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# Evaluation of hemostatic biomarker abnormalities that precede platelet count decline in critically ill patients with sepsis☆,☆☆

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**Abstract**

**Purpose:** The hemostatic biomarkers for early diagnosis of sepsis-associated coagulopathy have not been identified. The purpose of this study was to evaluate hemostatic biomarker abnormalities preceding a decrease in platelet count, which is a surrogate indicator of overt coagulopathy in sepsis.

**Materials and Methods:** Seventy-five septic patients with a platelet count more than $80 \times 10^3/\mu L$ were retrospectively analyzed. Hemostatic biomarkers at intensive care unit admission were compared between patients with and patients without a subsequent decrease in platelet count ($\geq 30\%$ within 5 days), and the ability of biomarkers to predict a decrease in platelet count was evaluated.

**Results:** Forty-two patients (56.0%) developed a subsequent decrease in platelet count. Severity of illness, incidence of organ dysfunction, and 28-day mortality rate were higher in patients with a subsequent decrease in platelet count. There were significant differences between patients with and patients without a subsequent decrease in platelet count in prothrombin time–international normalized ratio, fibrinogen, thrombin-antithrombin complex, antithrombin, protein C (PC), plasminogen, and $\alpha_2$-plasmin inhibitor ($\alpha_2$-PI). Receiver operating characteristic curve analysis showed that PC (area under the curve, 0.869; 95% confidence interval, 0.699-0.951) and $\alpha_2$-PI (area under the curve, 0.885; 95% confidence interval, 0.714-0.959) were strong predictors of a subsequent decrease in platelet count.

☆ Authors' contributions: K.K. conceived and designed the study. K.K. and S.T. prepared the data for analysis. K.K. conducted the data analysis. S.M. assisted with interpretation of the results. Y.S., J.M., and S.N. supervised the study. K.K. and S.M. drafted the article. All authors read and approved the manuscript. K.K. and S.M. take responsibility for the manuscript as a whole.

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**Conclusions:** Decreased PC and $\alpha_2$-PI activity preceded a decrease in platelet count in intensive care unit patients with sepsis.


## 1. Introduction

Coagulation and fibrinolytic abnormalities are observed in most patients with sepsis [1]. Severe inflammation in sepsis is associated with tissue factor–mediated activation of coagulation, which leads to thrombin generation and results in widespread fibrin deposition. The severity of coagulopathy in sepsis ranges from subclinical abnormalities, which are detectable by a mild increase in fibrin degradation products (FDPs) and prolongation of global clotting times, to fulminant disseminated intravascular coagulation (DIC), characterized by widespread microvascular thrombosis [2]. A number of studies have reported on the association between DIC and organ failure and found that DIC is an independent risk factor for mortality in patients with sepsis [2-5]. Early diagnosis and treatment may therefore improve outcomes in septic patients with DIC [6].

The International Society on Thrombosis and Haemostasis (ISTH) criteria are currently widely used for diagnosing DIC [7] and are a strong independent predictor of mortality in patients with severe sepsis [8]. Although the ISTH criteria for overt DIC are simple and clinically useful, they have some limitations to be applied for early stage of DIC. The ISTH criteria define nonovert DIC as the stage before overt DIC, for the purpose of early diagnosis [7]. However, previous studies have shown that few patients with nonovert DIC progress to overt DIC and that mortality rates are similar between patients with nonovert DIC and patients with overt DIC [8], suggesting that septic coagulopathy diagnosed according to the ISTH criteria for nonovert DIC may not necessarily be an early stage of overt DIC.

Previous studies have evaluated a number of hemostatic biomarkers including D-dimer, antithrombin (AT), thrombin-AT complex (TAT), plasmin–$\alpha_2$-plasmin inhibitor complex (PIC), and plasminogen activator inhibitor-1 (PAI-1); however, no single marker that can effectively diagnose early stage of DIC has been identified [9,10]. It is therefore important to develop clinical markers that can detect progression of septic coagulopathy in initial phase, so that early intervention can be instituted.

The objective of this study was to evaluate the ability of hemostatic biomarkers for predicting progression of coagulopathy in septic patients admitted to the intensive care unit (ICU). We used a decrease in platelet count as a marker for overt stage of septic coagulopathy. Platelet activation, consumption, and destruction may occur at the endothelial cell surface as a result of thrombin generation and fibrin meshwork formation secondary to coagulation activation. Platelet count decreases over a few days after the development of sepsis [5], which may indicate ongoing activation of coagulation [11]. Thrombocytopenia may reflect the advanced stage of DIC, which is associated with late death in patients with severe sepsis [5,12]. We therefore considered that a decreasing platelet count could be an indicator of disease progression in sepsis-induced coagulopathy.

## 2. Methods

### 2.1. Patients

The medical records of all patients admitted to the ICU at Jichi Medical University Hospital from September 2010 to December 2011 were retrospectively reviewed. Patients with a diagnosis of sepsis and a platelet count of more than $80 \times 10^3/\mu L$ on the day of ICU admission were included in the study. Sepsis was defined as fulfillment of at least 2 of the 4 criteria for systemic inflammatory response syndrome [13] and proven or suspected infection. Exclusion criteria were as follows: age younger than 18 years, prior hematologic disorder including platelet disorder, liver cirrhosis or failure, chronic renal failure with dialysis, history of chemotherapy, anticoagulation therapy with or without AT substitution, and blood transfusion during the preceding 4 weeks. This study was approved by the Institutional Research Ethics Committee of Jichi Medical University, which did not consider informed consent to be necessary because of the study design.

Our facility provides 24-hour coverage of attending ICU physicians. Management of patients followed the Surviving Sepsis Campaign Guideline [14], with the goal of initial resuscitation and infection control. Treatment for DIC was at the discretion of the responsible ICU physicians. The basic approach to treatment was anticoagulation therapy using gabexate mesilate (a serine protease inhibitor) [15,16], with or without AT substitution therapy. Some patients with a bleeding risk, or with complications, were transfused with platelet concentrate or fresh-frozen plasma at the discretion of the treating physicians.

### 2.2. Data collection

Descriptive data including demographic data, diagnoses, sources of infection, and clinical data were collected from the electronic medical records of all eligible patients. Acute Physiology and Chronic Health Evaluation (APACHE) II [17] and Simplified Acute Physiology (SAPS) II [18] scores were calculated to estimate the severity of disease within the