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Full Length Article

Immature platelet fraction predicts coagulopathy-related platelet consumption and mortality in patients with sepsis

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ABSTRACT

Introduction: The diagnostic and prognostic value of immature platelet fraction (IPF) in sepsis has not been determined. This study aimed to assess whether IPF is an early predictor of platelet decline due to coagulopathy and is associated with mortality in patients with sepsis.
Materials and methods: In total, 149 patients with a platelet count of ≥80 × 10^3/μL on intensive care unit admission (101 with sepsis, 48 controls without sepsis) were prospectively evaluated. We measured IPF on admission and observed for development of subsequent platelet count decline (defined as a >30% decrease or <80 × 10^3/μL) in 5 days, and mortality at 28 days. The absolute immature platelet count (AIPC) was calculated to evaluate thrombopoiesis.
Results: Forty-seven patients with sepsis subsequently developed a decrease in platelet count. The IPF was highest in patients whose platelet count decreased, followed by patients without a decrease in platelet count and controls (median, 4.3% [3.1%–8.1%] *vs.* 3.7% [2.6%–4.6%] *vs.* 2.1% [1.6%–3.5%], respectively; $P < 0.0001$). The AIPC was similar in patients with and without a decrease in platelet count (7.6 [4.2–10.0] *vs.* 5.9 [4.2–8.7] × 10^3/μL, respectively; $P = 0.32$). Coagulation derangement was more severe in patients who did than did not subsequently develop a decreased platelet count. Cox regression and receiver operator characteristic curve analysis revealed that IPF was a strong independent predictor of mortality, with accuracy similar to a standard prognostic scoring system.
Conclusions: The admission IPF in septic patients predicts a subsequent decrease in platelet count, indicating platelet consumption with ongoing coagulopathy and risk of poor prognosis.

1. Introduction

Platelets play a pivotal role in antimicrobial host defense, linking the processes of inflammation and coagulation [1–3]. Substantial evidence suggests that platelets detect and respond to bacterial infections with specific receptors such as Toll-like receptors and release cytokines and chemokines. In parallel, proinflammatory cytokines produced by host responses against infection activate the coagulation cascade, leading to massive generation of thrombin, which is the most potent platelet agonist [4]. Activated platelets interact with leukocytes and endothelial cells, provide a phospholipid surface for coagulation, and are consumed by being captured on a microvascular fibrin meshwork. Thrombocytopenia is therefore common in patients with severe infection or sepsis and indicates a serious pathophysiological status associated with coagulopathy [1,5].

Numerous studies have shown that thrombocytopenia is associated with a poor prognosis in critically ill patients [6,7]. Most studies have evaluated the baseline platelet count as a prognostic factor, but the development of thrombocytopenia after intensive care unit (ICU) admission may hold greater prognostic significance. Even a 30% decrease in platelet count during the ICU stay has been shown to be associated with increased mortality [8]. In addition, thrombocytopenia is a relevant marker of severe coagulopathy or disseminated intravascular coagulation (DIC) in patients with sepsis, and DIC itself is an independent risk factor for mortality [5,9]. Hence, a marker that detects an initial drop in platelet count may help to stratify patients at risk for severe coagulopathy and a poor prognosis in the early course of sepsis.

Abbreviations: ICU, intensive care unit; DIC, disseminated intravascular coagulation; IPF, immature platelet fraction; AIPC, absolute immature platelet count; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; PT-INR, prothrombin time-international normalized ratio; FDP, fibrin degradation products; AT, antithrombin; TAT, thrombin-antithrombin complex; AUC, area under the curve.

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During the last several years, new technology has appeared in the form of the commercial automatic analyzer, which has allowed for the measurement of immature platelet fraction (IPF) in daily clinical practice [10]. The IPF has been shown to be a reliable alternative to reticulated platelet as an indicator of increased platelet turnover, and it can compensate for the limitation that the reticulated platelet is difficult to standardize [11]. The major advantage of IPF measurement is that it is quantified automatically by means of a reproducible laboratory test and can be established as part of a routine complete blood count.

The IPF is commonly reported as the percentage IPF (the percentage of platelets with above-threshold RNA), but it can also be expressed as the absolute immature platelet count (AIPC), which is the actual number of immature platelets per unit volume (%IPF × platelet count). A high IPF indicates platelet consumption or recovering thrombocytopenic disorders, while a low IPF or low AIPC is seen in an aplastic state. Several studies have demonstrated the clinical utility of IPF in laboratory diagnosis of thrombocytopenia due to peripheral platelet destruction, particularly autoimmune thrombocytopenic purpura and thrombotic thrombocytopenic purpura [12,13]. The IPF was recently introduced as a novel diagnostic biomarker for infection and developing sepsis [14,15]. To our knowledge, however, no studies have evaluated the clinical value of IPF for coagulopathy or its prognostic value in patients with sepsis.

In this study, we evaluated IPF in association with a subsequent decrease in platelet count and coagulopathy and assessed the prognostic value of a single determination of IPF in patients with sepsis. We hypothesized that IPF may identify impending thrombocytopenia in septic coagulopathy and therefore be associated with mortality in patients with sepsis.

2. Materials and methods

2.1. Study design and setting

This was a single-center, prospective observational study of patients with sepsis admitted to a medical-surgical ICU at a tertiary hospital (Jichi Medical University Hospital) from October 2013 to February 2015. The study was strictly observational, and all interventions and laboratory tests were part of our routine practice. Clinical decisions were made at the discretion of attending ICU physicians. All patients were managed in accordance with the Surviving Sepsis Campaign Guideline with the goal of initial resuscitation and infection control [16] and received mechanical thromboprophylactic treatment without concomitant low-dose heparin until the absence of active bleeding or severe coagulopathy was established. Patients at risk of bleeding or complications were transfused with platelet concentrates or fresh frozen plasma at the discretion of the ICU physician. The conduct of the study was approved by the Institutional Research Ethics Committee of Jichi Medical University.

2.2. Patients

Patients were enrolled at the time of ICU admission if they fulfilled the criteria for sepsis, had a platelet count of $\geq 80 \times 10^3/\mu L$, and were studied for 5 consecutive days (days 1–5) during their ICU stay. Sepsis was diagnosed according to the criteria of the 2001 International Sepsis Definitions Conference [17]. A control group was also evaluated and comprised patients admitted to the ICU after elective surgery for noninfectious diseases. No patients in the control group had signs of infection in the 4 weeks before surgery.

The exclusion criteria included an age of <18 years, missing laboratory data, presence of hematologic disorders, decompensated liver cirrhosis (Child–Pugh class B or C), a history of chemotherapy, and a history of a blood transfusion during the preceding 4 weeks.

2.3. Data collection

Clinical and demographic data, including age, sex, and comorbidities, were recorded on ICU admission. The Acute Physiology and Chronic Health Evaluation (APACHE) II score, a standard severity and prognostic score for critically ill patients, was also calculated on admission [18]. The Sequential Organ Failure Assessment (SOFA) score [19] excluding coagulation (platelet count) and the overt DIC score according to the International Society on Thrombosis and Haemostasis (ISTH) criteria were determined daily. Clinical variables and treatments, such as transfusion of blood products including red blood cells, fresh frozen plasma, and platelet concentrates, were also recorded daily. Clinical outcomes were assessed by the number of ICU-free days during the first 28 days [20] and all-cause 28-day mortality.

2.4. Measurement of IPF

The IPF was measured automatically with a hematology analyzer (XE-5000; Sysmex, Kobe, Japan) when the first complete blood count was obtained on day 1 (the day of ICU admission) and on days 2 to 5. Measurement of IPF was performed in the dedicated platelet channel of the hematology analyzer by flow cytometry, using a proprietary fluorescent dye containing polymethine and oxazine. These dyes penetrate the cell membrane, staining the DNA and RNA in platelets. Platelets are divided into two groups—mature and immature—according to the intensity of cell fluorescence, which correlates with the RNA content and is consequently higher in immature platelets. The IPF corresponds to the fraction (%) of immature platelets in the total platelet population [14,15]. The AIPC was calculated as the absolute number of immature platelets per unit volume (%IPF × platelet count).

2.5. Measurement of inflammatory and coagulation biomarkers

The following parameters were measured from day 1 (the time of ICU admission) to day 3 in patients with sepsis: routine biochemistry and inflammatory markers such as *C*-reactive protein and procalcitonin and coagulation test parameters including prothrombin time, prothrombin time-international normalized ratio (PT-INR), fibrinogen, fibrin degradation products (FDP), antithrombin (AT), plasminogen, and thrombin-AT complex (TAT). All assays were performed in the clinical laboratories of Jichi Medical University Hospital.

2.6. Data analysis

We defined a subsequent decrease in platelet count as a decrease of >30% and/or platelet count of $<80 \times 10^3/\mu L$ within 5 days of ICU admission. The study population was grouped according to the presence or absence of a subsequent decrease in platelet count. The control group included patients without sepsis admitted after elective surgery. Statistical differences between the groups were analyzed using Student's *t*-test, the Wilcoxon rank-sum test, and the χ^2 or Fisher's exact test as appropriate. Differences in IPF among the three groups were compared with one-way analysis of variance, followed by the Tukey–Kramer *post-hoc* test. Receiver operating characteristic curve analysis and the derived area under the curve (AUC) statistic provided prognostic accuracy of a marker or composite score for 28-day mortality. The prognostic value of the variables was also evaluated with univariate and multivariate analysis in the Cox regression model. All *P*-values reported are two-tailed, and $P < 0.05$ was considered statistically significant. Data were analyzed using JMP version 12 (SAS Institute, Tokyo, Japan).