10.1515/chilat-2016-0007

ORIGINAL ARTICLE

Incidence and Predictive Value of Thrombocytopenia in Patients with Severe Community Acquired Pneumonia

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SUMMARY
Introduction. Thrombocytopenia is frequently encountered in intensive care unit (ICU) patients. The cause of thrombocytopenia is multifactorial, it develops as a result of infection, inflammation and depletion of coagulation factors. Therefore, thrombocytopenia could potentially serve as an indicator of severity of the illness and an outcome predictor in patients with severe community-acquired pneumonia (CAP).
Aim of the study. To determine incidence and predictive value of thrombocytopenia in ICU patients with severe CAP.
Material and methods. We carried out a retrospective study based on clinical records from patients admitted to the Pauls Stradins Clinical University Hospital Intensive Care and Reanimation Unit from 2011 to 2014. Thrombocytopenia was defined as platelet count ≤150×109/L.
Results. A total of 98 patients were included in this study, 58 (59%) men and 40 (41%) women. The mean (±SD) age of patients was 61±17.9 years, 54% died and 46% survived. 57 patients (58%) developed thrombocytopenia, in 58% it was present at the admission to ICU, and 42% developed thrombocytopenia during their stay in ICU. The lowest platelet count, in survivors was on fifth day in ICU, while in non-survivors on fourth day in ICU. Platelet count on admission to ICU (ROC AUC: 0.610, p=0.095) had lower discriminative power for ICU mortality than SOFA score (ROC AUC: 0.729, p=0.001) and CURB-65 score (ROC AUC: 0.680, p=0.006). Patients with thrombocytopenia at any point of ICU stay had higher hospital mortality in comparison to patients without thrombocytopenia. (36 (63.1%) vs 17 (41.1%), p=0.041). In thrombocytopenic patients non-resolution of thrombocytopenia during the ICU stay was associated with higher mortality (OR 5.5; 95% CI, 1.6-18.7, p=0.006). After adjusting for age, gender and SOFA score, non-resolution of thrombocytopenia remained to be an independent mortality predictor (OR 8, 95% CI 1.7-37, p=0.008)
Conclusions. Thrombocytopenia is frequently encountered in patients with severe CAP. Thrombocytopenia at any point of ICU stay is associated with higher hospital mortality. Resolution of thrombocytopenia is associated with better clinical outcome.
Key words: thrombocytopenia, severe community acquired pneumonia, mortality, intensive care

INTRODUCTION

Thrombocytopenia is defined as platelet count $<150\times10^9$/L (1). Depending on the mechanism thrombocytopenia can be classified into following types: thrombocytopenia that develops as a result of a decreased production of platelets, thrombocytopenia that develops as a result of an increased destruction of platelets, dilutional and distributive thrombocytopenia, and pseudothrombocytopenia (2).

Thrombocytopenia is encountered in 20-40% of ICU patients (2, 3, 4). The cause of thrombocytopenia in critically ill patients is multifactorial, it develops as a result of infection, inflammation and depletion of coagulation factors (5). Certain conditions, such as massive hemotransfusion, sepsis, acute respiratory distress syndrome, heparin-induced thrombocytopenia (HIT), diffuse intravascular coagulation are common causes of thrombocytopenia in critically ill (2). During the first days of ICU stay patients develop a transient decrease in platelet count (6, 7). Akca and colleagues found that the lowest platelet count in critically ill patients is on fourth day of ICU stay, in survivors it returns to admission level by the day 9 of ICU stay and continues to rise afterwards, whereas in non-survivors platelet count returns to admission levels by the end of the first week, but does not continue to rise afterwards (6).

In surgical ICU and in trauma ICU thrombocytopenia usually develops as a result of bleeding and massive hemotransfusions (8). On the other hand, in medical ICU bleeding usually occurs as a consequence of thrombocytopenia (9). Critically ill patients with platelet count $<50\times10^9$/L have a four to fivefold increased risk for bleeding in comparison to patients with platelet count $>50\times10^9$/L (9). It is known that thrombocytopenia has a negative prognostic value in ICU patients and is an independent risk factor for mortality in these patients (4, 10). Moreover, significant changes in platelet count (6), degree of thrombocytopenia (11, 12) and non-resolution of thrombocytopenia (13) also have a negative prognostic value in ICU patients.

Severe community acquired pneumonia is a community acquired pneumonia that requires treatment in ICU (14). Approximately 10% of patients hospitalized with CAP require treatment in ICU and mortality from this condition is 21-58% (15-17). Respiratory failure from pneumonia is one of the most common conditions treated in ICU. Thrombocytopenia on admission to ICU is encountered in 25% of patients with severe CAP (11). In context of critical care thrombocytopenia has mostly

been studied in critically ill patients in general. Currently the amount of published data on thrombocytopenia in patients with severe CAP is limited, thus it is important to determine whether thrombocytopenia and changes in platelet count can be used as prognostic marker in this group of patients.

AIM OF THE STUDY

The aim of our study was to determine the incidence and predictive value of thrombocytopenia in patients with severe community-acquired pneumonia.

MATERIAL AND METHODS

We conducted a retrospective cohort study using clinical records from patients admitted to the Pauls Stradins Clinical University Hospital Intensive Care and Reanimation Unit between January 1, 2011 and December 31, 2014. Patient records were obtained from Pauls Stradins Clinical University Hospital Archive.

Adult patients (>18 years) with diagnosis of severe CAP were included in this study. We excluded patients who had any of the following criteria: acquired or congenital thrombocytopathy, recent chemotherapy, non-fractioned heparin therapy, alcohol abuse, hepatic cirrhosis, immunocompromised state (HIV infection and organ transplant recipients) and less than 2 daily blood tests.

We registered and analyzed the following data obtained from the clinical records: age, gender, length of stay (LOS) in ICU, hospital outcome, ICU outcome, full diagnosis, causative microbial organism, SOFA score on admission to ICU, CURB-65 score on admission to the hospital, leukocyte count on admission to ICU, C-reactive protein value on admission to ICU, daily platelet count (up to 20 days of ICU stay or death, whichever happened earlier). In results related to mortality, ICU mortality was analyzed unless stated otherwise.

Thrombocytopenia was defined as platelet count $\leq 150 \times 10^9$/L (1). Thrombocytopenia was classified into the following categories based on platelet count: mild thrombocytopenia (platelet count 100-150 $\times 10^9$/L), moderate (50-100 $\times 10^9$/L), severe (20-50 $\times 10^9$/L), very severe (0-20 $\times 10^9$/L) (18). Severe community acquired pneumonia was defined as a community acquired pneumonia that required treatment in ICU (14).

Statistical analysis was performed using software SPSS 22.0. Data were tested for normality using Kolmogorov-Smirnov test. Normally distributed data were compared using Independent Samples T-Test and displayed as mean ± standard deviation (SD). Data with skewed distribution were compared using Mann-Whitney U test and displayed as median and interquartile range [IQR]. For comparison of categorical data Chi-Square test was used and data were displayed as percentages and absolute values. Multiple logistic regression analysis was used to determine whether non-resolution of thrombocytopenia is associated with higher mortality and odds ratio (OR) and 95% confidence interval (CI) was calculated. Spearman correlation (r_s) analysis was performed to find correlations. Receiver-operator (ROC) curves and analysis of area under the curve (AUC) were used to determine discriminative power. P value <0.05 was considered statistically significant.

RESULTS

Between January 1, 2011 and December 31, 2014, 313 patients were admitted to ICU with diagnosis of pneumonia, of whom we excluded 105 patients because either a clinical record could not be found (7 patients), or it was not a community acquired pneumonia (98 patients). Out of remaining 208 patients with severe CAP, we excluded 110 patients due to preexisting exclusion criteria: less than two daily blood tests available (18 patients), alcohol abuse (40 patients), hepatic cirrhosis (8 patients), non-fractioned heparin therapy (22 patients), HIV infection (7 patients), recent chemotherapy (8 patients), patients who had organ transplantation (5 patients), splenectomy (1 patient) and splenomegaly (1 patient). A total of 98 patients were included in the study, 58 (59%) men and 40 (41%) women. The mean age was 61±17.9 years. ICU mortality was 46% (n=45), while hospital mortality was 54% (n=53). Median [IQR] LOS in ICU was 7 [3-18] days.

Thrombocytopenia was encountered in 57 (58%) patients during their stay in ICU, of them in 33 (58%) patients it was present on admission to ICU, while in 24 patients (42%) it developed during their stay in ICU. The median [IQR] duration of thrombocytopenia was 4 [2-7] days. The lowest median [IQR] platelet count in survivors was on fifth day of ICU stay, 173 [128-290] $\times 10^9$/L, whereas in non-survivors it was on fourth day of ICU stay, 120 [57-188] $\times 10^9$/L. In non-survivors platelet count was lower than in survivors from second until fifth day of ICU stay (Figure 1).

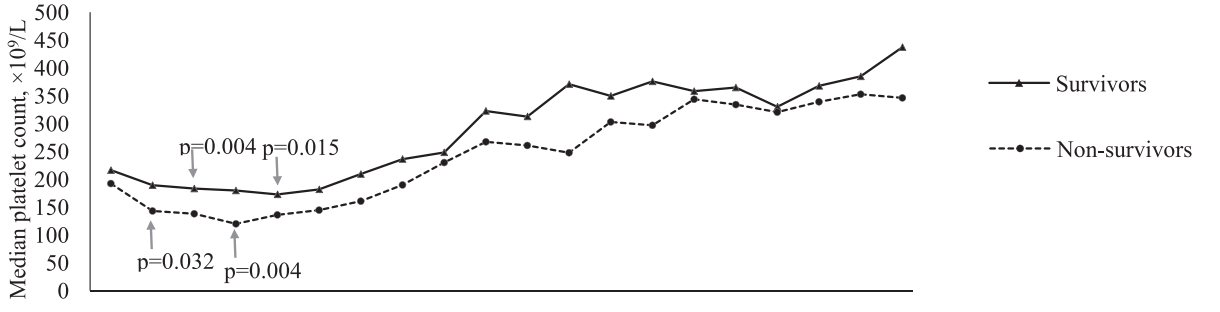

Fig.1. Kinetics of platelet count in survivors and non-survivors
P values are displayed for days in ICU when there was a statistically significant difference in platelet count between survivors and non-survivors

Platelet count on admission to ICU did not differ significantly between survivors and non-survivors. Moreover, presence of thrombocytopenia and degrees of thrombocytopenia also did not differ significantly between the two groups (Table 1).

Table 1. Platelet count and presence of thrombocytopenia in survivors and non-survivors

	Non-survivors, n=44	Survivors, n=54	p value
Median [IQR] platelet count on admission to ICU, $\times10^9$/L	193 [106-257]	217 [139-314]	0.062
Thrombocytopenia on admission to ICU, n (%)	19 (43.2%)	14 (25.9%)	0.072
Mild (platelet count 100-150 $\times10^9$/L)	8 (18.2%)	7 (13%)	0.475
Moderate (platelet count 50-100 $\times10^9$/L)	8 (18.2%)	4 (7.4%)	0.129
Severe (platelet count (20-50 $\times10^9$/L)	2 (4.5%)	2 (3.7%)	1
Very severe (platelet count 0-20$\times10^9$/L)	1 (2.3%)	1 (1.9%)	1

Platelet count on admission to ICU had lower discriminative power for mortality in comparison to SOFA score and CURB-65 score (ROC AUC: 0.610 vs 0.729 vs 0.680). SOFA score was the best mortality predictor (ROC AUC 0.729, p=0.001) with cut-off value of 7 points (sensitivity 69%, specificity 70%) (Figure 2, Table 2).

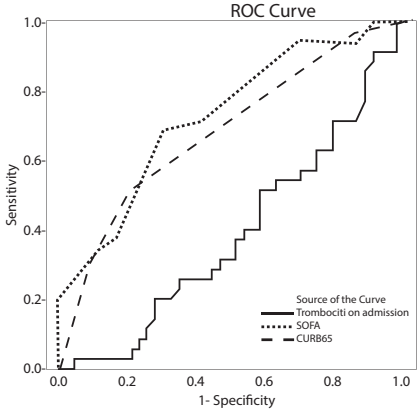

Fig. 2. ROC curves for platelet count on admission to ICU, SOFA score and CURB-65 score in respect to ICU mortality

Platelet count on admission to ICU positively correlated with leukocyte count (r_s=0.58, p<0.001) and negatively correlated with SOFA score (r_s=-0.352, p=0.001), but did not correlate with CURB-65 score (r_s=-0.021, p=0.851), CRP (r_s=-0.29, p=0.779) and erythrocyte count (r_s=0.013, p=0.901).

Comparing patients with thrombocytopenia at any point of ICU stay and patients without thrombocytopenia we found that patients with thrombocytopenia had higher hospital mortality (36 (63.2%) vs 17 (41.5%), p=0.041), however, ICU mortality did not differ significantly (30 (52.6%) vs 14 (34.1%), p=0.099). Patients with thrombocytopenia had higher SOFA score (median [IQR]: 8 [5-11] vs 4 [3-6.8], p<0.001), while CURB-65 score did not differ significantly between the two groups. Patients with thrombocytopenia had lower leukocyte count than patients without thrombocytopenia (mean (±SD): 10±9.5 vs 16±8.9 $\times10^9$/L, p=0.008) (Table 3).

Table 3. Demographics and severity of illness in patients with thrombocytopenia at any point of ICU stay and without thrombocytopenia

	With thrombocytopenia, n=57	Without thrombocytopenia, n=41	p value
Age, years, mean (±SD)	59.6±16,5	63.7±19.5	0.258
Gender, male, n (%)	23 (56.1%)	35 (61.4%)	0.678
ICU mortality	30 (52.6%)	14 (34.1%)	0.099
Hospital mortality	36 (63.2%)	17 (41.5%)	0.041
ICU LOS, days, median [IQR]	7 [3-18]	7 [3-14]	0.908
SOFA score, median [IQR]	8 [5-11]	4 [3-6.8]	<0.001
CURB-65 score, median [IQR]	2 [1-4]	2 [1-2.8]	0.148
Leucocyte count, $\times10^9$/L, mean (±SD)	10±9.5	16±8.9	0.008
CRP, mg/dL, median [IQR]	172.7 [65-265.3]	169.7 [92.7-239.6]	0.760

Table 2. AUC and cut-off values of platelet count on admission to ICU, SOFA score and CURB-65 score in respect to ICU mortality

	AUC	95% CI	p value	Cut-off value	Sensitivity	Specificity
Platelet count on admission to ICU	0.610	0.484-0.735	0.095	<195$\times10^9$/L	51%	42%
SOFA score	0.729	0.617-0.840	0.001	>7 points	69%	70%
CURB-65 score	0.680	0.561-0.800	0.006	>3 points	51%	79%

Out of 57 patients who had thrombocytopenia, in 40 patients (70%) thrombocytopenia did not resolve during ICU stay. Patients with non-resolution of thrombocytopenia had higher mortality in comparison to patients in whom thrombocytopenia resolved (26 (65%) vs 4 (24%), p=0.008). Non-resolution of thrombocytopenia was associated with higher mortality (OR 5.5, 95% CI 1.6-18.7, p=0.006). After adjusting for age, gender and SOFA score we found non-resolution of thrombocytopenia to be an independent risk factor for mortality (OR 8, 95% CI 1.7-37, p=0.008) (Table 4).

DISCUSSION

Since the amount of published data on thrombocytopenia in patients with severe CAP is limited we also compared our results to studies where thrombocytopenia was investigated in patients with sepsis and critically in patients.

Our findings were similar to the study carried out by Brogly and colleagues, in which thrombocytopenia was studied in patients with severe CAP: they also did not find difference in ICU mortality between patients with thrombocytopenia and without thrombocytopenia, and they had similar incidence of thrombocytopenia on admission to ICU (11).

In respect to non-resolution of thrombocytopenia as a predictor of a negative outcome our findings were similar to study carried out by Vencata and colleagues on patients with severe sepsis and septic shock. In their study non-resolution of thrombocytopenia was associated with higher mortality and they also did not find the difference in mortality (28 day mortality) between patients with thrombocytopenia and patients without thrombocytopenia (13).

Concerning results related to platelet count kinetics our results were similar to studies carried out by Akca and colleagues (6) and Moreau and colleagues (19), who studied platelet count in critically ill patients, and to previously mentioned study by Vencata and colleagues (13). Both in our study and the study by Vencata and colleagues duration of thrombocytopenia was four days. In the studies by Akca and colleagues and Moreau and colleagues the lowest platelet count in both survivors and in non-survivors was on fourth day of ICU stay, in our study non-survivors had the lowest platelet on fourth day of ICU stay, while survivors on fifth.

We found correlation between platelet count and leukocyte count, but did not find correlation between platelet count and CRP, which might be attributed to the fact that during a severe inflammation hemophagocytosis of hematopoietic cells takes place (20, 21) and also due to changes in blood volume. However, we did not find a correlation between platelet count and erythrocyte count. Erythrocyte count should have also been affected by changes in blood volume and hemophagocytosis, because erythrocytes, leukocytes and platelets are produced from the same precursor cell. Possibly this absence of correlation between platelets and erythrocytes could be explained by the fact that erythrocytes have longer lifespan in comparison to platelets and leukocytes and thus change in their count is not as rapid. Since both leukocytes and platelets (22, 23] are actively involved in inflammation, correlation between them could be explained by a consumption in inflammatory processes.

There are certain limitations in our study. Firstly, we used SOFA score to determine severity of illness. Platelet count is one of the parameters assessed by SOFA score, thus it would have been more correctly to use other scoring system which does not comprise platelet count, such as APACHE II scoring system. Also, as we studied thrombocytopenia in patients with pneumonia, we could not exclude patients who received antibiotics. It is well known that certain antibiotics, such as penicillin may cause thrombocytopenia (24). Since we carried out a retrospective study we could not analyze correlation between platelet count and procalcitonin levels, because it was determined in a limited number of patients. In patients with CAP, level of procalcitonin is related to severity of illness and is an effective mortality predictor (25). In similar studies (13) patients who received non-fractioned heparin therapy were not excluded, because if heparin-induced thrombocytopenia (HIT) was suspected, anti-platelet factor 4/heparin antibodies were assessed. Since our study is retrospective, and in Latvia these antibodies are not routinely assessed in suspicion of HIT, we had to exclude patients who received non-fractioned heparin therapy, because we could not acknowledge the numbers of patients with HIT and how it could have affected our results.

CONCLUSIONS

Thrombocytopenia is frequently encountered in patients with severe community-acquired pneumonia. Thrombocytopenia at any point of ICU stay is associated with higher hospital mortality. Resolution of thrombocytopenia is associated with better clinical outcome.

Conflict of interest: None

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