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Acute kidney injury, but not sepsis, is associated with higher procedure-related bleeding in patients with decompensated cirrhosis

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Abstract

Background—Bleeding after low-risk invasive procedures can be life-threatening or can lead to further complications in decompensated cirrhosis patients. In unstratified cohorts of hospitalized patients with cirrhosis, the rate of procedure-related bleeding is low despite abnormal coagulation parameters. Our objective was to identify patients with decompensated cirrhosis at a high risk of developing procedure-related bleeding in whom the value of pre-procedure transfusions could be assessed.

Methods—Hospitalized patients with cirrhosis who developed post-paracentesis hemoperitoneum confirmed by CT scan, from the period of January 2012 to August 2016, constituted the study group. They were compared to patients hospitalized in the same period in whom post-paracentesis hemoperitoneum was suspected but ruled out by CT scan. A retrospective chart review was conducted to determine specifics of the adverse event, patient characteristics and risk factors for bleeding.

Results—On multivariate analysis, acute kidney injury prior to paracentesis was the only independent predictor of post-paracentesis hemoperitoneum (OR 4.3, 95% CI 1.3–13.5, $P = .01$), independent of MELD score, large volume paracentesis, sepsis, platelets, INR and haemoglobin levels.

Conclusions—Infection/sepsis is generally considered predictive of bleeding in cirrhosis. Our study suggests that acute kidney injury, and not sepsis, is the most important predictor of post-procedure bleeding in patients with decompensated cirrhosis. Although end-stage renal disease is a known cause of bleeding in non-cirrhotic patients, there are no studies establishing acute kidney injury as a risk factor for post-procedure bleeding in cirrhosis. Future studies investigating blood product transfusion needs in cirrhosis prior to procedures should carefully look at patients with acute kidney injury.

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CONFLICT OF INTEREST

The authors do not have any disclosures to report.

Keywords

acute kidney injury; bleeding; coagulopathy; cirrhosis; liver complications

1 | INTRODUCTION

Bleeding complications after low-risk invasive procedures such as paracentesis in patients with decompensated cirrhosis can be life-threatening or lead to further decompensation.^{1–4} Previous guidelines have recommended correction of international normalized ratio (INR) and platelet count through the use of fresh frozen plasma and platelet transfusion before invasive procedures to prevent bleeding.⁵ However, the usefulness of such correction is uncertain as it is now clear that patients with cirrhosis, particularly those who are decompensated (ie those with ascites) have a delicate balance between a hypocoagulable (decreased prothrombotic factors, increased bleeding tendency) and a hypercoagulable state (increased prothrombotic factors, increased thrombotic tendency), alterations that are not appropriately assessed by conventional laboratory parameters, specifically prothrombin time, INR, fibrinogen and platelets.^{6–8}

A previous study showed that the rate of severe haemorrhage among hospitalized liver patients undergoing paracentesis is low, occurring in only 0.2% of cases;⁹ however, the study was limited by an unstratified cohort of patients which prevented assessment of other potential risks factors for bleeding. A recent study using thromboelastography (TEG) to direct blood product transfusions prior to procedures in all hospitalized patients with cirrhosis demonstrated that TEG, while decreasing blood product requirements, did not change bleeding outcomes. In fact, only one patient (2%) had post-procedure bleeding after paracentesis even considering that patients had an INR >1.8 and a platelet count <50 × 10⁹/L.¹⁰ The main limitation of this study, as acknowledged by the authors, was the exclusion of patients with sepsis who were thought to be the group at the highest risk of bleeding.

The objective of our study was therefore to identify patients with decompensated cirrhosis at a high risk of developing post-procedure haemorrhage that would then constitute the target of future studies using TEG or other strategies that would decrease not only blood product transfusion, but also post-procedure bleeding.

2 | PATIENTS AND METHODS**2.1 | Patient selection**

Patients with cirrhosis and ascites who had been hospitalized at Yale New Haven Hospital and had an inpatient paracentesis during the period of January 2012 to August 2016 were included in the study. Among this cohort, two groups of patients were selected—patients who developed post-paracentesis hemoperitoneum (PPH) confirmed by abdominal computed tomography (CT) and patients in whom PPH was suspected but ruled out by imaging. Individuals with other causes of hemoperitoneum not related to a paracentesis were excluded (ie hepatocellular carcinoma, bleeding diathesis, liver metastases, trauma/fall, post-

biopsy, post-surgery, post-TACE [transcatheter arterial chemoembolization], post-ablation, recent liver transplant).

2.2 | Study design

This was a retrospective, single-centre, case-controlled study, approved by the Yale Human Investigation Committee (#1609018375). A search of the electronic medical chart system was performed for patients with ICD-9 code for “cirrhosis” (571.0–571.9) OR “ascites” (789.5, 789.59) AND who had the key word “hemoperitoneum” present in any note in the chart, including history and physical exam notes, progress notes and imaging reports. This search was performed through EPIC database by the Yale University Research Joint Data Analytics Team.

As shown in Figure 1, 242 patients had an ICD-9 code of cirrhosis or ascites and the term “hemoperitoneum” in their medical charts. Review of these charts resulted in exclusion of 66 patients because they either had cirrhosis without ascites ($n = 42$) or ascites without cirrhosis ($n = 24$). Of the remaining 176 patients, 86 were excluded due to hemoperitoneum from causes other than paracentesis (ie HCC, post-biopsy, surgery, trauma, TACE/RFA), resulting in 90 cirrhosis patients decompensated by ascites and with suspected PPH. PPH was defined as presence of hemoperitoneum based on CT abdomen report in addition to, recent paracentesis, no other potential aetiology for bleeding, and significant suspicion by the medical team that bleeding was secondary to paracentesis based on their documentation in progress notes. Given this definition, four patients were excluded due to lack of confirmation by CT scan (hemoperitoneum was suspected based on anaemia and/or physical exam only). Out of the 86 patients who underwent CT abdomen, 24 patients had hemoperitoneum (PPH group) and 62 patients had hemoperitoneum ruled out by imaging (control group). As pre-paracentesis labs were used to determine predictors of bleeding, three patients without pre-paracentesis labs (paracentesis was performed as outpatient prior to hospitalization) were excluded from the PPH group.

2.3 | Data collection

A retrospective chart review was conducted to determine specifics of the adverse event, patient demographics, clinical characteristics and laboratory values prior to the paracentesis that led to hemoperitoneum or suspected hemoperitoneum. Causes for admission and concomitant complications (sepsis, acute kidney injury, encephalopathy, variceal bleeding) were also recorded. Presence of acute kidney injury (AKI) prior to the paracentesis was defined by the Ascites Club Criteria¹¹ and sepsis was defined as positive systemic inflammatory response syndrome (SIRS) in addition to an identified source of infection.

2.4 | Statistical analysis

The primary endpoint of the study was to determine predictors of post-paracentesis hemoperitoneum among patients with cirrhosis and ascites. Baseline characteristics between the PPH and control groups were compared using Chi-square test or Fisher’s exact test (when cell value was small, < 5) for categorical data, and Wilcoxon rank sum test for non-parametric variables. Univariate analysis was performed to determine predictors of post-paracentesis hemoperitoneum. A multivariate logistic regression analysis with variables that

had a P value .15 on univariate analysis was used to determine predictors of post-paracentesis hemoperitoneum. P .05 was considered significant. All analyses were completed using SPSS 17 (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc).

3 | RESULTS

As shown in Table 1, among all variables, only the presence of acute kidney injury was significantly different between patients with PPH and controls with 71% of patients with PPH having AKI compared to 32% patients without PPH. Notably, neither coagulation parameters (platelets, INR) nor severity of liver disease (MELD, liver decompensation) were different between our two groups. On univariate analysis, AKI ($P < .01$), sepsis ($P = .08$), volume removed $>2L$ ($P = .12$) and AST ($P = .15$) were significant risk factors for hemoperitoneum. A multivariate logistic regression model including AKI, sepsis, volume removed $>2L$ and AST showed that AKI prior to paracentesis was the only independent predictor of PPH (OR 4.3, 95% CI 1.3–13.5, $P = .01$) (Figure 2).

Among the 21 patients who developed PPH, 19 (90%) required blood transfusions and 12 (57%) had haemorrhagic shock leading to transfer to a higher level of care (step down or intensive care unit). Four out of the 12 patients with haemorrhagic shock underwent embolization by interventional radiology. Six patients (29%) died, mostly after transition to comfort measures only (5 out of the 6 patients) due to further liver decompensation including bleeding, infection, worsening renal disease, coagulopathy and/or encephalopathy.

4 | DISCUSSION

Patients with cirrhosis often require invasive procedures, the most frequent being paracentesis. In unselected cirrhosis patients, bleeding complications from paracentesis are reported to be relatively low, approximately 0.2%.⁹ However, our study shows that among decompensated cirrhosis patients with acute kidney injury, the risk of bleeding increases fourfold and is associated with significant mortality. To our knowledge, this is the first study establishing AKI as a risk factor for post-procedure bleeding in cirrhosis.

Although treatment of renal failure in cirrhotic patients is recommended prior to invasive procedures to prevent bleeding complications,¹² this strategy is based on expert opinion and information derived from end-stage renal disease in non-cirrhotic patients.^{13–16} It is known that end-stage renal disease patients have abnormal coagulation parameters, acquired platelet dysfunction, abnormal platelet-vessel wall interaction and anaemia that make them prone to bleeding. Interestingly, our control group had a higher prevalence of chronic kidney disease compared to the hemoperitoneum group (16% vs 0%), suggesting that among patients with decompensated cirrhosis, coagulation/platelet defects seen in renal disease are more significant in the acute setting.

The presence of infection/sepsis is generally considered predictive of bleeding. In fact, previous study looking at TEG parameters in patients with cirrhosis and bacterial infections found that endotoxin may inhibit coagulation by stimulating a heparin-like substance.¹⁷ Additionally, sepsis is one of the main precipitants of AKI in patients with cirrhosis¹⁸ and

they are difficult to dissociate. As shown in Table 2, 61% (14 out of 23 patients) of the cases of sepsis were associated with AKI and this combination was most common in the hemoperitoneum group. However, sepsis per se was not more common and AKI without sepsis was almost as common as AKI with sepsis in this group. As a result, in our multivariable analysis, AKI (but not sepsis) was the only variable predictive of the presence of hemoperitoneum.

Our study was limited by a small sample size of hemoperitoneum episodes, partly due to our strict criteria that required confirmation by imaging (rather than a bloody paracentesis, physical exam or clinical suspicion). We believe that this strict criterion allowed us to select the population most at risk for significant, life-threatening bleeding and who requires potential intervention. Additionally, the lack of data for fibrinogen levels (as physicians do not check fibrinogen during routine labs prior to paracentesis) prevented us from evaluating an additional marker of coagulopathy among our two groups.

In conclusion, acute kidney injury is the single most important factor in predicting risk for significant bleeding in cirrhosis patients decompensated by ascites. Further studies investigating blood product transfusion requirements prior to invasive procedures in patients with decompensated cirrhosis should stratify patients by presence or absence of AKI.

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Abbreviations

AKI	acute kidney injury
INR	international normalized ratio
PPH	post-paracentesis hemoperitoneum
TEG	thromboelastography

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Key points

- In patients with decompensated cirrhosis, bleeding after low-risk invasive procedures (eg paracentesis) can be life-threatening or can lead to further decompensation.
- Routine coagulation parameters are not predictive of bleeding risk and cannot be reliably used to guide blood product transfusion strategy.
- Acute kidney injury is the only independent predictor (independent of sepsis or clotting tests) of post-paracentesis hemoperitoneum in decompensated cirrhosis, increasing the risk of bleeding by fourfold.
- Future studies investigating blood product transfusion requirements prior to invasive procedures in decompensated cirrhosis should stratify patients by presence or absence of acute kidney injury.

FIGURE 1.
Flow diagram of study cohort

FIGURE 2.

Acute kidney injury is the only significant risk factor for post-paracentesis hemoperitoneum

TABLE 1

Baseline characteristics and laboratory values

Characteristics	Hemoperitoneum (N = 21)	Controls (N = 62)	P value
Age (range)	55 (28–71)	59 (37–80)	.70
Male Gender (%)	13 (62%)	38 (61%)	.96
Aetiology of Cirrhosis (%)			
Alcohol ± HCV	16 (76%)	37 (60%)	.20
HCV	1 (5%)	10 (16%)	.28
Other	4 (19%)	15 (24%)	.77
MELD score (range)	28 (14–45)	25 (8–50)	.46
Reason for Admission			
Abdominal pain/distention	8 (38%)	13 (21%)	.12
AMS or HE	6 (29%)	14 (23%)	.58
Renal failure/AKI	3 (14%)	14 (23%)	.54
Fatigue/suspected Infection	4 (19%)	14 (23%)	1.00
GI bleed	0 (0%)	7 (11%)	.18
Other	2 (10%)	15 (24%)	.22
Decompensation			
HE	18 (86%)	51 (82%)	.71
Ascites	21 (100%)	62 (100%)	1.00
Variceal bleed	8 (38%)	23 (37%)	.93
Chronic kidney disease (%)	0 (0%)	10 (16.1%)	.06
Refractory ascites (%)	11 (52%)	30 (48%)	.75
INR (range)	1.53 (1–4)	1.85 (1.07–4.68)	.34
Haemoglobin (range)	8.1 (6.6–13.5)	8.3 (4.2–12.3)	.94
Platelets (range)	99 (27–409)	70.5 (11–346)	.11
AST (range)	57 (13–330)	45.5 (12–360)	.10
AKI at time of paracentesis (%)	15 (71.4%)	20 (32.3%)	.002
Alcoholic hepatitis (%)	2 (9.5%)	5 (8%)	1.00
Sepsis at time of paracentesis (%)	9 (42.9%)	14 (22.6%)	.07
ICU/SDU (%)	6 (29%)	22 (35%)	.56
Volume removed >2L (%)	8 (38%)	13 (21%)	.12

Results depicted as median (range) and number (%).

AKI, acute kidney injury; AMS, altered mental status; CKD, chronic kidney disease; HCV, hepatitis C virus; HE, hepatic encephalopathy; ICU, intensive care unit; INR, international normalized ratio; SDU, step down unit.

Bolded item (AKI at time of paracentesis) show the characteristic with statistical significance ($P < .05$).

TABLE 2

Number of patients with acute kidney injury (AKI) and sepsis

	AKI only	Sepsis only	AKI + Sepsis
Hemoperitoneum group (N = 21)	7 (33%)	1 (5%)	8 (38%)
Controls (N = 62)	14 (23%)	8 (13%)	6 (10%)