyn Ellerbe,[2] Valerie Durkalski,[2] Michael Schilsky,[3] Robert J. Fontana,[4] Carolyn Peterseim,[2] William M. Lee ,[5] and the Acute Liver Failure Study Group

In patients with acute liver failure (ALF), elevated prothrombin time and thrombocytopenia can fuel a perception of a bleeding tendency. However, the incidence, site, risk factors, and clinical significance of bleeding complications have not been quantified in a large cohort of patients with ALF. We studied 1,770 adult patients enrolled in the ALF Study Group Registry between 1998 and 2016. Bleeding complications and blood component transfusions were collected for 7 days after admission. The relationship of bleeding complications to 21-day mortality was assessed. Despite a median international normalized ratio of 2.7 and platelet count of 96×10^9/L on admission, bleeding complications were observed in only 187 patients (11%), including 173 spontaneous and 22 postprocedural bleeding episodes. Eighty-four percent of spontaneous bleeding episodes were from an upper gastrointestinal source and rarely resulted in red blood cell transfusion. Twenty patients experienced an intracranial bleed; half of these occurred spontaneously and half after intracranial pressure monitor placement, and this was the proximate cause of death in 20% and 50%, respectively. Bleeders and patients who received red blood cell transfusions were more acutely ill from extrahepatic organ system failure but not from hepatocellular failure. Consistent with this observation, bleeding complications were associated with lower platelet counts but not higher international normalized ratio. Transfusion of any blood component was associated with nearly 2-fold increased death or need for liver transplantation at day 21, but bleeding complications were the proximate cause of death in only 5% of cases. *Conclusions*. Despite a perceived bleeding diathesis, clinically significant bleeding is uncommon in patients with ALF; bleeding complications in patients with ALF are markers of severe systemic inflammation rather than of coagulopathy and so portend a poor prognosis. (HEPATOLOGY 2018;67:1931-1942)

Abnormal hemostasis is integral to the definition of acute liver failure (ALF) and is characterized by an elevated international normalized ratio (INR) of the prothrombin time.[1] Recent studies have suggested that, despite the frequently intimidating elevation of the INR and moderate thrombocytopenia, global hemostasis in most patients with ALF remains normal or "rebalanced," at least *in vitro*.[2,3] Compensatory mechanisms have been identified for each phase of hemostasis in patients with ALF such that prohemostatic drivers may actually overcompensate for deficient liver-derived coagulation factors and result in a relative hypercoagulable state.[4]

Whether *in vitro* rebalance equates with clinical rebalance and a low risk of bleeding complications in patients with ALF has not been determined. Early clinical series suggested that patients with ALF had a propensity to bleed and that bleeding episodes resulted in increased morbidity and mortality.[5-7] Capillary-

Abbreviations: ALF, acute liver failure; APAP, acetaminophen; CI, confidence interval; ICP, intracranial pressure; INR, international normalized ratio; LT, liver transplantation; RBC, red blood cell; rFVIIa, recombinant factor VIIa; RRT, renal replacement therapy; SIRS, systemic inflammatory response syndrome; TFS, transplant-free survival/survivors; UGI, upper gastrointestinal.

Received June 13, 2017; accepted November 27, 2017.

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.29694/suppinfo.

The Acute Liver Failure Study Group receives funding from the National Institutes of Health, National Institute of Diabetes, Digestive and Kidney Diseases (U-01 58369).

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.29694

Potential conflict of interest: Dr. Fontana advises Alnylam and AbbVie. He received grants from Bristol-Myers Squibb and Gilead. Dr. Lee consults for Novartis and Sanofi. He received grants from Gilead, Merck, Ocera, and Exalenz.

type bleeding from mucosal erosions of the upper gastrointestinal (UGI) tract were most frequently identified as the source of bleeding, but other mucosal sites included the nasopharynx, lung, and female genitourinary tract.[7] Curiously, there has been scant mention of the bleeding incidence or its contribution to the morbidity and mortality of patients with ALF in recent series, leading to a perception that bleeding complications are not an important determinant of outcome. For example, in one of the largest series of ALF patients ever reported (over 2,000 cases), bleeding was not mentioned as a complication of ALF or a cofactor in poor outcome.[8] The absence of a contemporary update on the incidence and significance of bleeding complications and the recent laboratory evidence of rebalanced hemostasis may have contributed to the recommendation that "no routine correction of coagulation abnormalities" is warranted in patients with ALF.[9]

Routine assays of hemostasis performed *in vitro* may not reflect hemostasis *in vivo* accurately; all coagulation assays are deficient in certain components of the hemostatic system, for example, endothelial factors,[10] anticoagulant pathways, and activated platelets. Nevertheless, clinicians continue to rely on the INR to assess bleeding risk, either from spontaneous bleeding or after an invasive procedure. In the present study, we have sought to reanalyze the risk of bleeding in patients with ALF enrolled in the US ALF Study Group Registry. The registry has prospectively collected clinical and laboratory data on more than 2,800 patients with ALF since 1998, including bleeding complications and transfusions of blood components early after admission. In the present work, we quantified the incidence of spontaneous and postprocedural bleeding complications; estimated the severity of bleeding; and explored the indications for blood component transfusion, associated bleeding complications, and receipt of transfusions to 21-day outcome of patients with ALF.

Patients and Methods

PATIENTS

Study patients were recently described,[11] and accrual in the present study followed the algorithm in Supporting Fig. S1. ALF was defined by standard criteria reported by the ALF Study Group.[12] All patients with ALF in the ALF Study Group Registry enrolled between January 1, 1998, and January 1, 2016, were eligible for inclusion. Of the 2,345 patients who were screened, 575 (24%) were excluded for missing data. The 21-day outcome of the remaining 1,770 patients who met entry criteria included 781 (44%) who recovered without liver transplantation (LT; spontaneous survivors), 430 (24%) who underwent LT, and 559 (32%) who died.

As the percent of excluded patients due to missing data was significant, we performed a comparison of included and excluded registry enrollees (Supporting Table S1). Excluded patients appear to have been less acutely ill than included patients, and the missing data suggest that they were less intensively followed. Specifically, excluded patients were less likely to have the systemic inflammatory response syndrome (SIRS), were less likely to have high-grade hepatic encephalopathy, and had higher platelet counts and lower INRs on admission than included patients. Excluded patients were also slightly less likely to have had a bleeding complication after study admission (7.4% versus 10.6%), less likely to receive a blood component transfusion during admission, and less likely to have died at 21 days than included patients. However, bleeding complications as the cause of death were similar in the two groups.

ARTICLE INFORMATION:

From the [1]Hume-Lee Transplant Center of Virginia Commonwealth University, Richmond, VA; [2]Department of Biostatistics, Medical University of South Carolina, Charleston, SC; [3]Division of Gastroenterology and Hepatology, Yale University, New Haven, CT; [4]Division of Gastroenterology, University of Michigan, Ann Arbor, MI; [5]University of Texas-Southwestern Medical Center, Dallas, TX.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

R. Todd Stravitz, M.D., F.A.A.S.L.D.
Hume-Lee Transplant Center of Virginia Commonwealth University
PO Box 980341
Richmond, VA 23298-0341
E-mail: Richard.Stravitz@VCUHealth.org
Tel: +1-804-828-8514

TABLE 1. Sites and Causes of Bleeding Complications in Patients With ALF

Cause of Bleeding	Bleeding Site	Total Occurrences* (n)	Cause of Death (n)
Spontaneous	UGI	163	3
	Intracranial	10	2
Postprocedural	Venous access site	8	0
	Intracranial (ICP monitor)	10	5
	Nasopharyngeal	2	0
	Genitourinary	2	0
Total		195	10

*n = 2 had both spontaneous UGI and spontaneous intracranial bleeding; n = 2 had both spontaneous UGI and postprocedural intracranial bleeding; n = 4 had both spontaneous UGI and postprocedural bleeding at venous access site.

DEFINITIONS AND DATA COLLECTION

Bleeding complications were reported daily by the study site clinical investigators from admission (day 1) through day 7. No formal definition of bleeding was specified in the registry's manual of operations, although sites were required to specify on each day whether bleeding had occurred and, if so, the site of origin. Bleeding was recorded as "gastrointestinal" or "other," where the other site of bleeding was required to be entered manually. The case report forms for all bleeders were reviewed by the study's principal investigator (R.T.S.), classified as either spontaneous (non-procedure-related) or postprocedural, and further classified according to the site of bleeding. The adjudication process was deliberately designed to be overly inclusive without regard to the severity of bleeding or whether the bleeding episode resulted in red blood cell (RBC) transfusion. Additional bleeders were identified through review of case report forms where subjects were identified as having a hemorrhage on imaging studies, as an intracranial pressure (ICP) complication, or as the cause of death. Case report forms of all patients in whom the site's clinical investigator indicated that a bleeding complication contributed to a patient's death by day 21 were reviewed in order to adjudicate the role of bleeding in the death and to classify the bleeding as spontaneous or postprocedural. Daily recording of the following was also required: transfusion of blood products (RBCs, platelets, and plasma); administration of vitamin K, recombinant activated factor VII (rFVIIa), gastric acid suppression, vasopressors, and *N*-acetylcysteine; and management decisions including hemodialysis, renal replacement therapy (RRT), mechanical ventilation, liver biopsy, and ICP monitoring. Subjects were not considered bleeders if the episode occurred during or after LT.

STATISTICAL ANALYSIS

SAS software (version 9.4; Cary, NC) was used to perform statistical analyses. Baseline variables were described using counts and percentages for categorical data or means and standard deviations (medians and interquartile ranges) for continuous normal (skewed) data. For variables identified as clinically relevant, statistical tests were performed using chi-squared, analysis of variance, or Kruskal-Wallis tests. Modeling of hemoglobin, platelet, and INR values over time was performed using a linear mixed model with unstructured covariance for each patient to account for the within-patient correlation across measurement days, where bleeding was defined as a dichotomous indicator of bleeding at any time between admission and day 7, LT, discharge, or death. The figures illustrate mean hemoglobin, platelet, and INR estimates for each observation day adjusted for the correlation across measurement days (i.e., least square means). Hazards of LT or death are shown as Kaplan-Meier curves with log-rank test statistics. All statistical tests are reported as two-sided with a type I error rate of 5%.

Results

INCIDENCE AND CLINICAL CHARACTERISTICS OF BLEEDING COMPLICATIONS

A total of 1,770 adults with ALF entered the study, of whom 430 (24%) underwent LT and 559 (32%) died by day 21. Two hundred thirty-seven patients (13%) underwent ICP monitor placement, the procedure with the highest potential morbidity and mortality from bleeding complications. One hundred ninety-five bleeding complications occurred in 187 patients with ALF (Table 1), for an overall incidence of 10.6%

TABLE 2. Demographic and Clinical Features of Patients With ALF With and Without Bleeding Complications During Days 1-7

Clinical Feature	n	Nonbleeders (n = 1,583) n ± SD (%)	Bleeders (n = 187) n ± SD (%)	*P*
Demographics				
Age (years)	1,770	41 ± 15	42 ± 14	0.499
Gender (% female)	1,770	1,109 (70.1)	112 (59.9)	0.006
Race (% Caucasian)	1,770	1,164 (73.5)	145 (77.5)	0.274
APAP etiology of ALF	1,770	710 (44.9)	88 (47.1)	0.62
Clinical features on admission				
Symptoms to enrollment (days)	1,719	6 ± 13	5 ± 11	0.100
Plasma before admission	1,720	644 (41.9)	118 (64.8)	<0.001
Anticoagulants	1,770	41 (2.6)	5 (2.7)	—
Aspirin	1,770	83 (5.2)	17 (9.1)	0.047
SIRS (% ≥ 2 components)	1,364	894 (74.4)	130 (80.2)	0.127
SIRS-temperature (n <36°C or >38°C)	1,710	425 (28)	66 (37)	0.014
SIRS-pulse (beats/minute)	1,757	97 ± 29	105 ± 32	<0.001
SIRS-respiratory rate (breaths/minute)	1,721	19 ± 8	20 ± 10	0.09
SIRS-PCO_2 (mm Hg)	1,335	31 ± 10	30 ± 10	0.028
SIRS-WBC (N <4 or >12×10^9/L)	1,770	723 (46)	100 (53)	0.052
Ammonia (μM)	1,032	99.0 ± 95.0	93.0 ± 79.5	0.244
Encephalopathy grade 3/4	1,721	733 (47.8)	115 (61.5)	<0.001
Creatinine (mg/dL)	1,766	1.6 ± 2.1	2.2 ± 2.3	<0.001
INR	1,770	2.8 ± 2.2	2.7 ± 2.4	0.895
Total bilirubin (mg/dL)	1,752	7.6 ± 16.4	6.8 ± 13.1	0.226
Albumin (g/dL)	1,616	2.7 ± 0.8	2.7 ± 0.6	0.549
Lactate (mg/dL)	971	4.4 ± 6.0	5.4 ± 8.2	0.002
Bicarbonate (mg/dL)	1,481	22.0 ± 8.0	20.0 ± 10.0	0.002
Phosphate (mg/dL)	1,539	3.1 ± 2.3	3.8 ± 2.9	<0.001
Platelet count (×10^9/L)	1,770	128 ± 108	96 ± 92	<0.001
WBC (×10^9/L)	1,770	10.1 ± 8.1	10.6 ± 9.7	0.239
Hemoglobin (g/dL)	1,764	11.1 ± 3.1	10.3 ± 2.8	<0.001
Clinical features after admission, days 1-7				
INR peak	1,770	3.3 ± 2.7	3.2 ± 3.3	0.22
Platelet count nadir (×10^9/L)	1,770	77 ± 81	53 ± 45	<0.001
Hemoglobin nadir (g/dL)	1,770	9.2 ± 2.5	8.4 ± 2.1	<0.001
Encephalopathy grade 3/4	1,734	981 (63.4)	161 (86.1)	<0.001
Infection	1,770	155 (9.8)	16 (8.6)	0.682
Interventions after admission, days 1-7				
ICP monitor placement	1,634	201 (13.8)	36 (20.7)	0.019
RRT	1,770	534 (33.7)	107 (57.2)	<0.001
Vasopressors	1,770	531 (33.5)	121 (64.7)	<0.001
N-Acetylcysteine	1,770	967 (61.1)	121 (64.7)	0.378
Gastric acid suppression	1,770	1,267 (80.0)	162 (86.6)	0.039
RBC transfusion	1,770	265 (16.7)	30 (16.0)	0.89
Plasma transfusion	1,770	531 (33.5)	120 (64.2)	<0.001
Platelet transfusion	1,770	849 (53.6)	145 (77.5)	<0.001
Outcomes at day 21				
TFS	1,770	723 (45.7)	58 (31.0)	<0.001
LT	1,757	407 (25.9)	23 (12.4)	<0.001
Died after LT	430	39 (9.6)	1 (4.3)	<0.001
Died	1,770	492 (31.1)	107 (57.2)	<0.001

Abbreviations: PCO_2, partial pressure of carbon dioxide; WBC, white blood cell.

during the first 7 days of admission; 8 patients experienced more than one bleeding complication. Of all bleeding episodes, 173 were spontaneous (89%) and 22 were postprocedural (11%). The vast majority of spontaneous bleeding complications were from a UGI source (163 of 173 complications; 94%), with 10 additional spontaneous bleeds occurring at an intracranial site either before placement or in the absence of an ICP monitor. Postprocedural bleeding from venous access sites was recorded in 8 cases, a nasopharyngeal source after nasogastric tube placement in 2 cases, a genitourinary source after urinary bladder catheterization in 2 cases, and after ICP monitor placement in 10 cases, 5 of which resulted in death. In patients with a

recorded primary cause of death (484/599), bleeding complications (spontaneous or postprocedural) were deemed the proximate cause of death in 10 patients (2.1%), 7 of whom had spontaneous or post-ICP monitor intracranial bleeding. An additional 6 patients who died between 8 and 21 days also had bleeding listed as a cause of death (3.3%). Bleeding episodes most frequently occurred on a single day after admission to the study site (58%) or resolved within 2 days (22%) and most commonly occurred on day 1 (52%; data not shown).

COMPARISON OF PATIENTS WITH AND WITHOUT BLEEDING COMPLICATIONS

Clinical features of bleeders and nonbleeders are compared in Table 2. Bleeders were more often male than nonbleeders (40 versus 30%, respectively; $P = 0.006$) but were otherwise demographically similar. Bleeding complications occurred as frequently in patients with acetaminophen (APAP)–induced as in those with non-APAP-induced etiology. The time delay of presentation for medical care (onset of ALF symptoms to study enrollment) was similar between the two groups (5 versus 6 days in bleeders and nonbleeders, respectively; $P = 0.10$). Although bleeding episodes prior to transfer to the study site were not recorded, bleeders were more likely to have received plasma transfusion prior to study admission (65 versus 42%, respectively; $P < 0.001$) and more likely to have been taking aspirin on admission (9 versus 5%, respectively; $P = 0.045$) than nonbleeders. However, there was no difference in the proportion of patients on anticoagulants at the time of study admission in the two groups.

Bleeders were generally more systemically ill than nonbleeders and had more extrahepatic organ dysfunction (Table 2). Although the prevalence of SIRS defined as two or more positive components was only modestly higher in bleeders than nonbleeders (80 versus 74%, respectively; $P = 0.127$), individual components of SIRS reflected a greater severity of systemic inflammation in bleeders, including the two-sided temperature (<36°C or >38°C, 37% versus 28%, $P = 0.014$) and white blood cell criteria (<4 or $>12 \times 10^9$/L, 53% versus 46%, $P = 0.052$), pulse ($P < 0.001$), and partial pressure of CO_2 ($P = 0.028$), with a trend toward a higher respiratory rate in bleeders ($P = 0.09$). Bleeders more frequently developed high-grade (grade 3 or 4) hepatic encephalopathy (62% versus 48% on admission and 86% versus 63% over days 1-7) and had higher serum creatinine (2.2 ± 2.3 versus 1.6 ± 2.1 mg/dL), higher lactate (5.4 ± 8.2 versus 4.4 ± 6.0 mg/dL), lower bicarbonate (20.0 ± 10.0 versus 22.0 ± 8.0 mg/dL), and higher phosphate (3.8 ± 2.9 versus 3.1 ± 2.3 mg/dL) than nonbleeders ($P < 0.001$, except for lactate and bicarbonate, $P = 0.002$). Although abnormal laboratory parameters of extrahepatic organ dysfunction were more severe in bleeders, bleeders and nonbleeders had similar degrees of liver dysfunction as assessed by INR, bilirubin, ammonia, and albumin, which were not statistically different between the two groups.

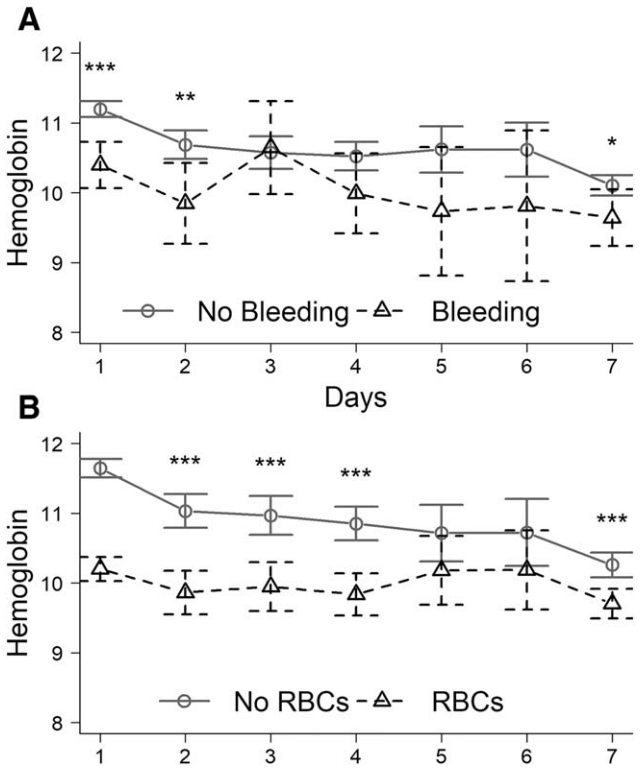

FIG. 1. Blood hemoglobin concentration (grams per deciliter) on each day after admission for ALF. (A) Hemoglobin according to study day in early bleeders versus nonbleeders. (B) Hemoglobin according to study day in patients who received RBC transfusions versus those who did not. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

Baseline hemoglobin on admission to the study in bleeders was lower than that in nonbleeders (10.3 ± 2.8 versus 11.1 ± 3.1 g/dL, respectively; $P < 0.001$); nadir hemoglobin over the first 7 days of admission was also lower in bleeders than nonbleeders (8.4 ± 2.1 versus 9.2 ± 2.5 g/dL; $P < 0.001$). However, the mean percent decrease in hemoglobin from admission to nadir in bleeders and nonbleeders was similar (decrease of 15%

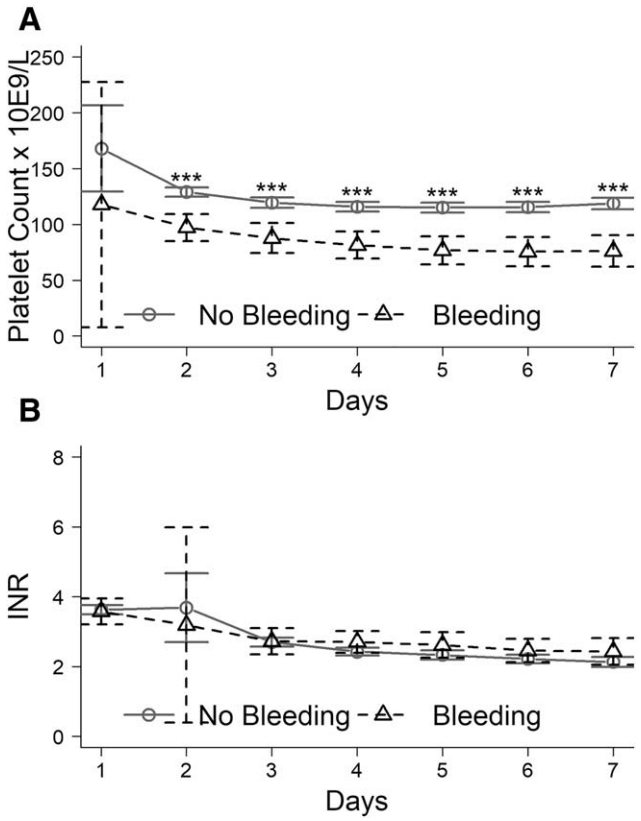

FIG. 2. INR (A) and platelet count (B) of patients on days 1-7 after admission to the study according to the occurrence of bleeding complications. ***$P < 0.001$.

and 14%, respectively), and the hemoglobin concentration was similar between the groups on each day after day 2 (Fig. 1A).

Although both the admission and the nadir platelet count were lower in bleeders (96 ± 92 and $53 \pm 45 \times 10^9$/L) than nonbleeders (128 ± 108 and $77 \pm 81 \times 10^9$/L, respectively; both $P < 0.001$), the admission and peak INR in bleeders (2.7 ± 2.4 and 3.2 ± 3.3) were not significantly different from peaks in nonbleeders (2.8 ± 2.2 and 3.3 ± 2.7, respectively). In fact, bleeders had significantly lower platelet counts than nonbleeders on each study day ($P < 0.001$ for each day; Fig. 2A), while INR was similar between the groups on each day (Fig. 2B). There was no relationship of the platelet count to the INR on admission in bleeders or nonbleeders ($r^2 = 0.03$ and 0.01, respectively; data not shown).

Bleeders also received many more therapeutic interventions than nonbleeders, reflecting the severity of their systemic illness (Table 2). The incidence of ICP monitor placement (20% versus 14%) and RRT (57% versus 34%); the administration of vasopressors (65% versus 34%) and gastric acid suppressants (87% versus 80%); and the transfusion of plasma (64% versus 34%) and platelets (78% versus 54%) were higher in bleeders than nonbleeders, respectively (all $P < 0.001$ except for ICP monitor placement and gastric acid suppressants, $P = 0.019$ and $P = 0.039$, respectively). Interestingly, transfusion of RBC in bleeders was not different from that in nonbleeders (16% versus 17%, respectively), again suggesting that the magnitude of the bleeding complication was small. The administration of *N*-acetylcysteine, which theoretically might increase bleeding episodes by decreasing von Willebrand factor multimer size,[13] was not associated with bleeding complications.

COMPARISON OF PATIENTS WHO RECEIVED AND DID NOT RECEIVE RBC TRANSFUSIONS

The clinical characteristics of patients who received RBC transfusions differed from those of bleeders in several regards. Many more patients received RBC transfusions (651/1,770; 37%) than experienced bleeding complications (187/1,770; 11%); of the 651 patients who received RBC transfusions, only 120 (18%) experienced bleeding complications (Table 3). However, bleeding complications were significantly more common in patients who received RBC transfusions than in those who did not (18% versus 6%, respectively; $P < 0.001$). Although a greater proportion of bleeders than nonbleeders were men, a greater proportion of those who received RBC transfusions than those who did not were women (73% versus 67%, respectively; $P = 0.003$), possibly due to the fact that women entered the study with a lower mean hemoglobin than did men (10.7 versus 11.9 g/dL, data not shown). In addition, comparison of serum hemoglobin concentrations in RBC-transfused and nontransfused patients (Fig. 1B) suggests that the former were transfused for anemia on admission rather than an acute drop in hemoglobin after admission. Indeed, the mean decrease in hemoglobin from admission to nadir in RBC-transfused and nontransfused patients was similar (15% and 13%, respectively), and the difference in hemoglobin in transfused and nontransfused patients (Fig. 1B) was greater than the difference between bleeders and nonbleeders (Fig. 1A), both suggesting that the indication for transfusion was anemia rather than bleeding.

Otherwise, patients who received RBC transfusions resembled bleeders (Table 3): they were more acutely ill than those who were not transfused, more frequently

TABLE 3. Clinical Characteristics of Patients With ALF Who Received or Did Not Receive RBC Transfusion During Days 1-7

Clinical Feature	n	No RBC Transfusions n = 1,119 (Mean n, %)	RBC Transfusions n = 651 (Mean n, %)	*P*
Demographics				
Age (years)	1,770	42 ± 15	41 ± 14	0.15
Gender (% female)	1,770	744 (66.5)	477 (73.3)	0.003
Race (Caucasian)	1,770	842 (75.2)	467 (71.7)	0.117
APAP etiology of ALF	1,770	523 (46.7)	275 (42.2)	0.075
Clinical features on admission				
SIRS (% ≥ 2)	1,364	580 (72.0)	444 (79.4)	0.002
Ammonia (μM)	1,032	98.0 ± 90.0	101.0 ± 97.0	0.826
Encephalopathy grade (% 3/4)	1,721	451 (41.9)	397 (61.6)	<0.001
Creatinine (mg/dL)	1,766	1.3 ± 1.9	2.1 ± 2.3	<0.001
INR	1,770	2.9 ± 2.2	2.8 ± 2.2	0.129
Total bilirubin (mg/dL)	1,752	7.0 ± 15.6	8.0 ± 17.0	<0.001
Albumin (g/dL)	1,616	2.7 ± 0.7	2.7 ± 0.8	0.17
Lactate (mg/dL)	971	3.9 ± 4.7	5.9 ± 7.7	<0.001
Bicarbonate (mg/dL)	1,481	22.0 ± 8.0	20.0 ± 8.8	<0.001
Phosphate (mg/dL)	1,539	3.0 ± 2.2	3.4 ± 2.7	<0.001
Platelet count ($\times 10^9$/L)	1,770	133.0 ± 104.0	108.0 ± 102.5	<0.001
WBC ($\times 10^9$/L)	1,770	9.6 ± 7.4	10.9 ± 9.9	<0.001
Hemoglobin (g/dL)	1,764	11.5 ± 2.9	9.9 ± 2.9	<0.001
Clinical features after admission, days 1-7				
INR peak	1,770	3.3 ± 2.7	3.3 ± 2.8	0.586
Platelet count nadir ($\times 10^9$/L)	1,770	94.0 ± 81.0	50.0 ± 48.0	<0.001
Hemoglobin nadir (g/dL)	1,770	9.8 ± 2.5	8.2 ± 1.6	<0.001
Encephalopathy grade 3/4	1,734	613 (56.3)	529 (82.0)	<0.001
Infection	1,770	125 (11.2)	46 (7.1)	0.006
Bleeding complication	1,770	67 (6.0)	120 (18.4)	<0.001
Interventions after admission, days 1-7				
ICP monitor placement	1,634	99 (9.4)	138 (23.7)	<0.001
RRT	1,770	271 (24.2)	370 (56.8)	<0.001
Vasopressors	1,770	300 (26.8)	352 (54.1)	<0.001
N-Acetylcysteine	1,770	722 (64.5)	366 (56.2)	<0.001
Gastric acid suppression	1,770	892 (79.7)	537 (82.5)	0.172
Plasma transfusion	1,770	210 (18.8)	85 (13.1)	0.002
Platelet transfusion	1,770	451 (40.3)	543 (83.4)	<0.001

Abbreviation: WBC, white blood cell.

met SIRS criteria ($P = 0.002$), had a higher proportion of patients reaching high-grade (3 or 4) encephalopathy ($P < 0.001$), had laboratory parameters reflecting more severe systemic illness, and received more therapeutic interventions than those who did not receive RBC transfusions. Also similar to bleeders, receiving RBC transfusions had no consistent relationship to the severity of liver injury by INR but was significantly related to the platelet count, a marker of systemic inflammation.

RELATIONSHIP OF BLOOD COMPONENT TRANSFUSION TO BLEEDING COMPLICATIONS

Although patients who experienced bleeding complications were more likely to receive transfusion of platelets and/or plasma than nonbleeders (Table 2), the majority of blood components transfused did not appear to be in response to bleeding complications. Over the first 7 days of admission, 37%, 56%, and 26% of study patients received RBC, plasma, and platelets, respectively (Table 4). However, most patients who received RBC, plasma, or platelets were nonbleeders (82%, 85%, and 81%, respectively). In addition, 5%-6% of patients transfused received blood components before the occurrence of their bleeding complication, indicating that bleeding was not the indication for the transfusion. Therefore, at a minimum, 87%, 91%, and 86% of patients who received RBC, plasma, and platelets, respectively, were transfused for an indication other than active bleeding (for example, for nonhemorrhagic anemia or prophylaxis before an invasive procedure).

The practice of administering blood products (RBC, plasma, and/or platelets) during days 1-7 for any

TABLE 4. Relationship of Blood Component Administration to Early Bleeding Complications

	Patients Receiving Blood Component Transfusions, n (%)				
		Bleeders Transfused			
Blood Component	Total Transfused	Before Bleeding	At or After Bleeding*	Nonbleeders Transfused	Total Transfused for Nonbleeding Indication†
RBC	651 (37%)	34 (5.2%)	86 (13%)	531 (82%)	565 (87%)
Plasma	994 (56%)	60 (6.0%)	85 (8.6%)	849 (85%)	909 (91%)
Platelets	435 (26%)	22 (5.1%)	60 (14%)	353 (81%)	375 (86%)

*Defined as patients who received blood component transfusion on the same day as, or any day after, bleeding complication.
†Includes nonbleeders who received blood component transfusions and bleeders who received transfusions before their bleeding episodes.

indication has decreased by 2.6%/year between 1998 and 2015. Nevertheless, the incidence of bleeding complications has remained stable over the same time frame (mean 10.7 ± 3.8%/year) (Supporting Fig. S2). Because the majority of transfusions were given as prophylaxis, this observation suggests that withholding transfusions has not increased bleeding complications in patients with ALF.

RELATIONSHIP OF BLOOD PRODUCT TRANSFUSION AND BLEEDING COMPLICATIONS TO OUTCOME OF ALF

The incidence of bleeding complications according to 21-day outcome in spontaneous survivors, those who underwent LT, and those who died was 7%, 5%, and 18%, respectively. The data in Table 5 depict the association of blood product transfusion, vitamin K, and rFVIIa during the first 7 days of admission to outcome at day 21. Patients who received RBC, plasma, or platelet transfusions were nearly twice as likely to have died or undergone LT at day 21 than nontransfused patients. Of the 944 patients who died or underwent LT, RBC, plasma, or platelets were transfused in 45%, 70%, and 32%, respectively; of 713 spontaneous survivors, transfusions were recorded in 27%, 39%, and 16%, respectively (all $P < 0.001$). Receipt of any blood product was observed in approximately 70% of patients who died or underwent LT but only approximately 30% of spontaneous survivors (data not shown). Although relatively few patients received rFVIIa (n = 37), most died or underwent LT (76%); and the prevalence of receiving rFVIIa was over 3-fold higher in this group compared to spontaneous survivors ($P = 0.022$). Outcomes were significantly better in patients who received vitamin K than those who did not, with vitamin K received by 20% of spontaneous survivors but by only 15% of those who died or underwent LT ($P = 0.006$).

As a total study population, bleeding complications during the first 7 days of admission were associated with negative outcomes at day 21, with a transplant-free survival (TFS) rate among bleeders of 28% (median time to transplant/death 6 days; 95% confidence interval [CI], 4-7 days), while the TFS rate among nonbleeders was 45% (median time to transplant/death 12 days; 95% CI, 9-18 days; $P < 0.001$; data not shown). However, the Kaplan-Meier curves

TABLE 5. Relationship Between Transfusion of RBC, Plasma, or Platelets Between Days 1 and 7 to Outcome of ALF at Day 21

	Outcome at Day 21				
		Nonspontaneous Survivors			
Treatment During Inpatient (Days 1-7)	Spontaneous Survivors (n = 713) n (%)	All (n = 944) n (%)	LT (n = 430) n (%)	Death (n = 599) n (%)	P*
Vitamin K	152 (20%)	143 (15%)	54 (13%)	92 (15%)	0.006
rVIIa	9 (1.2%)	28 (2.8%)	16 (4%)	13 (2%)	0.022
RBC transfusion	207 (27%)	444 (45%)	197 (46%)	278 (46%)	<0.001
Plasma transfusion	302 (39%)	692 (70%)	312 (73%)	415 (69%)	<0.001
Platelet transfusion	122 (16%)	313 (32%)	141 (33%)	192 (32%)	<0.001

**P* value compares probability of receiving the indicated treatment between spontaneous survivors and subjects who received LT and/or died.

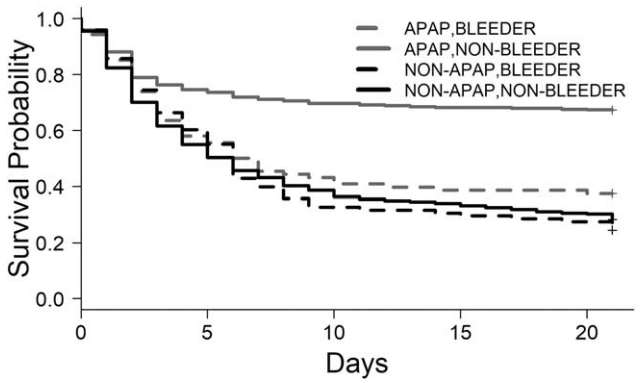

FIG. 3. Kaplan-Meier curve of TFS according to the occurrence of bleeding complications between days 1 and 7 in patients with APAP-induced and non-APAP-induced ALF. Overall, the TFS among nonbleeders was 45.2%, with a median time to transplant/death occurring at 12 (95% CI, 9-18) days, and that among bleeders was 27.6%, with a median time to transplant/death occurring at 6 (95% CI, 4-7) days ($P < 0.001$). According to etiology, this difference is due to a difference in patients with APAP-induced ALF ($P < 0.001$); there was no significant difference in TFS in patients with non-APAP-induced ALF according to the occurrence of bleeding complications.

in Fig. 3 show that the presence of bleeding complications only affected TFS in patients with APAP-induced ALF (TFS 34% in bleeders versus 63% in nonbleeders; $P < 0.001$) but not in patients with non-APAP ALF.

Discussion

The incidence of bleeding complications in this large, contemporary population with ALF was approximately 11%, the majority of whom had clinically insignificant bleeding. These findings from the ALF Study Group Registry contrast with older historical reports, in which many patients not only bled but died from the bleed. In an early autopsy series of patients with ALF, Gazzard et al.[6] reported that ~30% died of a bleeding complication, ~90% of whom bled from a gastrointestinal source. Other early series reported that the incidence of bleeding complications ranged between 50% and 70%, with death reported from bleeding in ≥30%.[5,7,14] Although the incidence and mortality of bleeding complications have decreased for critically ill patients in general,[15] these data support the emerging consensus that patients with ALF are not at major risk of significant bleeding complications despite their dramatically elevated INR.

The International Society of Thrombosis and Haemostasis has defined "major bleeding" as causing death, occurring in a critical area or organ (including intracranial), and/or the need for RBC transfusion in the setting of a bleed associated with a ≥2 g/dL drop in hemoglobin.[16] The preponderance of evidence in the present series suggests that few bleeding complications in patients with ALF would be categorized as major or even clinically significant. First, 87% of RBC-transfused patients received the transfusion for an indication other than a bleeding complication, presumably for anemia (Table 4). Second, the magnitude of decrease in hemoglobin from study admission to nadir within 7 days was nearly identical in patients who experienced bleeding complications and those who did not (decrease of 15 versus 14%, respectively). Third, in patients who died with a reason for death recorded, only 10 of 1,770 patients reviewed were considered to have died as a consequence of a bleeding complication, 7 of whom died of intracranial hemorrhage, with 5 of these likely related to ICP monitor placement. Finally, differences in mortality between bleeders and nonbleeders were only observed after day 7 (Fig. 3), suggesting a temporal dissociation between the bleeding episode and death. The finding that 10 patients had intracranial bleeds in the absence of an ICP monitor, presumably a complication of cerebral edema, has not been reported.

Although postprocedural bleeding complications remain a significant concern for clinicians caring for patients with ALF, the data suggest that they are rare. For example, 641 patients underwent central venous catheter placement for RRT, yet there were fewer than five instances of bleeding at the insertion site (0.8%); no other more serious bleeding complications were reported. The observation appears to support a recent series from an intensive care liver unit, in which 658 central venous cannulations in 283 patients (~35% with APAP overdose) with INR ≥1.5 and/or platelet count $\leq 150 \times 10^9$/L and without routine plasma or platelet transfusion resulted in only one serious bleeding complication, a hemothorax.[17] Our low incidence of bleeding after RRT catheter insertion may have been influenced by blood product prophylaxis, but the above study in which plasma and platelets were only transfused in 1.8% and 4.2% of patients, respectively, also raises the question of whether such prophylaxis was necessary in the first place. The observation that there has been a steady decline in blood component transfusion over the 17 years of data collection by the ALF Study Group without an increase in bleeding

complications (Supporting Fig. S2) also raises this question. Intracranial bleeding after ICP monitor placement, however, remains a significant threat, although it is uncommon, occurring in 10 of 237 (4.2%) of our study patients, 5 of whom (2%) probably died of complications of the bleed. These statistics compare favorably with fatal bleeding complication rates of 1%, 5%, and 4% of patients with ALF who received ICP monitors in epidural, subdural, and intraparenchymal locations, respectively.[18] These data highlight the fact that placement of an ICP carries a significant risk of intracranial bleeding and death.

Despite their generally mild severity, bleeding complications were associated with lower 21-day TFS (Fig. 3) but only for patients with APAP-induced ALF. The occurrence of bleeding complications had no effect on TFS in patients with non-APAP-induced ALF. In other analyses, we have found the occurrence of bleeding complications in patients with APAP-induced ALF to be a marker of particularly severe acute illness (data not shown). The 21-day outcome of LT or death was nearly 2-fold higher in patients who received transfusion of any blood component within the first 7 days of admission (Table 5). Therefore, it is also conceivable that administering blood components early after admission has adverse effects that are particularly significant for patients with APAP-induced ALF, possibly by exacerbating a preexisting hypercoagulable state, resulting in microvascular thrombosis within the liver and peripheral circulation and compounding the primary liver injury[19] and poor peripheral tissue perfusion,[20] respectively. Other hazards of blood product transfusion, such as volume overload, transfusion-associated lung injury, immune dysregulation, and exacerbation of intracranial hypertension, are also possible.

The data also suggest that bleeding complications and the development of anemia are primarily due to severe systemic inflammation. In Tables 2 and 3, both bleeders and those receiving RBC transfusions are characterized by clinical features and laboratories suggestive of more severe systemic injury than nonbleeders and nontransfused patients, respectively. The finding that platelet count was significantly lower in bleeders and RBC-transfused patients is consistent with this hypothesis because we have recently shown in the same patient population that the decline in platelet count after admission is proportional to the severity of systemic complications and SIRS.[11] The fact that the INR is not different between these populations is also consistent with our previous observations that the INR does not vary with the severity of systemic inflammation. Another interpretation of these data might be that lower platelet count, but not a higher INR, is a more important risk factor for bleeding complications, as has been suggested by other authors.[6]

For the vast majority of patients with ALF and UGI bleeding, the likely source is stress-related mucosal disease, a manifestation of critical illness characterized by intense systemic inflammation.[21] In a recent survey of >1,000 intensive care unit patients, clinically significant UGI bleeding occurred in only 2.6%, but risk factors included three integral features of the ALF syndrome: liver disease (odds ratio, 7.6), coagulopathy (odds ratio, 5.2), and RRT (odds ratio, 6.9).[15] The responsible lesion, subepithelial hemorrhage, is caused by gastric mucosal ischemia proportional to the severity of underlying illness, rather than defective hemostasis.[21] Consequently, prophylaxis with acid suppression has not been universally shown to decrease its incidence.[22] Although early studies in patients with ALF suggested benefit from histamine-2-receptor antagonists,[23] our data suggest no apparent benefit from gastric acid inhibition. The difference between early and contemporary series may be a recent overall decrease in stress-related mucosal disease as a result of improved intensive care unit care, resulting in decreased mucosal hypoperfusion.[22]

There are multiple possible explanations for the low incidence and mild severity of bleeding complications in patients with ALF. Thrombin generation in ALF is generally normal *in vitro* in the presence of thrombomodulin.[24,25] Deficiency of liver-derived procoagulant proteins is proportional to deficiency of anticoagulant proteins.[2] Von Willebrand factor and factor VIII levels are increased dramatically due to endothelial activation/injury from SIRS.[26,27] Procoagulant microparticles are released by systemic inflammation.[28] Finally, fibrinolysis is severely impaired such that clot lysis in many patients cannot be detected.[24] Another obvious possibility remains unproven: administering prophylactic blood components to treat the high INR and low platelets is effective in decreasing bleeding complications.

We acknowledge limitations in our data and conclusions. The ALF Study Group Registry was not designed to link bleeding complications to specific procedures, blood product transfusions, and episodes of hemodynamic instability; and *post hoc* analyses without predefined research questions increase the risk of bias. Missing data led to exclusion of 24% of registry participants with the consequences noted in Supporting

Table S1: the apparent exclusion of less acutely ill patients from the analysis. We emphasize, however, that we aimed to describe a "worst-case scenario" in order not to underemphasize the risks of bleeding in patients with ALF; and the exclusion of these patients should, therefore, not have contributed to an underestimate of the risk. Although an earlier version of the *Registry Operations Protocol Manual* required quantitation of administered blood products, a later version has not. The clinical indication for transfusion of a specific blood product was also not captured. Therefore, some of our conclusions were admittedly reached on circumstantial evidence.

In conclusion, bleeding complications in patients with ALF are primarily clinically insignificant. Spontaneous bleeding complications are comprised overwhelmingly of self-limited UGI bleeding, which appears to have decreased in incidence and severity over the last 40 years. Postprocedural complications remain rare, and those linked to the death of patients with ALF were universally complications of ICP monitor placement. Transfusion of blood components is associated with increased 21-day poor outcome (LT and/or death). Future study must answer an important question raised by this report: does prohemostatic blood component transfusion decrease bleeding complications or adversely affect patients with ALF?

Acknowledgment: We acknowledge the support of our National Institute of Diabetes and Digestive and Kidney Diseases project officers, Drs. Edward Doo and Averell Sherker.

REFERENCES

1) Trey C, Davidson CS. The management of fulminant hepatic failure. Prog Liver Dis 1970;3:282-298.
2) Stravitz RT, Lisman T, Luketic VA, Sterling RK, Puri P, Fuchs M, et al. Minimal effects of acute liver injury/acute liver failure on hemostasis as assessed by thromboelastography. J Hepatol 2012;56:129-136.
3) Agarwal B, Wright G, Gatt A, Riddell A, Vemala V, Mallett S, et al. Evaluation of coagulation abnormalities in acute liver failure. J Hepatol 2012;57:780-786.
4) Lisman T, Stravitz RT. Rebalanced hemostasis in patients with acute liver failure. Semin Thromb Hemost 2015;41:468-473.
5) Ritt DJ, Whelan G, Werner DJ, Eigenbrodt EH, Schenker S, Combes B. Acute hepatic necrosis with stupor or coma. An analysis of thirty-one patients. Medicine (Baltimore) 1969;48:151-172.
6) Gazzard BG, Portmann B, Murray-Lyon IM, Williams R. Causes of death in fulminant hepatic failure and relationship to quantitative histological assessment of parenchymal damage. Q J Med 1975;44:615-626.
7) Tandon BN, Joshi YK, Tandon M. Acute liver failure. Experience with 145 patients. J Clin Gastroenterol 1986;8:664-668.
8) Bernal W, Hyyrylainen A, Gera A, Audimoolam VK, McPhail MJ, Auzinger G, et al. Lessons from look-back in acute liver failure? A single centre experience of 3300 patients. J Hepatol 2013;59:74-80.
9) Bernal W, Wendon J. Acute liver failure. N Engl J Med 2013;369:2525-2534.
10) Tripodi A, Salerno F, Chantarangkul V, Clerici M, Cazzaniga M, Primignani M, et al. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. HEPATOLOGY 2005;41:553-558.
11) Stravitz RT, Ellerbe C, Durkalski V, Reuben A, Lisman T, Lee WM. Thrombocytopenia is associated with multi-organ system failure in patients with acute liver failure. Clin Gastroenterol Hepatol 2016;14:613-620.
12) Reuben A, Tillman H, Fontana RJ, Davern T, McGuire B, Stravitz RT, et al. Outcomes in adults with acute liver failure between 1998 and 2013: an observational cohort study. Ann Intern Med 2016;164:724-732.
13) Chen J, Reheman A, Gushiken FC, Nolasco L, Fu X, Moake JL, et al. *N*-Acetylcysteine reduces the size and activity of von Willebrand factor in human plasma and mice. J Clin Invest 2011;121:593-603.
14) Saunders SJ, Hickman R, Macdonald R, Terblanche J. The treatment of acute liver failure. Prog Liver Dis 1972;4:333-344.
15) Krag M, Perner A, Wetterslev J, Wise MP, Borthwick M, Bendel S, et al. Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. Intensive Care Med 2015;41:833-845.
16) Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-694.
17) Fisher NC, Mutimer DJ. Central venous cannulation in patients with liver disease and coagulopathy—a prospective audit. Intensive Care Med 1999;25:481-485.
18) Blei AT, Olafsson S, Webster S, Levy R. Complications of intracranial pressure monitoring in fulminant hepatic failure. Lancet 1993;341:157-158.
19) Ganey PE, Luyendyk JP, Newport SW, Eagle TM, Maddox JF, Mackman N, et al. Role of the coagulation system in acetaminophen-induced hepatotoxicity in mice. HEPATOLOGY 2007;46:1177-1186.
20) Harrison PM, Wendon JA, Gimson AE, Alexander GJ, Williams R. Improvement by acetylcysteine of hemodynamics and oxygen transport in fulminant hepatic failure. N Engl J Med 1991;324:1852-1857.
21) Laine L, Takeuchi K, Tarnawski A. Gastric mucosal defense and cytoprotection: bench to bedside. Gastroenterology 2008;135:41-60.
22) Faisy C, Guerot E, Diehl JL, Iftimovici E, Fagon JY. Clinically significant gastrointestinal bleeding in critically ill patients with and without stress-ulcer prophylaxis. Intensive Care Med 2003;29:1306-1313.
23) Macdougall BR, Bailey RJ, Williams R. H2-receptor antagonists and antacids in the prevention of acute gastrointestinal haemorrhage in fulminant hepatic failure. Two controlled trials. Lancet 1977;1:617-619.

24) Lisman T, Bakhtiari K, Adelmeijer J, Meijers JC, Porte RJ, Stravitz RT. Intact thrombin generation and decreased fibrinolytic capacity in patients with acute liver injury or acute liver failure. J Thromb Haemost 2012;10:1312-1319.
25) Habib M, Roberts LN, Patel RK, Wendon J, Bernal W, Arya R. Evidence of rebalanced coagulation in acute liver injury and acute liver failure as measured by thrombin generation. Liver Int 2014;34:672-678.
26) Hugenholtz GC, Adelmeijer J, Meijers JC, Porte RJ, Stravitz RT, Lisman T. An unbalance between von Willebrand factor and ADAMTS13 in acute liver failure: implications for hemostasis and clinical outcome. HEPATOLOGY 2013;58:752-761.
27) Agarwal B, Gatt A, Riddell A, Wright G, Chowdary P, Jalan R, et al. Hemostasis in patients with acute kidney injury secondary to acute liver failure. Kidney Int 2013;84:158-163.
28) Stravitz RT, Bowling R, Bradford RL, Key NS, Glover S, Thacker LR, et al. Role of procoagulant microparticles in mediating complications and outcome of acute liver injury/acute liver failure. HEPATOLOGY 2013;58:304-313.

Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.29694/suppinfo.