Incremental Prognostic Value of Platelet Count in Patients With Acute Heart Failure
— A Retrospective Observational Study —

Satoshi Yamaguchi, MD; Masami Abe, MD; Tomohiro Arakaki, MD; Osamu Arasaki, MD; Michio Shimabukuro, MD, PhD

Background: Acute heart failure (AHF) triggers platelet aggregation and platelet markers are associated with the severity of AHF. The present study aimed to investigate the prognostic value of platelet count (PLT) in patients with AHF.

Methods and Results: This single-center retrospective observational study analyzed 425 consecutive patients with AHF. The patients were divided into groups based on tertiles of PLT: low (PLT1 <170,000/μL), intermediate (170,000/μL ≤ PLT <230,000/μL), and high (PLT3 ≥230,000/μL). The endpoint was all-cause death with a composite endpoint of all-cause death and HF rehospitalization. Survival analysis was performed, and Cox proportional hazard models adjusted by an established risk score (Get With The Guidelines score) were generated. The PLT1 group had the worst survival for all-cause death (log-rank, P=0.003) and the composite endpoint (P=0.009). A significant trend of increasing survival was observed for all-cause death (log-rank trend, P<0.001) and the composite endpoint (P=0.002) in the following order: PLT1, PLT2, and PLT3. Adjusted Cox proportional hazard models demonstrated that low PLT was a risk factor of all-cause death and the composite endpoint.

Conclusions: Low PLT was associated with risk for all-cause death and HF rehospitalization in patients with AHF.

Key Words: Acute heart failure; Biomarkers; Platelet count
**Methods**

**Participants**
This single-center retrospective study at a Japanese community hospital enrolled 469 consecutive patients admitted to the cardiology ward because of AHF. At least 2 cardiologists certified by the Japanese Circulation Society diagnosed AHF in the clinic or emergency room between June 2014 and July 2016. The diagnosis of AHF was based on the Framingham criteria. All patients had HF exacerbation with New York Heart Association class III or IV and at least one of the following signs of congestion: pulmonary edema, pitting edema in the lower extremities, distended jugular vein, and/or pleural effusion. None of the patients required a cardiac support device, such as intra-aortic balloon pump or left ventricular assist device for cardiogenic shock, nor had they concurrent acute myocardial infarction on admission. No cases of liver cirrhosis were detected in the study population. We excluded 44 patients because their PLT was not measured, so a total of 425 patients were eligible for analysis (Figure 1).

Prior to the allocation, we planned 3 group comparisons to confirm the trend of survival. The 1-year mortality rate was estimated to be 10% in the lowest mortality group and 25% in the highest mortality group. With a power of 0.8 and a error of 0.05, each group required ≥78 patients. Considering feasibility, the patients were divided into 3 groups based on tertiles of PLT: low (PLT1 <170,000/μL), intermediate (170,000/μL ≤ PLT<230,000/μL), and high (PLT3 ≥ 230,000/μL).

The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethical committee at Tomishiro Central Hospital. Informed consent was waived because of the observational nature of the study. For confidentiality, all data were de-identified and analyzed anonymously.

**Data Collection**
We conducted an in-depth review of the medical chart to collect both demographic and laboratory data.

All blood samples were obtained from the brachial veins and stored in a test tube (Venoject VP-DK052K05, Terumo, Japan). After sampling, blood cells were immediately counted using XE2100 (Sysmex Corp., Kobe, Japan).

Based on the PLT on admission and at 30 days before hospital admission (baseline PLT) if available, we calculated the percent change in PLT: \[(PLT\text{ on admission})−(baseline\text{ PLT})]/(baseline\text{ PLT})\times100.

**Statistical Analysis**
All missing data were checked. The normality of the continuous variables was assessed using histograms. Continuous variables with normal and skewed distribution were expressed as mean±SD and median [25%, 75%], respectively. Categorical variables were expressed as number (%). BNP, CRP, and BUN had highly right-skewed distributions and were log-transformed (logBNP, logCRP, and logBUN) to achieve normal distribution. The demographic characteristics and laboratory data on admission were summarized, and data on PLT1, PLT2, and PLT3 were compared. One-way analysis of variance and Kruskal-Wallis test were used for the comparison of normally
Survival analysis was performed for all-cause death in 425 patients (Figure 1). Time zero was the date of hospital admission, and observation was censored at all-cause death as the event or last hospital visit without an event. To compare survival among the 3...
groups. Kaplan-Meier curves were generated, and log-rank test and log-rank trend test were performed to test the trend in the following order: PLT1, PLT2, and PLT3. Posthoc analysis was performed for comparison among the 3 groups using Holm’s test.

**Cox Proportional Hazard Model** We generated univariate Cox hazard regression models for all-cause death and Cox cause-specific proportional hazard models for the composite endpoint to compute the hazard ratios with 95% confidence intervals. Each of the following 8 factors was included in a separate model: the Get With The Guidelines (GWTG) score, an established risk score; PLT (PLT1 to PLT3 and PLT2 to PLT3); biomarkers including MPV, logBNP, logCRP, N/L ratio, and logBUN. Each of 6 factors other than the GWTG score and BUN was entered into Cox hazard models adjusted by GWTG score. BUN was taken into account for GWTG score calculation. For these models, cases with missing data for the variables of interest were excluded (list-wise deletion).

**Correlation Between PLT and Biomarkers** Pearson’s or Spearman’s correlation coefficient was used to analyze the relationship between PLT and the following biomarkers: MPV, logBNP, logCRP, N/L ratio, and logBUN.

**Correlation Between PLT and Age** Pearson’s correlation coefficient was used to evaluate the relationship between PLT and age.

**Subgroup Analysis for Change in PLT** The patients were subdivided accordingly to baseline PLT. A total of 217 patients were eligible for subgroup analysis. We compared the baseline PLT and PLT on admission using Wilcoxon’s signed-rank test in the overall subgroup population and in each group.

**All analyses used R 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) and EZR 1.3.6 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).** All reported P values are two-tailed, and P<0.05 was considered statistically significant.

### Results

**Participants**

The mean age of the participants was 79±12 years, with 202 (48%) male participants (**Table 1** and **Supplementary Table**). The mean GWTG score was 38±7. The PLT1 group

![Figure 2. Kaplan-Meier curves for (A) all-cause death and (B) composite endpoint of all-cause death and heart failure rehospitalization. Tertiles of platelet count: low (PLT1 <170,000/μL), intermediate (170,000/μL ≤ PLT <230,000/μL), and high (PLT ≥230,000/μL). Post-hoc analysis is shown in Supplementary Figure.](image)

**Table 2. Cox Proportional Hazard Model for All-Cause Death**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate</th>
<th>Adjusted by GWTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>GWTG score, 1 point increase each</td>
<td>Event/n HR 95% CI P value</td>
<td>Event/n HR 95% CI P value</td>
</tr>
<tr>
<td>PLT2 to PLT2</td>
<td>100/424 1.83 1.08–3.12 0.026</td>
<td>98/419 1.71 0.99–2.94 0.054</td>
</tr>
<tr>
<td>PLT1 to PLT3</td>
<td>100/424 2.43 1.45–4.08 &lt;0.001</td>
<td>98/419 2.02 1.19–3.42 0.01</td>
</tr>
<tr>
<td>Mean platelet volume, 1 fL increase each</td>
<td>23/147 1 0.69–1.45 0.99</td>
<td>23/145 0.99 0.71–1.37 0.93</td>
</tr>
<tr>
<td>LogBNP, 1 log (pg/mL) increase each</td>
<td>39/149 2.26 1.45–3.5 &lt;0.001</td>
<td>37/145 1.81 1.14–2.88 0.012</td>
</tr>
<tr>
<td>LogCRP, 1 log (mg/dL) increase each</td>
<td>71/239 1.31 1.11–1.54 0.002</td>
<td>69/234 1.32 1.11–1.58 0.002</td>
</tr>
<tr>
<td>N/L, 1 increase each</td>
<td>37/147 1.18 1.08–1.28 &lt;0.001</td>
<td>36/143 1.14 1.05–1.25 0.003</td>
</tr>
<tr>
<td>LogBUN, 1 log (mg/dL) increase each</td>
<td>98/419 2.81 1.84–4.29 &lt;0.001</td>
<td>(Included in GWTG)</td>
</tr>
</tbody>
</table>

PLT on hospital admission was tertiled into control as PLT3, moderate depletion as PLT2, and severe depletion as PLT1. Abbreviations as in Table 1.
Table 3. Cox Proportional Model for Composite Endpoint of All-Cause Death and Rehospitalization for Heart Failure Exacerbation

<table>
<thead>
<tr>
<th>Event/n</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GWTG score, 1 point increase each</td>
<td>184/420</td>
<td>1.07</td>
<td>0.95–1.09</td>
</tr>
<tr>
<td>PLT2 to PLT3</td>
<td>186/425</td>
<td>1.36</td>
<td>0.94–1.97</td>
</tr>
<tr>
<td>PLT1 to PLT3</td>
<td>186/425</td>
<td>1.78</td>
<td>1.24–2.55</td>
</tr>
<tr>
<td>Mean platelet volume, 1 fL increase each</td>
<td>41/148</td>
<td>0.76</td>
<td>0.56–1.03</td>
</tr>
<tr>
<td>LogBNP, 1 log (pg/mL) increase each</td>
<td>74/150</td>
<td>1.83</td>
<td>1.33–2.52</td>
</tr>
<tr>
<td>LogCRP, 1 log (mg/dL) increase each</td>
<td>118/239</td>
<td>0.99</td>
<td>0.88–1.11</td>
</tr>
<tr>
<td>N/L, 1 increase each</td>
<td>69/147</td>
<td>1.05</td>
<td>0.97–1.14</td>
</tr>
<tr>
<td>LogBUN, 1 log (mg/dL) increase each</td>
<td>184/420</td>
<td>2.07</td>
<td>1.54–2.79</td>
</tr>
</tbody>
</table>

The participants were tertiled into PLT1 as severe platelet depletion, PLT2 as moderate depletion, and PLT3 as control. Abbreviations as in Table 1.

Table 4. Correlations Between PLT and Prognostic Markers in Acute Heart Failure

<table>
<thead>
<tr>
<th>Factor</th>
<th>n</th>
<th>Correlation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLT vs. mean platelet volume</td>
<td>148</td>
<td>r=−0.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PLT vs. logBNP</td>
<td>150</td>
<td>r=−0.152</td>
<td>0.063</td>
</tr>
<tr>
<td>PLT vs. logCRP</td>
<td>239</td>
<td>r=−0.04</td>
<td>0.54</td>
</tr>
<tr>
<td>PLT vs. N/L</td>
<td>147</td>
<td>p=−0.001</td>
<td>0.99</td>
</tr>
<tr>
<td>PLT vs. logBUN</td>
<td>420</td>
<td>r=−0.191</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PLT vs. IVC diameter</td>
<td>362</td>
<td>p=−0.09</td>
<td>0.088</td>
</tr>
</tbody>
</table>

logBNP, log-transformed BNP; logBUN, log-transformed BUN; logCRP, log-transformed CRP; r, Pearson’s correlation coefficient; ρ, Spearman’s correlation coefficient. Other abbreviations as in Table 1.

Survival Analysis

During the follow-up (201 [92, 396] days), 100 (24%) patients died, and 86 (20%) patients were readmitted to hospital because of HF exacerbation.

As shown in Figure 2A and Supplementary Figure A there was a significant difference in the incidence of death among the 3 groups according to the Kaplan-Meier curves for the comparison of all-cause death (P=0.014 for the comparison of the 3 groups: PLT1 42/142 (30%) vs. PLT3 22/141 (16%), P=0.02) and survival (log-rank, P=0.003). Both the PLT1 and PLT2 groups had poor survival compared with the PLT3 group (PLT 1 vs. PLT3, P=0.003; PLT2 vs. PLT3, P=0.033). A significant trend of increasing survival for all-cause death was observed in the following order: PLT1, PLT2, and PLT3 (log-rank trend, P<0.001).

Figure 2B and Supplementary Figure B is the Kaplan-Meier curves for the comparison of composite endpoint among the 3 groups and no statistical difference was observed in the incidence of composite endpoint (PLT1 52/141 (37%), PLT2 63/142 (44%), PLT3 71/142 (50%); P=0.087 for the comparison of the 3 groups). However, a significant difference among the groups was observed in terms of survival (log-rank, P=0.009). The PLT1 group had poor survival compared with the PLT3 group (P=0.007). A significant trend of increasing survival was observed in the following order: PLT1, PLT2, and PLT3 (log-rank trend, P=0.002).

Cox Proportional Hazard Model for All-Cause Death

Univariate Cox proportional hazard models demonstrated that GWTG score, PLT1 and PLT2, increased logBNP, increased logCRP, elevated N/L ratio, and increased log-BUN were significant risk factors for all-cause death in AHF (Table 2). Cox proportional hazard models adjusted by GWTG score also demonstrated that PLT1, increased logBNP, increased logCRP, and elevated N/L ratio were significant risk factors for all-cause death in AHF (Table 2).

Cox Proportional Hazard Model for Composite Endpoint

Univariate Cox proportional hazard models demonstrated that GWTG score, PLT1, increased logBNP, and increased logBUN were significant risk factors for the composite endpoint in AHF (Table 3). Cox proportional hazard models adjusted by GWTG score also demonstrated that PLT1 and increased logBNP were significant risk factors for the composite endpoint in AHF (Table 3).

Correlations Between PLT, Biomarkers and Age

A significant negative correlation was found between PLT and MPV (Pearson’s r=−0.35, P<0.001) and between PLT and logBUN (Pearson’s r=−0.191, P<0.001) (Table 4). There was a significant negative correlation between age and PLT (r=−0.12, P=0.02; Figure 3).
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Recent studies revealed that AHF was evoked not solely by cardiac problems but also by systemic physiological changes such as a pro-oxidant and inflammatory state. The PLT may reflect those systemic changes and indicate the severity of AHF. Our study included patients with AHF with preserved and reduced EF, and showed that thrombocytopenia was associated with worse prognosis in such patients.

Previous studies reported that increased MPV was associated with worse prognosis in patients with HF, whereas PLT showed a borderline difference between patients with HF who died or survived within 30 days of admission. Those studies included patients with stable HF who did not require hospitalization. We found a different change in PLT before hospitalization between the 1st and 3rd tertiles of PLT on admission. PLT may change according to the severity of HF exacerbation and had prognostic value in our study population.

The PLT1 and PLT2 groups had higher total bilirubin, but there was no significant difference in BNP between the groups (Table 1). However, this may reflect the preexisting long-standing congestive state resulting in congestive hepatopathy, not the short-term congestive state at admission, because BNP is thought to reflect only the short-term congestive state at admission, considering its half-life. Therefore, low PLT on hospital admission for HF might reflect long-standing congestion and coexisting congestive hepatopathy. The IVC diameter showed a trend of a negative correlation with PLT (Table 4). The finding of a relationship between BNP and PLT and with the IVC diameter indicated that the congestive state may be associated with a decrease in PLT.

Discussion

To the best of our knowledge, this study is the first to show the incremental prognostic value of PLT in AHF. We have 5 major findings. First, low PLT was a risk factor for all-cause death and the composite endpoint of all-cause death and rehospitalization for HF. The PLT decreased in the PLT1 group. In contrast, the PLT increased in the PLT3 group. Second, a significant negative correlation was found between PLT and MPV. Third, a significant correlation was found between PLT and logBUN. Fourth, there was a significant negative correlation between PLT and age in AHF (Figure 4). Fifth, the PLT1 and PLT3 groups had different changes in PLT prior to hospital admission.

Prognostic Value of PLT

The current study found that low PLT is a risk factor for all-cause death and HF rehospitalization. Mojadidi et al demonstrated that thrombocytopenia (<100,000/μL) was associated with 1-year death in patients who were first diagnosed as having HF with reduced EF (<40%). Recent studies revealed that AHF was evoked not solely by cardiac problems but also by systemic physiological changes such as a pro-oxidant and inflammatory state. The PLT may reflect those systemic changes and indicate the severity of AHF. Our study included patients with AHF with preserved and reduced EF, and showed that thrombocytopenia was associated with worse prognosis in such patients.

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![Figure 4.](image-url) Change in platelet count (PLT) prior to hospital admission for acute heart failure. PLT sampled 30 days prior to hospital admission and on admission. Error bar shows mean ± standard deviation (SD). Tertiles of PLT: low (PLT1 <170,000/μL), intermediate (170,000/μL ≤ PLT<230,000/μL), and high (PLT ≥230,000/μL).

Change in PLT Prior to Hospital Admission

In the overall population, the PLT1 and PLT2 groups had lower baseline PLT than the PLT3 group (Table 1).

In the subgroup analysis, there was a significant decrease from baseline PLT to PLT at admission in the PLT1 group (baseline PLT, 14.7 ± 4.4/μL and admission PLT, 12.6 ± 3.4/μL; P=0.002; Figure 4). In contrast, the PLT did not change prior to hospital admission in the PLT2 group (baseline PLT, 19.6 ± 4.2/μL and admission PLT, 19.6 ± 1.7/μL; P=0.77), and the PLT increased significantly prior to hospital admission in the PLT3 group (baseline PLT, 25.5 ± 7.4/μL and admission PLT, 29.6 ± 7.6/μL; P<0.001).

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PLT to some extent. However, this trend was very weak. Multiple factors including congestion seem to contribute to the PLT change.

Correlation Between PLT and Other Biomarkers
A significant negative correlation was found between PLT and MPV. Platelets are held within cytoplasmic fragments of megakaryocytes and disk-shaped anucleate particles. The average life span of platelets is 8–10 days, and their size does not change throughout their life span. Moreover, megakaryocytopoiesis determines the size of platelets, and an inverse relationship between PLT and MPV is generally observed with increased production of megakaryocytes. Some physiological states such as inflammation, RAA activation, and platelet recruitment induce megakaryocytopoiesis.

Relationship Between PLT and Age in AHF
An age-related reduction in the PLT was observed in our study population. The PLT1 group had older patients compared with the PLT2 and PLT3 groups (Table 1). The GWTG score is a summarized risk score that includes age; thus, the Cox proportional hazard model adjusted for GWTG score demonstrated PLT reduction was still a risk factor after adjustment by age. When focusing on the relationship between PLT and age (Figure 3), the negative correlation was weak (r = −0.12, P = 0.02). PLT reduction in AHF seemed to be modulated more closely by other factors caused by HF such as a congestive state or platelet activation than age.

Change in PLT Prior to Hospital Admission
Subgroup analysis indicated that platelet depletion was not observed in all AHF patients. The PLT1 and PLT3 groups had different changes in PLT prior to hospital admission. This subgroup analysis had a considerable number of excluded patients because no data for the PLT 30 days prior to hospital admission were available (Figure 1). A significant negative correlation was found between PLT and logBUN, for which there are 2 possible explanations: RAA activation and renal function. BUN has been reported as a surrogate marker of RAA activation. Schäfer et al reported that angiotensin-converting enzyme inhibitors suppressed platelet activation in a rat HF model. In the present study, RAA activation might be the reason for the increase in BUN; in addition, RAA activation might cause platelet production, recruitment, aggregation, and consumption. In renal failure, BUN is increased, whereas the clearance of cytokines is decreased. Worsening renal failure frequently occurs in patients with AHF. In this study, the PLT1 group had higher serum creatinine and lower estimated glomerular filtration rate than the PLT3 group. Furthermore, the PLT1 group was presumed to have worse renal function than the PLT3 group. Impaired renal function might prolong pro-inflammatory cytokine clearance and induce platelet recruitment and consumption.

Clinical Significance
A doctor other than a cardiologist, such as an emergency doctor, might encounter patients with AHF and treat them in the primary care setting because AHF is quite common. Blood cell count must be evaluated in all patients with AHF and the PLT is routinely measured in the clinical setting. In fact, there were fewer missing data for PLT than for the other biomarkers such as MPV, BNP, CRP, and N/L ratio in our study population. In the light of this observation, the use of the PLT is reasonable for risk stratification in AHF from the viewpoint of data availability.

Study Limitations
First, a racial difference in PLT has been reported, and the present study only included Japanese patients. Therefore, generalization of findings with regard to other populations may be limited. Second, vascular resistance, cardiac structure, left ventricular aneurysm, and severe left ventricular wall motion abnormality, which might affect the PLT, were not examined. Third, we could not obtain information on coexisting liver disease because none of the patients in our study population had liver cirrhosis. Lastly, liver abnormality was not evaluated using ultrasonography or noninvasive indocyanine green clearance test. Thus, we could not provide information on liver function other than transaminase level.

Conclusions
In summary, platelet depletion may occur together with underlying pathophysiological changes including congestion and RAA activation in AHF. Low PLT was associated with poor prognosis in patients with AHF. PLT is widely measured in clinical settings and can be readily available for use as a risk marker in AHF.

Acknowledgments
We thank the following: Yoji Takami, Shimon Toma, and Chio Iseki for assisting in data collection and management; the medical technicians at Tomishiro Central Hospital for performing blood sampling and reporting laboratory data results; Atsushi Kakazu, Kazuaki Okuyama, Toshiya Chinen, Masanori Kakazu, Masahiro Tamashiro, Hideaki Sonoi, Hideo Takaesu, Masaki Tabuchi, and Akihiko Yamachi for caring for the patients; Yumi Ikahara and Shoko Nakaima for assisting with writing this manuscript.

Funding
This study had no financial support.
References


Supplementary Files
Please find supplementary file(s): http://dx.doi.org/10.1253/circ.CJ-18-0961