Thrombocytopenia Is Associated With Multi-organ System Failure in Patients With Acute Liver Failure

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BACKGROUND & AIMS: **Acute liver failure (ALF) is a syndrome characterized by an intense systemic inflammatory response (SIRS) and multi-organ system failure (MOSF). Platelet-derived microparticles increase in proportion to the severity of the SIRS and MOSF, and are associated with poor outcome. We investigated whether patients with ALF develop thrombocytopenia in proportion to the SIRS, MOSF, and poor outcome.**

METHODS: **In a retrospective study, we collected data on the post-admission platelet counts of 1598 patients included in the ALF Study Group Registry from 1998 through October 2012. We investigated correlations between platelet counts and clinical features of ALF, laboratory test results, and outcomes. Of the patients studied, 752 (47%) survived without liver transplantation, 390 (24%) received liver transplants, and 517 (32%) died.**

RESULTS: **In patients with SIRS, platelet counts decreased 2 to 7 days after admission, compared with patients without SIRS ($P \leq .001$). Patients with abnormal levels of creatinine, phosphate, lactate, or bicarbonate had significantly lower platelet counts than patients with normal levels of these laboratory values (all $P \leq .001$). The decrease in platelets during days 1 to 7 after admission was proportional to the grade of hepatic encephalopathy and requirement for vasopressor and renal replacement therapy. Although platelet numbers decreased after admission in the overall population, platelets were significantly lower 2 to 7 days after admission in patients with outcomes of death or liver transplantation than in patients who made spontaneous recoveries and survived. In contrast, international normalized ratios over time were not associated with SIRS, laboratory test results associated with poor outcomes, grade of hepatic encephalopathy, or requirement for renal replacement therapy.**

CONCLUSIONS: **The development of thrombocytopenia in patients with ALF is associated with the development of MOSF and poor outcome. We speculate that SIRS-induced activation of platelets, yielding microparticles, results in clearance of platelet remnants and subsequent thrombocytopenia.**

Keywords: Hemostasis; Plasma Membrane Fragmentation; Blood Cell; INR.

The syndrome of acute liver failure (ALF) is characterized by deranged hemostasis and the development of hepatic encephalopathy (HE) in a patient without previously known liver disease. In its most florid presentation, the primary liver injury initiates a systemic inflammatory response, resulting in multi-organ system failure (MOSF), which involves almost every organ system. Furthermore, a prothrombotic state within the microvasculature of the injured liver[1] and peripheral tissues[2] may exacerbate the primary liver injury and MOSF, respectively, with a secondary hypoxic injury. Although the severity of the systemic inflammatory response syndrome (SIRS)[3] and laboratory markers of MOSF (pH, creatinine, ammonia, lactate, phosphate, and international normalized ratio [INR]) correlate with poor outcome in ALF,[4–7] the mechanisms by which liver injury triggers MOSF and activation of hemostasis have not been well defined.

Abbreviations used in this paper: **ALF, acute liver failure; APAP, acetaminophen (paracetamol); HE, hepatic encephalopathy; ICP, intracranial pressure; INR, international normalized ratio; LT, liver transplantation; MOSF, multi-organ system failure; RRT, renal replacement therapy; SIRS, systemic inflammatory response syndrome.**

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2015.09.029

Platelets increasingly are recognized as important mediators of the SIRS and MOSF in patients with sepsis and other critical illnesses.[8,9] Indeed, a decreasing platelet count after admission to an intensive care unit is an ominous sign strongly associated with death.[10,11] Platelets occupy a central role in coordinating hemostasis and inflammation, and both activate, and are activated by, systemic inflammation, leading to end-organ injury.[8,12] Some proinflammatory and prothrombotic functions of platelets are mediated by platelet microparticles, fragments of plasma membrane measuring 0.1 to 1.0 μm, which are liberated after platelet activation and released into the circulation in response to the SIRS.[13]

Patients with ALF frequently develop thrombocytopenia by poorly understood mechanisms. Serum concentrations of thrombopoietin, a liver-derived hormone, do not correlate with the degree of thrombocytopenia and have been shown to be normal or increased in patients with ALF,[14] suggesting the presence of other mechanisms. In patients with ALF, we recently showed that the plasma concentrations of prothrombotic microparticles, the majority of which were platelet-derived, increased in proportion to the severity of the SIRS.[15] Furthermore, concentrations of microparticles paralleled increased laboratory markers of poor outcome, the systemic complications of ALF (ie, MOSF), including progression to high-grade HE, hypotension requiring vasopressors, renal failure, and death. As suggested by these data, if increased platelet-derived microparticles play a role in the pathogenesis of MOSF, we hypothesized that the converse also would be true, that the platelet count would decrease after admission for ALF in proportion to the severity of the SIRS, development of MOSF, and poor outcome.

Herein, we tested the hypothesis that a decrease in platelet count after admission for ALF signifies activation of the SIRS, and predicts evolution to MOSF and poor outcome (liver transplantation [LT] or death). To show that changes in platelet count do not simply reflect the extent of liver injury, we compared the relationship of these clinical end points with the most important laboratory marker of liver injury, the INR of the prothrombin time.

Methods

Patients and Data Collection

Consecutive participants in the ALF Study Group Registry from its inception in 1998 until October 2012 were assessed for eligibility. Inclusion criteria included acute injury (defined as a jaundice-to-HE interval of < 26 wk), the presence of coagulopathy (defined as INR $\geq$ 1.5), the presence of HE, and the absence of a previously identified chronic liver disease.[16] Laboratory data and systemic complications were collected for a maximum of 7 days (ie, days 1–7) after enrollment. Data were no longer collected on patients who received a LT, were discharged from the hospital, or died. All 4 SIRS components were available for day 1 only. Of the 1974 subjects enrolled before October 1, 2012, we restricted the analysis to patients who had complete bleeding, INR, and platelet measurements for the period from enrollment to the last observation day. Of the patients in the Registry, 81% (N = 1598) had data available on day 1 and, of these, 40% (N = 636) and 43% (N = 682) of subjects had INR and platelet data, respectively, for all 7 evaluable days (Supplementary Figure 1).

The ALF Study Group Registry was approved by the Institutional Review Boards of all participating centers, and informed consent was obtained from the nearest-of-kin of all participants.

Definitions of Complications and Outcomes

Definition of the SIRS was according to standard criteria.[17] Components of MOSF were defined as follows: high-grade HE (grades 3 or 4) according to standard West Haven Criteria, renal failure defined by the need for renal replacement therapy (RRT), and cardiovascular collapse defined as the need for vasopressors to maintain blood pressure in a range for adequate peripheral organ perfusion (not further specified). Spontaneous (transplant-free) survival, LT, and death were assessed at 21 days after enrollment.

Statistics

SAS software (version 9.3; Cary, NC) was used to perform statistical analyses. Baseline variables were described using counts and percentages for categoric data, or means and SDs (medians and interquartile ranges) for continuous normal (skewed) data. For variables identified as clinically relevant, statistical tests were performed using chi-square, analysis of variance, or Kruskal–Wallis tests. Modeling of 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. All figures show mean platelet and INR estimates for each observation day adjusted for the correlation across measurement days (ie, least-square means).

Some subjects received platelet and/or plasma transfusions within days 1 to 7 after enrollment, which could have affected the analysis of platelet count and INR, respectively. Specifically, 45% of patients received plasma and 9.8% platelets on day 1; the cumulative receipt of plasma and/or platelets for days 1 to 7 was 60% and 23%, respectively. The effects of plasma/platelets on the results of this study also were examined in statistical models using transfusion as a covariate.

All statistical tests are reported as 2-sided, with a type I error rate of 5%.