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Thrombocytopenia in critically ill patients: single center data analysis

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Abstract

Introduction: Thrombocytopenia (TP) is one of the most frequent abnormalities of hemostasis found in laboratory tests in critically ill patients. The aim of this study was to determine the frequency and most probable causes of TP in patients hospitalized in the Intensive Care Unit (ICU).

Material and methods: The documentation of all patients hospitalized in 2019 was analyzed retrospectively in the ICU of the university hospital. Patients diagnosed with TP at admission to the ward or during hospitalization were identified. Potential factors influencing the platelet count were analyzed.

Results: During the analyzed period, 291 patients were hospitalized. In 93 patients (32%), TP was diagnosed, including 61 patients at admission (21%), and the remaining 32 patients (11%) during hospitalization. Patients with TP had higher SAPS II, APACHE II and SOFA scores than patients without TP (p <0.001 for all). Mortality in patients with TP was twice as high as in patients without TP (58% vs. 29%, p <0.001). In 18 patients (6%), only one cause of TP was potentially identified, while in 39 patients (13%), four or more factors that could potentially cause TP were identified.

Conclusions: Thrombocytopenia is a relatively common problem in the critically ill population, but due to the challenges in differential diagnosis, a reliable assessment of the causes of its occurrence is difficult.

Key words: thrombocytopenia, critical care, intensive care unit

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Introduction

Thrombocytopenia (TP), usually defined as a decreased number of platelets (PLT) below 150 × 10^9/L, is one of the most frequent hemostatic abnormalities found in laboratory tests in critically ill patients [1]. PLT counts of greater than 50 × 10^9/L are generally not associated with clinical symptoms. Patients with PLT counts in the range of 30–50 × 10^9/L may experience episodes of excessive bleeding after injury, while patients with PLT counts in the range of 10–30 × 10^9/L may present with bleeding even after minor trauma. The risk of spontaneous bleeding occurs with PLT counts less than 10 × 10^9/L [2].

Previous studies have shown that TP occurs in up to half of patients admitted to the Department of Anesthesiology and Intensive Care Unit (ICU), and another 16% of patients develop TP during their stay in the ICU, which is an unfavorable prognostic factor. TP can have either a central (decreased myeloid platelets production) or a peripheral (increased destruction or abnormal distribution of platelets)

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cause. In the population of patients hospitalized in the ICU, determining the pathomechanism of TP is a challenge due to the frequent coexistence of many disorders affecting PLT function and the use of drugs and therapies inducing TP.

However, TP is rarely a primary hematological disorder. It is more often a secondary disorder that manifests itself as a result of physiological decompensation; hence, monitoring the trends of changes in platelets counts may be of prognostic value [3]. While mild TP requires extensive differential diagnosis, severe TP in ICUs usually results from disseminated intravascular coagulation (DIC), autoimmune disorders, or adverse drug reactions (ADRs) [3]. Determining TP pathomechanism is of key importance for implementing personalized therapy, although this is possible only in some patients.

The aim of this study was to assess the prevalence of, and attempt to identify the potential causes of, TP in a population of patients hospitalized in a mixed medical-surgical ICU.

Material and methods

A single-center, retrospective analysis of the medical records of patients treated in 2019 at the ICU in a university hospital was performed. All consecutive adult patients with PLT count <150 × 10^9/L at admission or during hospitalization were enrolled in the study. Demographic and clinical data were collected, including: age, gender, severity of patient condition at admission according to the APACHE II (Acute Physiology and Chronic Health Evaluation) and SAPS II (Simplified Acute Physiology Score) scoring systems, root cause of admission, presence of anemia [acc. to the World Health Organization (WHO) classification] [4], and the dichotomous outcome (i.e. death on ward or discharge).

Each patient underwent an individual assessment of potential TP causes, including sepsis according to the Surviving Sepsis Campaign definition [5], bleeding according to the WHO classification [6], liver diseases according to the International Classification of Diseases (ICD-10) [7], neoplastic disease, and antibiotic therapy, as well as rarer phenomena that can lead to a decrease in platelets count in peripheral blood, such as pseudothrombocytopenia and heparin-induced thrombocytopenia (HIT). The risk of TP occurrence was assessed on the 4T scale [8]. Additionally, the need to transfuse blood products [i.e. red blood cells (RBC) concentrate, fresh frozen plasma (FFP), platelets concentrate (PC), and cryoprecipitate] was analyzed. The effect of PCs transfusion was assessed (an absolute platelet count increment by 5 × 10^9/L at 24 hours after the end of transfusion was considered a satisfactory result) [6]. The PLT coefficient of variation (CV) was calculated, defined as the quotient of the standard deviation (SD) and the arithmetic mean of PLT counts obtained from five assessments performed during hospitalization: at admission, before PC transfusion, after PC transfusion (in patients receiving PC transfusion), and two additional measurements reflecting the trend of changes in platelets during the stay in the ICU.

Peripheral blood for PLT count determination was sampled with the use of a vacuum system into test tubes containing edetate [ethylenediaminetetraacetic acid (EDTA)] according to the center's routine procedures, immediately after admission to the ICU. The obtained material was analyzed with an XT-1800i device (Sysmex, Japan). When the attending physician deemed it appropriate, the result was verified in a laboratory in a Neubauer chamber.

Statistical analysis was performed with the use of licensed MedCalc software v.18 (MedCalc Software, Ostend, Belgium). Quantitative variables were presented as median and interquartile range (IQR). Qualitative variables were presented as absolute value and percentage. The difference between quantitative variables was assessed using the Kruskal-Wallis test. The chi-square test was used for qualitative variables. A p value <0.05 was considered statistically significant.

Results

In total, 291 patients were hospitalized in the analyzed period, and 93 (32%) of these patients were diagnosed with TP: 61 (66%) at admission, and the remaining 32 (34%) during their ICU stay. The mean platelets (PLT) count at admission was 118 × 10^9/L (IQR 73–166), and the mean PLT coefficient of variation during hospitalization was 0.29 (IQR 0.03–0.49). The severity of thrombocytopenia in ICU hospitalized patients is presented in Figure 1.

Table I presents selected demographic and clinical data in patients with and without TP. Patients with TP had a worse baseline general condition, i.e. statistically significantly higher scores on the SAPS II, APACHE II and SOFA scales than patients without TP, and mortality among patients with TP was twice as high as in patients without TP.

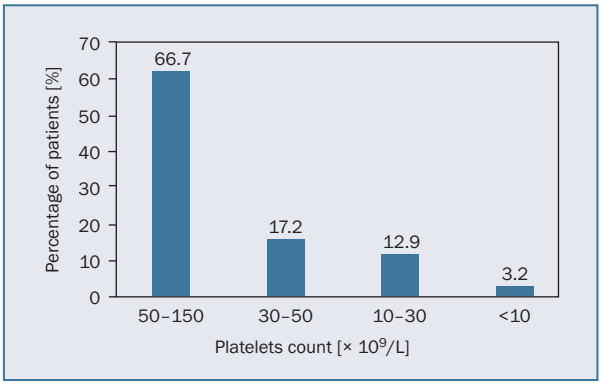

Figure 1. Severity of thrombocytopenia in Intensive Care Unit hospitalized patients

Table I. Selected demographic and clinical parameters in patients with and without thrombocytopenia (TP) hospitalized in Intensive Care Unit

Parameter	TP (+) n = 93	TP (–) n = 198	*p* value
Male gender; n [%]	53 (57%)	105 (53%)	0.41
Age, median (IQR), years	64 (54–69)	62 (48–71)	0.14
APACHE II; points (IQR)	23 (16–28)	16 (12–23)	0.0001
SAPS II; points (IQR)	50 (42–70)	42 (31–53)	0.0002
SOFA points (IQR)	10 (9–14)	8 (6–11)	<0.0001
Death; n [%]	54 (58%)	57 (29%)	<0.0001

IQR — interquartile range

Table II. Causes of thrombocytopenia (TP)

Possible cause of TP	Number of patients, n [%] (n = 93)
Antibiotic therapy	81 (87%)
Bleeding	43 (46%)
Sepsis	42 (45%)
Cancer	25 (27%)
Heparin-induced thrombocytopenia	2 (2%)

Table III. Bleeding severity according to World Health Organization (WHO) scale in patients with thrombocytopenia (TP) and active bleeding

WHO bleeding scale	Number of patients with active bleeding (n = 43)
Grade I	1
Grade II	17
Grade III	20
Grade IV	6

Table II sets out possible causes of TP in the studied population.

TP was diagnosed in 42 patients with sepsis, including 29 (69%) patients at admission, and 13 (31%) during their stay in ICU.

In total, 25 patients (27%) with TP were admitted to the ICU for surgical reasons. Active bleeding was found in 43 patients (46%), and the severity of bleeding according to the WHO scale is set out in Table III.

Anemia coexisting with TP was diagnosed in 83 patients (89%) during hospitalization. Figure 2 sets out the severity of anemia among TP patients.

In total, 25 patients (27%) with TP were diagnosed with cancer. Although heparin was used in 66 patients (71%), a high probability of HIT (i.e. 6–8 points in the 4T scale) was found in only two patients. No patient was diagnosed

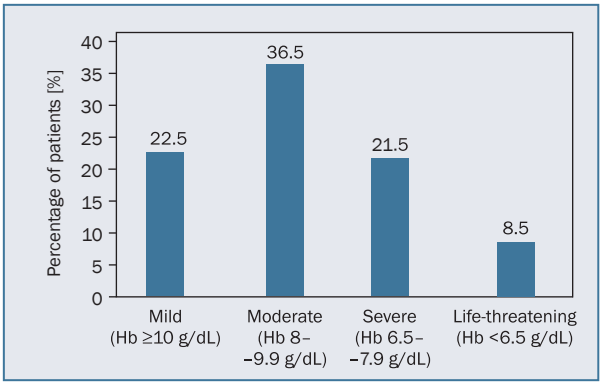

Figure 2. Severity of comorbid anemia in 83 patients with thrombocytopenia

Table IV. Transfusions of blood products

Transfused preparation	Number of patients (n = 55)
PC	22 (22.6%)
RBC concentrate	43 (46.24%)
FFP	32 (34.3%)
Cryoprecipitate	9 (9.7%)

PC — platelets concentrate; RBC — red blood cells; FFP — fresh frozen plasma

with pseudothrombocytopenia. Antibiotic therapy was used in 87% of patients, most often meropenem (n = 39), then vancomycin (n = 28), linezolid (n = 19), colistin (n = 14), piperacillin with tazobactam (n = 13) or ceftriaxone (n = 10). The use of any of these antibiotics did not reduce PLT count. Only three patients (3%) treated with cloxacillin had a statistically significant increase in the PLT coefficient of variation (0.30 vs. 0.77, $p = 0.03$). Only in 18 patients (19%) did TP have a potentially single cause, and in 39 patients (42%), TP could have developed as a result of four or more coexisting causes.

Of the patients in the study group, 55 required transfusions of blood products. The number of patients requiring blood products transfusion is set out in Table IV.

Due to the need to perform invasive procedures, 12 patients required transfusions of blood products. Due to active bleeding, 43 platelets concentrate (PC) packages were transfused, and among them eight episodes of bleeding were spontaneous. A total of 54 PC packages were transfused, of which 59% of transfusions achieved a satisfactory transfusion effect. The number of PC packages transfused in one patient is set out in Figure 3.

Discussion

In the presented group of patients, the two most common causes of TP were sepsis and blood loss, which at the same time remains one of the most common causes of

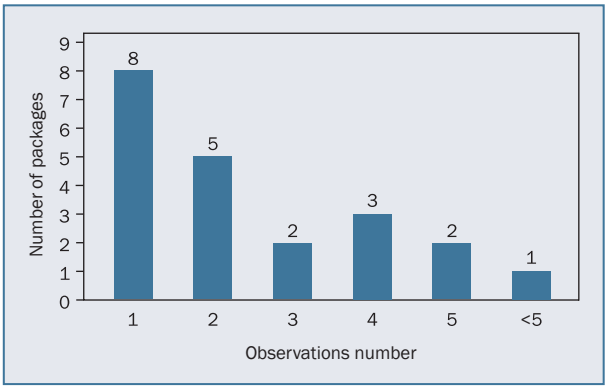

Figure 3. Number of infused packages of platelet concentrate

hospitalization in the ICU. Mortality in patients with TP was almost twice as high as in patients who did not develop TP during hospitalization.

Patients diagnosed with neoplastic disease are particularly vulnerable to hemostatic disorders. Decreased platelets count is observed in a significant group of oncological patients, which may result from bone marrow infiltration with neoplastic process (thus platelets production reduced) or iatrogenic causes related to anticancer therapies [9]. Although in our population a large group of patients was hospitalized for oncological reasons (mainly after oncological surgery), it has not been documented that the disease itself leads to TP. This is probably due to the fact that decreased platelets count is a chronic, progressive process, along with the disease stage.

Iatrogenic thrombocytopenia can result from commonly used medications, fluid therapy, and frequent blood sampling in critically ill patients. Witosz et al. [10] demonstrated a correlation between a 7-day positive fluid balance and a decrease in complete blood count parameters in patients hospitalized in the ICU. In our study group, the vast majority of patients received antibiotic therapy (87%) with drugs potentially inducing TP, but the PLT coefficient of variation assessment did not confirm such a relationship. In patients with sepsis, distinguishing whether the cause of thrombocytopenia is sepsis itself or antibiotic therapy is difficult (and in many cases impossible) due to the inability of discontinuing the antibiotic therapy. Despite the lack of literature reports on thrombocytopenia caused by cloxacillin, among the patients receiving antibiotic therapy in our department, the rate of thrombocytopenia was the greatest during the administration of this particular antibiotic.

Another cause of drug-associated TP is HIT, which is a rare immune phenomenon associated with antibodies against platelet factor 4 (PF4) complexes produced in response to heparin. Currently, it is believed that up to 10% of patients treated with heparin may develop anti-PF4 antibodies, but only a small group of patients susceptible to developing HIT will develop severe thrombosis and life-threatening thrombocytopenia, a condition referred to as heparin-induced thrombocytopenia and thrombosis (HITT) [8]. The incidence of HIT in the ICU is estimated at 1/100 patients [8]. In our study group, HIT was suspected in 2/93 patients.

Although not found in our study, pseudothrombocytopenia (PTCP) is a rare laboratory artifact with an estimated population incidence of 0.1–2% [1]. In PTCP, the reduction of PLT count below the lower range limit in a patient without symptoms of hemorrhagic diathesis results from the action of autoantibodies related to the presence of EDTA in the test tube, which causes platelets agglutination. In order to exclude PTCP, complete blood count (CBC) should be checked with an anticoagulant other than EDTA (e.g. sodium citrate). In our center, no case of PCTP was recorded in the analyzed period. Greinacher et al. assessed the incidence of thrombocytopenia in the ICU at 30–45%, with 20–30% of patients diagnosed with TP at admission, and a similar percentage developing TP during hospitalization [11].

In our study, the percentage of patients with thrombocytopenia was similar, but with a smaller percentage of patients (11%) developing TP during their stay in the ICU. Our findings pointing to sepsis and blood loss as the main causes of TP in ICU hospitalized patients are consistent with the results of other studies.

Our study has several important limitations. This was a retrospective analysis, which is related to the inability to assess all factors that may contribute to the development of TP during hospitalization, and causal inference is impossible. The second limitation is the small group of TP patients. However, the inclusion of nearly 300 patients in the original analysis seems to be sufficient to analyze the potential causes of TP, and the study has significant cognitive value from the clinical point of view. Finally, an evaluation of transfusion effectiveness has been made based on CBC on the day following the transfusion and the time criterion (i.e. precisely 24 hours after transfusion) was not always met.

Conclusions

Thrombocytopenia is a relatively common problem in the critically ill population, but due to the difficulties and limitations in differential diagnosis, a reliable assessment of the causes of its occurrence is difficult.

Authors' contributions

MD — project, data collection, final manuscript. KM — data collection, final manuscript. MP — project, statistical analysis, final manuscript. ŁK — draft, review, final manuscript.

Conflict of interest

None.

Financial support
None.

Ethics
The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to biomedical journals.

Approval of the Bioethics Committee
Due to the observational nature of the study, the Bioethics Committee abolished the need to obtain informed consent of participants to participate in the study (PCN/0022/KB/273/19).

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