 CHAPTER 8

BLUNTED RISE IN PLATELET COUNT IN CRITICALLY ILL PATIENTS IS ASSOCIATED WITH WORSE OUTCOME

M.W.N. Nijsten, H.J. ten Duis, J.G. Zijlstra,
R.J. Porte, J.H. Zwaveling, J.C. Paling, T.H. The

ABSTRACT

Objective: Low platelet counts (PC) are known to be associated with disease severity in critically ill patients, but the relevance of time-dependent changes of PC has not been investigated. We tested the hypothesis that a low rate of change of platelet counts (PC) after admission to the intensive care unit (ICU) is associated with mortality.

Design: Retrospective study.

Setting: A 12-bed surgical ICU of a university hospital.

Patients: All adult patients admitted for at least 4 days to the ICU over a 7-year period.

Methods On admission Acute Physiology and Chronic Health Evaluation (APACHE-II)-scores were calculated. PC and leukocyte counts were analyzed from admission to day 10. The daily rise of the platelet count ($\Delta PC/\Delta t$) from day 2 to day 10 was calculated. 30-day mortality as well as hospital mortality were determined.

Results: 1415 admissions were studied. Median PC (interquartile range) initially decreased and subsequently increased, with a higher PC in 1203 survivors than in 212 non-survivors from day 2 onward (302 (181- 438) vs. 129 (62- 228) $\cdot 10^9$/L at day 10; p<0.001). After stratification of patients per type of surgery, within each group PC was also higher in survivors. Mean $\Delta PC/\Delta t$ was more than 5 times higher in survivors compared to non-survivors: 30±46 vs. 6±28 $\cdot 10^9$/L/day (p<0.001). The area under the receiving-operating-characteristic curve of $\Delta PC/\Delta t$ for 30-day survival was 0.743, compared to 0.728 for APACHE-II. Leukocyte counts showed marginal differences between non-survivors and survivors.

Conclusion: A blunted or absent rise in PC in critically ill patients is associated with increased mortality. $\Delta PC/\Delta t$ is a readily available and cheap parameter to improve assessment of critically ill patients.

INTRODUCTION

Increased platelet production is a normal response after inflammatory insults such as trauma or infection. When patients recover after a significant inflammatory event, thrombocytosis is typically observed after approximately one week, with platelet counts leveling off to normal levels afterwards. This phenomenon can be seen as a late part of the acute phase response and has been shown to be mediated by cytokines, especially interleukin-6 [1,2]. In fact, in patients with chronic diseases such as rheumatoid arthritis or inflammatory bowel disease, thrombocytosis is a marker of persistent inflammation.

On the high end of the spectrum of disease severity - e.g. sepsis or major bleeding - low platelet counts are correlated with disease severity. Significant initial thrombocytopenia (platelet count <50-$10^9$/L) is known to be predictive of poor outcome in patients with sepsis or with a ruptured abdominal aortic aneurysm [3,4]. Once such patients have survived the first days following the acute event a complex interplay of factors will determine the ultimate outcome. Many parameters considered either pro-inflammatory or anti-inflammatory have been studied in the quest to predict and to influence outcome. Clinically useful measurement of parameters such as cytokines is difficult and associated with considerable costs.

Although many studies have recognized the value of baseline platelet counts in predicting outcome,
the meaning of subsequent time-dependent changes in platelet counts that do not excessively deviate from so-called normal values has not been studied. We have often noted that critically ill patients do not display thrombocytosis, although such a response might be expected because of the strong inflammatory stimuli that are present. To assess the clinical relevance of this phenomenon we systematically looked at platelet counts after admission to the intensive care unit (ICU). In addition leukocyte counts were also studied since leukocyte counts are frequently measured as an indicator of inflammation.

We hypothesized that a lower rise in platelet counts in the days following ICU-admission would be associated with adverse outcome. Since the objective was to observe sequential changes in the platelet count in patients that were especially at risk for a complicated course, we only studied patients that stayed at least 4 days in the unit.

### PATIENTS AND METHODS

All patients 15 years and older who were admitted between 1992 and 1998 to the surgical ICU of a tertiary teaching hospital for 4 days or more were retrospectively studied. Patients had to stay (and thus survive) at least 4 days in the unit in order to be included. Based on type of surgery, the following groups were defined: trauma, vascular surgery, abdominal surgery, liver transplantation and miscellaneous. All platelet count (normal range 150 to 350 \( \cdot 10^9/L \)) and leukocyte count (normal range 4 to 10 \( \cdot 10^9/L \)) measurements performed from ICU-admission to 10 days after ICU admission were analyzed. During ICU-stay, these measurements were performed daily by Coulter.

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<th>Survivors</th>
<th>Non-survivors</th>
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<td>First admissions</td>
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<td>133 / 79</td>
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<tr>
<td>APACHE-II</td>
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<td>23.6±6.9</td>
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**Groups**

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<tr>
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<td>21</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>436</td>
<td>94</td>
</tr>
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</table>

**Table 8.1 Patients studied**

Note that patients are counted on admission basis. APACHE-II scores are significantly different between the two groups (p<0.001)
Blunted rise in platelet counts in SICU patients

Counter (Beckman Coulter, Fullerton, California, United States). Acute Physiology and Chronic Health Evaluation (APACHE-II; [5]) scores were calculated on admission. Survival at 30 days after admission to the ICU and hospital mortality were determined.

Statistics
Readmissions to the ICU were also included, provided those occurred more than 30 days after a previous ICU-admission. Thus a patient who was admitted previously once and died during a later readmission was counted once as a survivor, and once as a non-survivor. When multiple determinations were made for a single patient on the same day, these values were averaged to one value for that day before daily group means were calculated. To quantify the daily increase of the platelet count linear regression estimates were calculated for each individual patient, as well as for patient groups. On the basis of the known bimodal change of platelet counts, the platelet count (PC) was assumed to change in a linear fashion from day 2 to day 10, as described by

$$PC=a \cdot t + b.$$  

For each patient the constant $a$ (slope) was calculated, denoted by $\Delta PC/\Delta t$ hereafter.
To assess the relation between the APACHE-II score and $\Delta PC/\Delta t$ with 30-day survival and hospital survival respectively, receiving-operating-characteristic (ROC) curves were constructed,

Figure 8.2a. Median platelet counts ($10^9/L$; interquartile range) for survivors (open circles) and non-survivors (closed circles) in trauma patients. The difference is significant ($p<0.001$). Non-survivors do not show the rise in platelet counts observed in survivors ($p<0.001$).

Figure 8.2a. Median platelet counts ($10^9/L$; interquartile range) for survivors (open circles) and non-survivors (closed circles) in trauma patients. The difference is significant ($p<0.001$).
with the area under the curve as a measure of discriminatory ability [6]. Data are expressed as medians with interquartile ranges or means \( \pm \) SD. Significances of differences were assessed with a Student’s \( t \)-test, and corrected according to Bonferroni in case of multiple comparisons.

RESULTS

During the 7-year study period a total of 3286 different patients aged 15-96 years, had 3940 admissions to our surgical ICU. Of these patients 383 died within 30 days. When only patients who were admitted for more than 4 days were included, 1311 patients (1415 admissions) remained for further analysis. In this group 212 (15% of admissions) patients died within 30 days after ICU-admission (Table 8.1). In 277 admissions the patients died during hospital stay. A total of 17364 platelet counts and 13695 leukocyte counts were analyzed. The median platelet count of the entire patient group initially dropped to a nadir of 113 (64-192) \( \cdot 10^9 \)/L on the second day after admission, and subsequently increased to 277 (157-424) \( \cdot 10^9 \)/L after 10 days.

When survivors and non-survivors were considered separately (Fig. 8.1) the platelet count on admission showed no difference. From day 2 to day 10 the platelet count in survivors was significantly higher than in non-survivors resulting in a platelet count at day 10 of 302 (181-428) \( \cdot 10^9 \)/L and 129 (62-228) \( \cdot 10^9 \)/L respectively. Although the mean platelet count differed markedly between patients groups, within all groups (i.e. trauma, vascular surgery, abdominal surgery, liver transplantation and miscellaneous) non-survivors consistently had lower rise in platelet counts as measured by mean \( \Delta PC/\Delta t \) (Fig. 8.2a-d). These differences were highly

Figure 8.2b. Median platelet counts (10^9/L; interquartile range) for survivors (open circles) and non-survivors (closed circles) in vascular surgery patients. The difference is significant (p<0.001).
Blunted rise in platelet counts in SICU patients

significant (p<0.001) for all groups with the exception of the liver transplantation group. For readmitted patients the time-dependent changes of the platelet count did not differ from patients who were first admitted.

As opposed to the platelet count, overall and subgroup leukocyte counts in survivors were slightly lower compared to non-survivors, with values of 13.4 (10.2-18.0) ×10⁹/L and 15.5 (11.4-21.2) ×10⁹/L at day 10 respectively (p=0.03). Patients with low APACHE-II-scores (<18) showed a somewhat higher platelet count than patients with high APACHE-II scores (≥18) with values of 308 (126-446) and 260 (153-416) ×10⁹/L at day 10 (p=0.03).

In 1290 admissions the daily change in platelet counts (ΔPC/Δt) between day 2 and 10 could be calculated: 30-day survivors had a value of 30±46 ×10⁹/L/day whereas non-survivors had a value of 6±28 ×10⁹/L/day (p<0.001). With respect to 30-day survival the area under the ROC was 0.743 for ΔPC/Δt (Fig. 8.3) and 0.728 for APACHE-II. The areas under the ROC for ΔPC/Δt and APACHE-II when calculated in respect to hospital survival where 0.736 and 0.708 respectively.

**Figure 8.2c.** Median platelet counts (10⁹/L; interquartile range) for survivors (open circles) and non-survivors (closed circles) in abdominal surgery patients. This difference is significant (p<0.001).
DISCUSSION
The aim of this study was to analyze the time-response of the platelet count in relation to outcome in critically ill patients. In patients who uneventfully recover from an inflammatory insult the platelet count displays a bimodal response with an initial decrease below baseline values for the first days, followed by an increase above the normal range after one week. In our study, the surviving trauma patients clearly showed such a response (Fig. 8.2a). Trauma patients sustained their injury and subsequent definitive surgery in most cases within 24 hours before ICU admission. Combined with the fact that nearly all of these patients were previously healthy and relatively young - as opposed to most patients in the other patient groups – this may explain why the bimodal time course of platelet counts was most marked in trauma patients.

In the other patient groups lower overall platelet counts were observed, especially in liver transplants (Fig. 8.2d). In this latter group, splenomegaly is a major determinant of low platelet counts. Nevertheless, in all patients groups we saw the same diverging pattern between those who eventually died and those who survived. Platelet counts in survivors were twice the value of non-survivors at day 10. When the rate of change $\Delta PC/\Delta t$ from day 2 onward was examined, this value was 5-fold higher in the survivors compared to non-survivors. If the change in platelet counts is considered from day 0 onward instead of from day 2 onward, the difference between survivors and non-survivors would be even more even more striking. But the reason for calculating $\Delta PC/\Delta t$ from day 2 onward, and not from day 0 onward, was to appropriately fit the bimodal time course of platelet counts.

![Figure 8.2d](image)

Figure 8.2d. Median platelet counts (109/L; interquartile range) for survivors (open circles) and non-survivors (closed circles) in liver transplantation patients.

The constancy and reproducibility of the platelet count in normal individuals has already been
established by Brecher [7] in 1953 and later by Ross [8] who showed a remarkable intra-individual stability of the platelet count over a 9-month period. Although for a normal population the platelet count may vary by 200 $\cdot 10^9$/L, from 150 to 350 $\cdot 10^9$/L, in any normal individual the range is only approximately 60 $\cdot 10^9$/L. The use of $\Delta$PC/$\Delta$t removes baseline inter-individual differences. That $\Delta$PC/$\Delta$t shows greater differences between survivors and non-survivors than the platelet count itself, underscores that Brecher’s observation on normal individuals is very relevant in patients as well.

The relation between a blunted rise in platelet counts and outcome is not restricted to surgical ICU patients, as shown for 206 patients at the medical ICU [9]. In this study which excluded patients with entities known to directly effect platelet counts (i.e. AIDS, leukemia, chemotherapy, immune thrombocytopenia and hemolytic uremic syndrome) survivors also showed significantly higher platelet counts from ICU-day 3 onward. In a recent study on the international EURICUS-II database compiling data from 1636 patients from 61 centers with both medical and surgical ICU patients, we also found that $\Delta$PC/$\Delta$t discriminates survivors from non-survivors [10].

That the platelet count can be a good parameter to follow-up critically ill patients is also reflected in the new emphasis on this parameter in recently introduced scoring systems for critically ill patients. The sequential organ failure assessment (SOFA) score [11] uses the platelet count and not the leukocyte count as one of its 6 components. Likewise, the multi-organ dysfunction score [12] uses the platelet count and not the leukocyte count as one of 7 components. The older, and still widely used APACHE-II uses the leukocyte count, but not the platelet count. It is obviously not our intention to promote $\Delta$PC/$\Delta$t as yet another prognostic scoring system, especially since a single parameter can never be the foundation of a prognostic score for such complex patients as there are at the ICU. But the fact that $\Delta$PC/$\Delta$t is as good as APACHE-II in predicting mortality is remarkable and makes it a candidate component of scoring systems. It should not be difficult to verify our findings on the existing databases that are the foundation of the above mentioned scores [11,12]. Since these scores already use platelet count as a component, they could be reanalyzed with the inclusion of $\Delta$PC/$\Delta$t.
The blunted rise of the platelet counts in the non-survivors must be the result of consumption that is relatively higher than production. Although it is difficult to discriminate between decreased platelet synthesis and increased consumption, it is probable that especially increased consumption of platelets is present. If bone marrow insufficiency or regulatory abnormalities are assumed to cause decreased platelet synthesis, this phenomenon is not reflected by decreased leukocyte counts in our patient set, since non-survivors even had higher leukocyte counts than survivors.

Consumption of platelets can be caused by disseminated intravascular coagulation (DIC) and sequestration in organs. DIC is frequently present in critically ill patients: it was found in 29 of 35 ICU-patients with systemic inflammatory response syndrome [13]. In the acute respiratory distress syndrome, the trapping of platelets in the lung has long been known [14]. Sigurdson et al. investigated platelet sequestration in ICU patients with $^{111}$Indium-labelled platelets at the bedside [15]. Patients with poor outcomes showed trapping of platelets in the gut as well as in the lung, liver and spleen. This phenomenon was observed 1 to 4 days before clinical sepsis or multiorgan failure. After liver transplantation, about 50% of the circulating platelets are sequestrated in the transplanted liver immediately after reperfusion [16]. It has been shown that platelet sequestration in the liver

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**Figure 8.3.** Receiver-operating characteristic curve that describes the relation between of various cut-off levels of the daily change in the platelet count ($\Delta \frac{PC}{dt}$) and the sensitivity (true positive fraction) and 1-specificity (false positive fraction) in predicting death within 30 days. The area under the ROC-curve is 0.743. The straight diagonal indicates the ROC of a parameter that has no predictive value at all. The upper arrow indicates that values of $\Delta \frac{PC}{dt} \leq 30 \cdot 10^9$/L/day have a sensitivity of 0.89 for predicting mortality, with a specificity of 0.42. A cut-off of $\Delta \frac{PC}{dt} \leq 0$ corresponds to a sensitivity of 0.38 and a specificity of 0.90.
Blunted rise in platelet counts in SICU patients

graft is associated with increased reperfusion damage. Persistent thrombocytopenia after transplantation was found to be associated with decreased survival [17], which is in agreement with the observations in the current study. Naturally the question arises if interventions aimed at preventing platelet consumption would affect outcome. Again, reanalysis of existing data sets of intervention studies with regard to \( \Delta PC/\Delta t \) would be of great interest. Such analyses could answer: a) if \( \Delta PC/\Delta t \) is related to outcome and b) if the intervention affected \( \Delta PC/\Delta t \). Thus, in patients that are not critically ill increased platelet counts often indicate ongoing inflammation and disease. But in critically ill patients the opposite is the case since a blunted rise in platelet counts - i.e. a low \( \Delta PC/\Delta t \) - has an unfavorable prognosis. The presence of a ‘normal’ platelet count after ICU-admission should not be automatically interpreted as desirable. Therefore the platelet count, routinely determined at low cost, should not only be used to detect thrombocytopenia or thrombocytosis. It should also be used to actively follow its time-dependent changes.

REFERENCES


Blunted rise in platelet counts in SICU patients