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Evaluation of Platelet Parameters as Prognostic Analysis in Cardiac Intensive Care Unit Patients

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Abstract

Objective: Platelet activation and consumption are common in critically ill patients and are associated with poorer prognosis. Inflammatory and thrombotic conditions may alter platelet size, which can be detected on routine blood cell analysis by evaluation of mean platelet volume. The aim of the present study was to investigate the evaluation of platelet parameters as a predictor of all-cause mortality in cardiac intensive care unit (ICU) patients.

Methods: Platelet count and mean platelet volume were measured daily in cardiac ICU and were classified in three categories of thrombocytopenia, according to the average value of platelet count during hospitalization: mild (100-149 X 10^9/L), moderate (50-99 X 10^9/L) and severe (<50 X 10^9/L). We excluded patients younger than 18 years, pregnant women, with cancer or hematological disease, who have had previous use of steroids or chemotherapy, those that were readmitted after hospital discharge and patients who died in the first 24 hrs after admission. A correlation analysis was performed to identify independent predictors of mortality.

Results: We included 165 patients (61 ± 16 years, 55.8% male, average length of stay in ICU was 10 ± 10 days). In total, 42 (25.4%) out of the 165 patients showed platelet count <150 X 10^9/L during hospitalization. Greater disease severity by the Sequential Organ Failure Assessment (SOFA) score (P<0.001) was observed among patients with moderate and severe thrombocytopenia, and a proportionally inverse relationship between mortality and platelet count for moderate thrombocytopenia (HR 2.303; IC 95% 1.148–4.619; p=0.019). The total median value of the mean platelet volume was 11.12, being this higher in patients with moderate and severe thrombocytopenia (11.94 and 12.10; p=0.002). Patients with thrombocytopenia that evolved with increasing platelet count and decreasing mean platelet volume had a favorable outcome.

Conclusion: A decrease of platelet count and increase in the level of mean platelet volume after admission in cardiac intensive care unit is associated with higher mortality, suggesting that platelet parameters have a prognostic impact.

Keywords: Cardiac intensive care unit; Daily platelet parameters; Mean platelet volume (MPV); Platelet count; Sequential organ failure assessment (SOFA); Acute physiology and chronic health evaluation II (APACHE II); Mortality

Abbreviations: ICU: Intensive Care Unit; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; PLT: Platelet Count; MPV: Mean Platelet Volume; PDW: Platelet Distribution Width; P-LCR: Platelet Large Cells Ratio; EDTA: Ethylene Diamine Tetra Acetic Acid.

Introduction

Thrombocytopenia is the most common hemostatic disorder in critically ill patients [1]. Thrombocytopenia is defined as a platelet count of <150,000/μL or a decrement of >50% from a previous measurement [2]. The causes of thrombocytopenia are numerous and varied, but basically they result from three processes: 1. Deficient platelet production, 2. Accelerated platelet destruction or increased consumption, 3. Abnormal distribution or dilution of platelets in the organism [3]. The incident thrombocytopenia (developing during the course of ICU stay) occurred in 13.0% to 44.1% of patients [4].

Most patients are exposed to heparin during their stay in the ICU and heparin-induced thrombocytopenia is often suspected, although rarely confirmed [5]. Other factors that have been associated with the development of thrombocytopenia in studies with high illness severity, sepsis and organ dysfunction [2]. The cause of a low platelet count in ICU may be difficult to determine and is often multifactorial [6].

Studies show that thrombocytopenia is associated with decreased survival in patients in ICU [7] and the decline in platelet count (PLT) during hospitalization in the ICU provides prognostic information [8].

Platelet parameters can be monitored through semi-invasive procedures for long periods. They help in diagnosis, early stage of disease, monitoring the progression and determining therapeutic results. The parameters include: PLT, mean platelet volume (MPV), platelet distribution width (PDW) and platelet large cells ratio (P-LCR) [9]. Among platelet indices, MPV is a potentially useful marker of platelet activity. The clinical importance of determining the MPV is related to the presence of increased platelet aggregation. The MPV has been linked to patients with coronary artery disease and severity of coronary atherosclerosis [10].

Prior studies have also demonstrated that platelet parameters are a prognostic indicator in general ICU, few data on patient admitted in the ICU acute cardiovascular disease exist. Therefore, the aim of the present study was to investigate the evaluation of platelet parameters as a predictor of all-cause mortality in ICU of the cardiac emergency unit to provide information that will allow anticipation of possible adverse outcomes.

Materials and Methods

Study Population and Protocol

An observational cohort, prospective and analytical study involving patients admitted to the cardiac ICU, with 10 beds, of the Cardiologic Emergency Unit (PROCAPE), a specialized tertiary care cardiovascular teaching hospital with 250 beds. The experimental design of this study has been approved by the Research Ethics Committee under number CAAE: 08412412.20000.5192, in Brazil Platform. All patients included in the study signed a free and informed consent form.

The study included patients admitted to the cardiac ICU of PROCAPE from May/2013 through January/2014 with clinical and/or surgical diseases. We excluded patients younger than 18 years, pregnant women, with cancer or hematological disease, who have had previous use of steroids or chemotherapy, those that were readmitted after hospital discharge and patients who died in the first 24 hrs after admission.

Demographic and clinical information were gathered from medical charts of patients, including age, period of observation, admission diagnosis in the cardiac ICU, severity of illness measured by APACHE II score [11], organic dysfunctions evaluated by the Sequential Organ Failure Assessment score (SOFA) [12] and laboratory data including platelet count and MPV. Patients were followed until hospital outcome, noting at this moment the length of stay in the cardiac ICU and in the hospital and the outcome (death or survival).

After the first 24 h of admission into the cardiac ICU, all patients had APACHE II and SOFA calculated. The SOFA score was also calculated on the 2nd and 3rd days of hospitalization in a cardiac ICU and later of 48/48 h until discharge from the cardiac ICU. Patients were classified in coronary (acute or chronic) [13,14] or not coronary (heart valve diseases, peri-miocardiopathies, cardiac arrhythmias). Patients were also classified into infected (sepsis) and uninfected obeying the criteria for systemic inflammatory response syndrome, plus an infectious focus documented or presumed (antibiotic use) [15].

Laboratory tests

PLT and MPV were performed by the automated method using the Sysmex XE-2100 device (Sysmex Europe GmbH, Norderstedt, Germany). Daily venous blood samples were collected in tubes containing anticoagulant ethylene diamine tetra acetic acid (EDTA), before 9 am until hospital discharge. Three categories of thrombocytopenia were defined: mild (100-149 X 10^9/L), moderate (50-99 X 10^9/L) and severe (<50 X 10^9/L) [1]. Each patient was classified in categories of thrombocytopenia using average daily PLT during the days of hospitalization.

Statistical analysis

Descriptive analysis was presented through absolute and relative frequencies of the main categorical variables. Quantitative analyses such as mean and standard deviations and comparison between groups were performed using chi-square tests (or Fisher's exact test when necessary) and numeric data were analyzed with t-Student tests. Kruskal-Wallis test was used for data with non-normal distribution. Hazard ratio between the variables platelet counts and mortality was calculated, and it was categorized through pre-defined cutoff point, diagnosis and outcome with respective 95% confidence intervals. Statistical significance level of $p<0.05$ was adopted. For the statistical analysis we used the SPSS (Statistical Program for Social Sciences) version 10.0 for Windows (SPPS Inc. Chicago, I11, USA).

Results

The study included 165 patients from a total of 212 (47 patients did not participate in the study due to the exclusion criteria: Neoplasia: 28, Death <24 hrs: 7, Chronic corticoid: 8, Refused: 2, Aged <18 years: 1, readmission: The mean age of these patients was 61 ± 16 years, 55.8% were male. The admission diagnosis in the ICU was coronary (48.8%) and non-coronary (51.2%), the majority (82.4%) coming mainly from the Cardiac Emergency (Table 1).

Characteristics	Normal (n =123)	Mild (n=24)	Moderate (n=15)	Severe (n=3)	Total (n=165)	P
Sex						
Male	71 (57.7)	12 (50.0)	7 (46.7)	2 (66.7)	92 (55.8)	
Female	52 (42.3)	12 (50.0)	8 (53.3)	1 (33.3)	73 (44.2)	.286
Age (years)	61 (± 17)	62 (± 16)	60 (± 16)	56 (± 25)	61 (± 16)	.945
Skin color						

White	49 (39.8)	7 (29.2)	6 (40.0)	1 (33.3)	63 (38.2)	
Black	21 (17.1)	3 (12.5)	4 (26.7)	0 (00.0)	28 (17.0)	
Brown	53 (43.1)	14 (58.3)	5 (33.3)	2 (66.7)	74 (44.8)	.714
Origin						
Emergency	105 (85.4)	17 (70.8)	12 (80.0)	2 (66.7)	136 (82.4)	
Infirmary	14 (11.4)	5 (20.8)	2 (13.3)	1 (33.3)	22 (13.3)	
TSRU	4 (3.3)	2 (8.3)	1 (6.7)	0 (00.0)	7 (4.2)	.299
Time of stay in the ICU (days)	11 ± 11	7 ± 7	10 ± 9	3 ± 3	10 ± 10	.303
Median time of stay in the ICU (days)	7	6	8	2	7	.140
Time of stay in the hospital (days)	31 ± 30	32 ± 31	19 ± 14	8 ± 8	30 ± 29	.575
Median time of stay in the ICU (days)	19	22	15	8	19	.358
Mortality						
ICU	45 (36.6)	9 (37.5)	10 (66.7)	1 (33.3)	65 (39.4)	.146
Hospital	14 (17.9)	3 (20.0)	2 (40.0)	1 (50.0)	20 (20.0)	.265
APACHE II	29.9 ± 9.5	22.0 ± 9.7	22.4 ± 8.5	33.7 ± 9.6	21.6 ± 9.5	.131
Median APACHE II	21.0	21.0	21.0	32.0	21.0	.225
APACHE II score						
<25 points	78 (63.4)	14 (58.3)	10 (66.7)	0 (00.0)	102(61.8)	
≥ 25 points	45 (36.6)	10 (41.7)	5 (33.3)	3 (100.0)	63 (38.2)	.186
SOFA	4.5 ± 3.4	6.7 ± 3.9	9.6 ± 3.9	14.7 ± 5.3	5.4 ± 4.1	<.001
Median SOFA	3.7	6.0	10.0	17.5	4.5	<.001
SOFA score						
<7 points	97 (78.9)	13 (54.2)	3 (20.0)	0 (00.0)	13 (68.5)	
≥ 7 points	26 (21.1)	11 (45.8)	12 (80.0)	3 (100.0)	52 (31.5)	<.001
VPM	11.05 ± 0.99	10.93 ± 2.53	12.04 ± 0.68	12.10 ± 0.99	11.11 ± 1.34	.085
Median VPM	11.03	11.34	11.94	12.10	11.12	.002
Sepsis						
Yes	67 (54.5)	13 (54.2)	9 (60.0)	2 (66.7)	91 (55.2)	
No	56 (45.5)	11 (45.8)	6 (40.0)	1 (33.3)	74 (44.8)	.970
Coronary patient						
Yes	65 (53.3)	11 (45.8)	3 (20.0)	1 (33.3)	80 (48.8)	
No	57 (46.7)	13 (54.2)	12 (80.0)	2 (66.7)	84 (51.2)	.074
Sepsis/Coronary						
With sepsis and coronary	26 (21.3)	4 (16.7)	1 (06.7)	0 (00.0)	31 (18.9)	
With sepsis and non-coronary	40 (32.8)	9 (37.5)	8 (53.3)	2 (66.7)	59 (36.0)	
Without sepsis and coronary	39 (32.0)	7 (29.2)	2 (13.3)	1 (33.3)	49 (29.9)	

Without sepsis and non-coronary	17 (13.9)	4 (16.7)	4 (26.7)	0 (00.0)	25 (15.2)	.561
Abbreviations: Platelet count categories (PLT) (X 10^9/L): normal (>150 X 10^9/L), mild (100-149 X 10^9/L), moderate (50-99 X 10^9/L) and severe (<50 X 10^9/L).						
Abbreviations: ICU, Intensive Care Unit; TSRU, Thoracic Surgery Recovery Unit; APACHE II, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; VPM, mean platelet volume. Results expressed as number (%), mean ± standard deviation or median. Used tests: Chi-square (or Fisher's exact test when necessary) for categorical variables and Student t-test for quantitative variables.						

Table 1: Demographic and clinical characteristics of patients in intensive care in accordance with the PLT.

On the first day of hospitalization in the cardiac ICU, the mean total score of APACHE II was 21.6 ± 9.5 and the SOFA score was 5.4 ± 4.1, reflecting high severity of disease and the presence of severe organ dysfunctions in the study population. The average length of stay of the patients in the cardiac ICU was 10 ± 10 days and in the hospital, 30 ± 29 days. The total mortality was 39.4%, being higher in the cardiac ICU (Table 1).

The total average platelet count in the cardiac ICU admission was 160 ± 88 X 10^9/L and the total median value of MPV was 11.12 fl, being higher in patients with moderate and severe thrombocytopenia (11.94 and 12.10; P = 0.002) (Table 1).

In total, 42 out of 165 patients (25.4%) had platelet count <150 X 10^9/L during hospitalization. Mild, moderate and severe thrombocytopenia developed in 24 (14.5%) 15 (9.1%) and 3 (1.8%) patients, respectively. Thrombocytopenia was not associated with sepsis, length of stay in the hospital or in the cardiac ICU (Table 1).

Comparing the mean APACHE II scores and platelet count levels, an average value of APACHE II 33.7 ± 9.6 was observed among the severe thrombocytopenia group, but no significant differences were detected (P=0.131). In the analysis of SOFA score in relation to the profile of platelet count, the difference between means was statistically significant for patients with moderate and severe thrombocytopenia (P <0.001) (Table 1).

A proportionally inverse relationship between mortality and platelet count was observed, with statistical significance for moderate thrombocytopenia (HR 2.303; IC 95% 1.148–4.619; P=0.019), even with higher hazard ratio for severe thrombocytopenia group (HR 3.806; IC 95% 0.514–28.204) (Table 2).

Number of platelets (X 10^9/L)	HR	IC 95%	P Value
None (≥ 150)	1.000	-	-
Mild (100-149)	1.621	0.782–3.360	0.194
Moderate (50-99)	2.303	1.148–4.619	0.019
Severe (<50)	3.806	0.514–28.204	0.191
Abbreviations: HR, hazard ratio; IC, Confidence interval.			

Table 2: Thrombocytopenia and mortality.

Figure 1 shows the Kaplan-Meier curve for different levels of thrombocytopenia categories, estimating that the more severe the thrombocytopenia, moderate to severe, the length of stay and mortality have an inverse behavior.

In the analysis with patients with thrombocytopenia, it was observed that increased PLT and drop of MPV was related to discharge outcome, in the case of patients hospitalized in the cardiac ICU (Table 3).

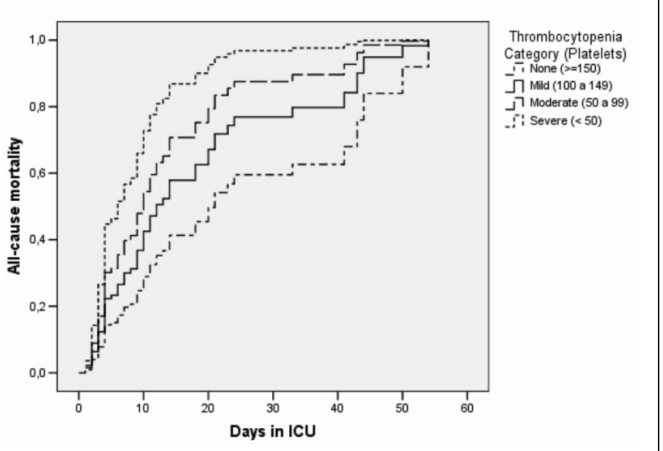

Figure 1: Kaplan-Meier curve for mortality (death). Patients categorized by platelet count during the period of hospital stay (days).

Variables	Evolution ICU				Total	
	Discharge		Death			
	N	%	N	%	N	%
Evaluation of PLT						
Increase	14	73.7%	6	37.5%	20	57.1%
Neutral	0	0.0%	1	6.3%	1	2.9%
Decrease	5	26.3%	9	56.3%	14	40.0%
Evaluation of MPV						
Increase	4	22.2%	9	69.2%	13	41.9%
Neutral	2	11.1%	0	0.0%	2	6.5%
Decrease	12	66.7%	4	30.8%	16	51.6%
Abbreviations: PLT, Platelet Count; MPV, Mean Platelet Volume; ICU, Intensive Care Unit; Neutral: Constant values through period of hospital stay.						

Table 3: Evaluation of PLT and MPV in patients with thrombocytopenia at the cardiac ICU.

The same behavior was found among patients admitted to the hospital ward after discharge of cardiac ICU (Table 4).

Variables	Hospital evolution				Total	
	Discharge		Death			
	n	%	n	%	n	%
Evaluation of PLT						
Increase	11	78.6%	3	60.0%	14	73.7%
Decrease	3	21.4%	2	40.0%	5	26.3%
Evaluation of MPV						
Increase	4	30.8%	0	0.0%	4	22.2%
Neutral	2	15.4%	0	0.0%	2	11.1%
Decrease	7	53.8%	5	100.0%	12	66.7%

Abbreviations: PLT, Platelet Count; MPV, Mean Platelet Volume; Neutral: Constant values through period of hospital stay.

Table 4: Evaluation of PLT and MPV in patients with hospital thrombocytopenia.

Discussion

The main finding of this study was that the daily quantification of PLT and MPV are important to the prognosis in patients cardiac ICU. We demonstrated a positive association between thrombocytopenia and high level of MPV with prognosis, using gravity as parameters the APACHE II and SOFA scores in patients admitted to the cardiac ICU. In addition, our study showed that decrease of PLT and increase in the level of MPV after admission in cardiac ICU is associated with higher mortality, suggesting that PLT and MPV should be daily quantified.

Thrombocytopenia is common in ICU patients, on admission or during their stay in ICU [8]. In our study, the prevalence of thrombocytopenia was 25.4%. The incidence of mild (platelet count <150 X 10^9/L), moderate (50-99 X 10^9/L) and severe (<50 X 10^9/L) thrombocytopenia were 14.5%, 9.1% and 1.8%, respectively. In a study conducted in a medical-surgical ICU, the prevalence of thrombocytopenia was 26.2% and the incidence of mild, moderate and severe thrombocytopenia was 15.3%, 5.1% and 1.6%, respectively [1]. The cause of thrombocytopenia in critically ill patients can be difficult to determine and usually has a multifactorial origin. Basically, thrombocytopenia is incurred by lower production, increased consumption and destruction or sequestration of platelets [16]. In our study, the diagnosis of coronary artery disease upon admission to the ICU or sepsis detection did not influence significantly the development of thrombocytopenia.

Regarding the relationship between thrombocytopenia and mortality, in the hospital and in the ICU, it was observed significant difference in patients with moderate thrombocytopenia (RR 2,303; IC 95% 1,148 - 4,619; P=0.019), demonstrating greater risk of death, even the hazard ratio for patients with severe thrombocytopenia being higher (RR 3,806; IC 95% 0,514-28,204; p=0.191). Williamson et al. [1] found that mortality in the hospital and in the ICU is associated with moderate and severe thrombocytopenia. Boechat et al. [17] found that thrombocytopenia and temporal trends with a decrease >50% or not recovery is a poor prognosis in the group of septic patients.

While associating thrombocytopenia with the prognostic score for admission, median APACHE II, it was observed that the greater the severity of the patient on admission, the higher the incidence of severe thrombocytopenia, however, without statistically significant difference (P=0.225), similar results were obtained by Boechat et al. [17] for septic patients. When associating PLT and MPV with SOFA score, a statistically significant correlation (P<.001) was observed, indicating a relationship between organic dysfunction, thrombocytopenia and median increased MPV. To Vanderschueren et al. [6], thrombocytopenia is more than just one of the causes of death in the ICU, it is a marker of risk, regardless of disease severity or organ dysfunction number, reflecting a serious breakdown in homeostasis.

MPV is in evidence in literature for being a variable that represents the size and platelet activity and thrombocytes are involved in coronary ischemic events. Platelets with high MPV are metabolically and enzymatically more active and secrete more mediators [18]. These mediators may contribute to inflammation and atherogenesis, which may explain an association between MPV and severity of coronary atherosclerosis [19]. In our study, the median value of the MPV was 11.12 fL, being higher in patients with moderate and severe thrombocytopenia, 11.94 fL and 12.10 fL, respectively (P=.002). Slavka et al. [20] observed that patients with MPV ≥ 11.01 fL are at higher risk of death from ischemic heart disease, with risk ratios comparable to those reported in cases of obesity or smoking. In our study population, thrombocytopenic patients on admission that presented an increase of PLT and decrease on the level of MPV during the period of hospitalization were associated with discharge outcome.

Finally, the PLT and MPV are performed through methods that do not require advanced and expensive technology. Instead, they are performed through simple, reliable and economical methods. Thus, we suggest that PLT and MPV must be investigated in the daily assessment of the patient as important prognostic markers in critically ill patients. However, the use of measurement of platelet parameters composed of PLT, MPV, PDW, P-LCR may be more sensitive in the prognostic evaluation of cardiac patients.

STUDY LIMITATIONS

The main limitation of this study was that it didn't investigate the underlying mechanisms of thrombocytopenia in critically ill patients that can be associated with the presence of disseminated intravascular coagulation, medications or other causes. Furthermore, the non-separation of coronary patients between acute and chronic may be a confounding bias, especially in view of MPV.

We also think that probably there was no significant association between mortality in severe thrombocytopenia group due to the sample size in this population. Also, the platelet count is part of the SOFA score, but not the MPV, which could be a bias in the interpretation of the data.

Conclusion

Platelet parameter, including MPV in this study, is an important prognostic tool in the daily follow-up of patients admitted to a cardiac ICU. However, we suggest further studies with a larger sample of patients in order to rule out potential confounding factors.

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