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Thrombocytopenia in sepsis: an important prognosis factor

Trombocitopenia na sepse: um importante marcador prognóstico

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ABSTRACT

Objective: To demonstrate an association between thrombocytopenia and platelet behavior in predicting mortality in septic patients.

Methods: Patients with criteria for sepsis at admission or at any time during hospitalization were selected; patients hospitalized for less than 24 hours were excluded. Thrombocytopenia was defined as a platelet count lower than 150.000/mm³, and recovery was defined as returning to levels above 150.000/mm³ after showing thrombocytopenia. We assessed the admission prognosis variables (APACHE II), platelet counts during the hospitalization and outcomes.

Results: Of the 56 patients included, 34 developed thrombocytopenia during sepsis (Group 1) and had a 76.4% mortality rate. The mortality rate among patients not showing thrombocytopenia (Group 2) was 40.9% (RR 1.87; 95% CI 1.12 - 3.12; $p = 0.0163$). In 44.1% of Group 1 patients, the

platelet counts drops by >50% compared with the admission counts; 93.3% of these patients eventually died (RR 1.48; 95% CI 0.93 - 2.36; $p = 0.0528$). Among the Group 1 patients showing recovered platelet counts, 53.3% survived; 100% of the patients with unrecovered thrombocytopenia died (RR 2.14; 95% CI 1.35 - 3.39; $p = 0.0003$). Among the patients with APACHE II scores > 22, the thrombocytopenic patients had an 81.8% mortality rate ($p = 0.25$), while no deaths occurred among the non-thrombocytopenic patients. For the patients with APACHE II scores ≤ 22, the mortality rate of the thrombocytopenic patients was 74% ($p = 0.0741$), versus 42.8% for the non-thrombocytopenic patients.

Conclusion: For this sample of septic patients, thrombocytopenia and its progression, defined as a >50% drop or failure to recover platelet count, were shown to be markers of poor prognosis.

Keywords: Thrombocytopenia; Sepsis; Prognosis

INTRODUCTION

Sepsis is currently a major concern. Within the last decade, several trials and protocols have focused on this condition, aiming to establish better measures for its management and prevention of potential complications. Therapeutic measures with considerable positive impacts have been largely emphasized; however, assessing the prognosis of sepsis remains difficult. Assessing the prognosis of diseases and therapies is part of regular medical care.⁽¹⁾ Mastering this challenge is largely related to the art of medical practice and leads to more objective care of the patient.⁽¹⁾

Prognostic score variables have been shown to be effective for the assessment of septic patients, especially the sequential assessments provided by the Sequential Organ Failure Assessment (SOFA). Several physiological

and blood chemistry parameters are used in daily practice in intensive care units. Simply observing the platelet counts may be very useful for assessing critical patients, especially those with sepsis. However, one single platelet count is not as valuable as sequential platelet counts throughout the course of sepsis.⁽²⁾

Thrombocytopenia is common in severely ill patients, and several studies have reported its association with poor prognosis.⁽²⁻⁷⁾ Considering the fundamental role of platelets in hemostasis and as markers of disseminated intravascular coagulation, a significant drop in platelet count is alarming in the setting of septic patients, as it is an independent factor predicting death.^(2,8-10) The aim of this study was to show an association between thrombocytopenia and platelet behavior in relation to mortality in septic patients.

METHODS

This was an observational, retrospective cohort study conducted between August 14, 2009 and July 16, 2010 (11 months) in the general intensive care unit (ICU) of a reference university hospital. This hospital has 137 beds, including 8 ICU beds. This study was properly approved by the ethics committee of the Universidade Severino Sombra (USS) - CAEE under the number 0130.0.326.000-10. The requirement to obtain a signed informed consent was waived in consideration of the study's observational and retrospective nature.

Patients with criteria for sepsis at admission or at any time during hospitalization were selected; patients hospitalized for less than 24 hours were excluded. Sepsis was diagnosed according to the International Sepsis Definitions Conference⁽¹¹⁾ criteria. The patients were not categorized according to sepsis severity (sepsis, severe sepsis and septic shock). We observed the admission prognosis variables (Acute Physiological and Chronic Health Evaluation II - APACHE II), platelet counts during hospitalization and outcomes. Thrombocytopenia was defined as a platelet count lower than $150.000/\text{mm}^3$, and recovery was defined as returning to levels above $150.000/\text{mm}^3$ after showing thrombocytopenia. The thrombocytopenic patients were categorized according to their nadir: $101.000 - 149.000/\text{mm}^3$; $51.000 - 100.000/\text{mm}^3$; $21.000 - 50.000/\text{mm}^3$ and $< 20.000/\text{mm}^3$.⁽⁶⁾ The last platelet count was the count on the day of discharge for surviving patients or on the day of death for nonsurviving patients. The platelet counts were determined using an automated counter (Kx21n, Sysmex®).

The data recorded for all patients were based on information retrieved from the medical charts. The data retrieved consisted of the medical chart number, date of admission, date of discharge or death, length of stay in days, name, age, gender, APACHE II score, ICU admission diagnosis, cause of sepsis, daily platelet counts, drops in platelet counts $>50\%$ compared with admission counts and recovery of platelet counts. The APACHE II score was completed at least 12 hours after admission, as recommended by Knaus et al.,⁽¹²⁾ and the variables were recorded in an appropriate form. When a given variable was not collected, zero was assigned for that variable. A boundary of 22 was defined⁽¹²⁾ for the APACHE II score to differentiate patients more or less likely to die during the hospital stay. The most accurate cutoff point was validated using an ROC curve.

The R statistical software was used for statistical analysis. The data were described using proportions and contingency tables for categorical variables and medians for continued variables. The chi-squared test or the Fisher's exact test were used in contingency tables, according to Siegel's criteria,⁽¹³⁾ to assess associations among the variables. Additionally, proportions and Wilcoxon tests were used to compare medians. The data were expressed as relative risks (RR) and respective 95% confidence intervals (CI). P values < 0.05 were considered statistically significant.

RESULTS

The study population was heterogeneous and included both medical and surgical patients, who were admitted for different reasons and whose sepsis was due to variable primary infection sites, with a predominance of respiratory (55.4%) and abdominal (25%) foci (Table 1). A total of 62 patients were assessed; six were excluded due to lengths of stay in the ICU shorter than 24 hours. Fifty-six septic patients were assessed. Half of the six excluded patients were discharged before 24 hours, and the other half died earlier than 24 hours. Of the three patients who died early, only one had thrombocytopenia; of the three discharged less than 24 hours from admission, none were thrombocytopenic. The mortality rate of septic patients (not categorized according to sepsis severity) was 62.5%. The median age was 59.5 years, and there was no gender predominance (28 men, 28 women). The median APACHE II scores were 17.5 overall, 12 for surviving patients, and 19 for those not surviving (see Figure 1). A total of 34 patients (60.7%) developed thrombocytopenia (Group 1), with a

Table 1 - Population characteristics according to mortality

	Non-surviving	Surviving	Total	p value	RR (95% CI)
Number of patients	35 (62.5)	21 (37.5)	56	0.0823	-
Age (years)	58 (22 - 85)	61 (12 - 88)	59.5 (12 - 88)	0.9595	-
Male	16 (57)	12 (43)	28	0.5809	-
Length of hospital stay (days)	7 (2 - 50)	7 (4 - 38)	7 (2 - 50)	0.6584	-
Group 1	6.5 (2 - 45)	7 (5 - 38)	7 (2 - 45)	0.5533	
Group 2	7 (2 - 50)	6 (4 - 19)	6.5 (2 - 50)	0.8659	
APACHE II score	19 (4 - 37)	12 (2 - 27)	17.5 (2 - 37)	0.0054	-
Group 1	20.5 (4 - 37)	17 (6 - 27)	20 (4 - 37)	0.3497	
Group 2	17 (7 - 22)	8 (2 - 23)	12 (2 - 23)	0.0606	
Platelet counts (x 10 ³ /mm ³)					
Admission	192 (37 - 840)	242 (67 - 526)	208.5 (37 - 840)	0.2825	-
Nadir	106 (6 - 287)	197 (45 - 393)	131 (6 - 393)	0.0045	-
Nadir (Group 1)	85.5 (6 - 149)	125.5 (45 - 143)	94.5 (6 - 149)	0.1329	-
Nadir (Group 2)	225 (153 - 287)	236 (151 - 393)	233 (151 - 393)	0.8937	-
On the last day	139 (6 - 533)	307 (151 - 598)	204 (6 - 598)	0.0001	-
Last day (Group 1)	111.5 (6 - 308)	348.5 (152 - 524)	137.5 (6 - 524)	0.0003	-
Last day (Group 2)	264 (153 - 533)	305 (151 - 598)	277.5 (151 - 598)	0.2921	-
Admission diagnosis					
Sepsis	7 (58.4)	5 (41.6)	12	0.7874	-
Respiratory	13 (65)	7 (35)	(20)		
Neurological	4 (66.6)	2 (33.4)	6		
Cardiovascular	2 (66.6)	1 (33.4)	3		
Abdominal	6 (54.5)	5 (45.5)	11		
Trauma	3 (100)	0 (0)	3		
Others	0 (0)	1 (100)	1		
Sepsis focus					
Respiratory	20 (64.5)	11 (35.5)	31	0.6871	-
Urinary	2 (40)	3 (60)	5		
Abdominal	9 (64.2)	5 (35.8)	14		
Soft tissues	3 (75)	1 (25)	4		
Neurological	1 (100)	0 (0)	1		
Mediastinum	0 (0)	1 (100)	1		
Characteristics of the thrombocytopenia					
Group 1	26 (76.4)	8 (23.6)	34	0.0163	1.87 (1.12 - 3.12)
Group 2	9 (40.9)	13 (59.1)	22		
Drop >50%	14 (93.3)	1 (6.7)	15	0.0528	1.48 (0.93 - 2.36)
Drop <50%	12 (63.1)	7 (36.9)	19		
Not recovered	19 (100)	0 (0)	19	0.0003	2.14 (1.35 - 3.39)
Recovered	7 (46.7)	8 (53.3)	15		
101.000 - 149.000/mm ³	10 (66.6)	5 (33.4)	15	0.7141	-
51.000 - 100.000/mm ³	12 (85.7)	2 (14.3)	14		
21.000 - 50.000/mm ³	3 (75)	1 (25)	4		
< 20.000/mm ³	1 (100)	0 (0)	1		
Admission score					
APACHE II >22	9 (75)	3 (25)	12	0.5011	
APACHE II ≤22	26 (59)	18 (41)	44		
Group 1 with APACHE II >22	9 (81.8)	2 (18.2)	11	1	
Group 1 with APACHE II ≤22	17 (74)	6 (26)	23		
Group 1 with APACHE II >22	9 (81.8)	2 (18.2)	11	0.2500	-
Group 2 with APACHE II >22	0 (0)	1 (100)	1		
Group 1 with APACHE II ≤22	17 (74)	6 (26)	23	0.0741	
Group 2 with APACHE II ≤22	9 (42.8)	12 (57.2)	21		
Condition at admission					
Pre-admission thrombocytopenia	10 (66.6)	5 (33.4)	15	0.4172	
Post-admission thrombocytopenia	16 (84.2)	3 (15.8)	19		
Sepsis at admission	19 (57.6)	14 (42.4)	33	0.5279	
Sepsis after admission	16 (69.5)	7 (30.5)	23		

- It was not possible to calculate; APACHE II - Acute Physiology and Chronic Health Evaluation; CI - confidence interval; RR - relative risk. Results expressed as a number (%) or median (minimum-maximum).

76.4% mortality rate, while patients who did not develop thrombocytopenia (Group 2) had a 40.9% mortality rate (RR 1.87; 95% CI 1.12 - 3.12; $p = 0.0163$). The platelet counts were higher in surviving versus nonsurviving patients, especially when comparing their nadirs (Figures

2 and 3) and last platelet counts (Figures 2 and 4).

In 44.1% of the thrombocytopenic patients, the platelet counts drops by >50% compared with the admission counts; 93.3% of these patients eventually died (RR 1.48; 95% CI 0.93 - 2.36; $p = 0.0528$). Among

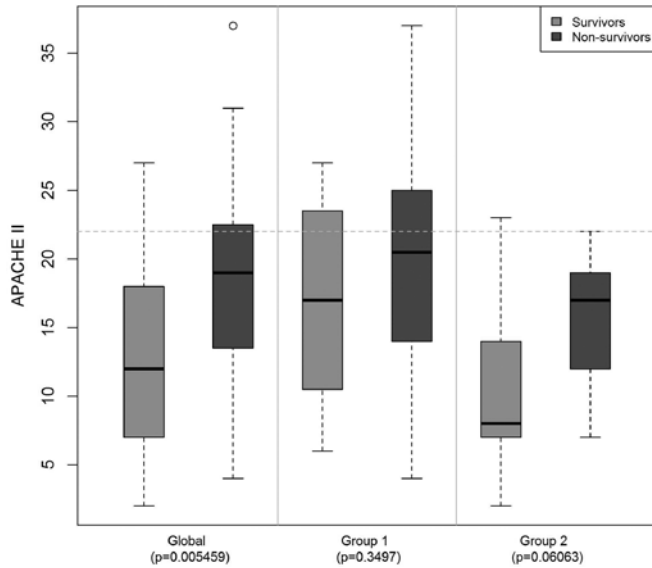


Figure 1 - Distribution of APACHE II scores by groups.
APACHE II - Acute Physiology and Chronic Health Evaluation.

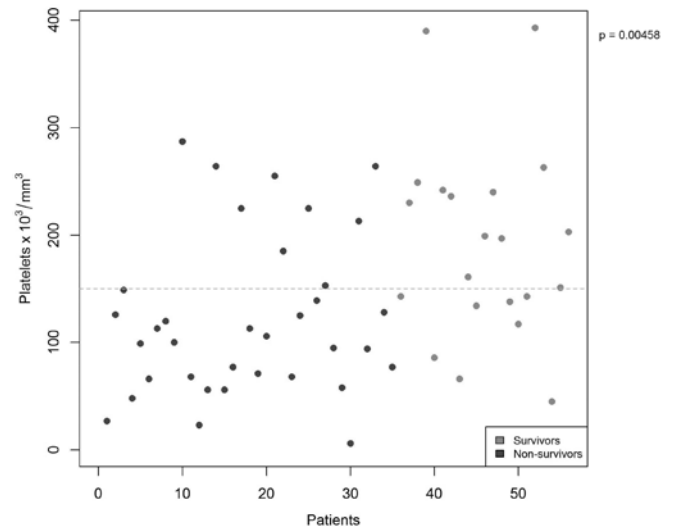


Figure 3 - Dispersion of platelet count nadirs.

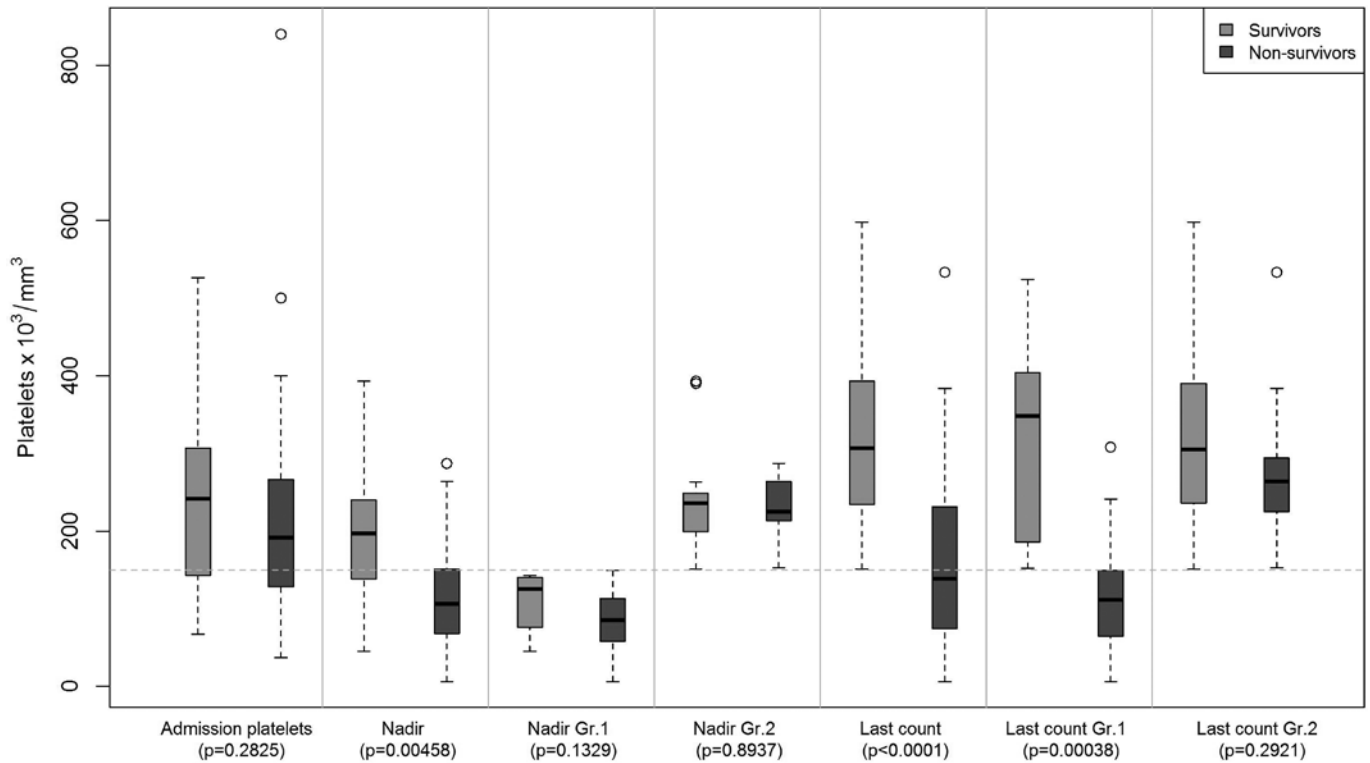


Figure 2 - Distribution of platelet counts.
Gr. 1 – thrombocytopenic patients; Gr. 2 – non-thrombocytopenic patients.

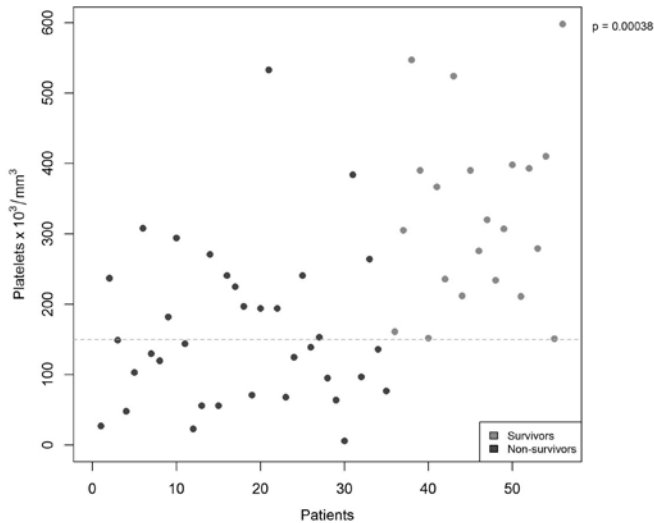


Figure 4 - Dispersion of the last platelet counts.

the thrombocytopenic patients showing recovered platelet counts, 53.3% survived, while 100% of the patients with unrecovered thrombocytopenia died (RR 2.14; 95% CI 1.35 - 3.39; $p = 0.0003$).

When comparing thrombocytopenic patients with APACHE II scores >22 and ≤22, the mortality rates were not significantly different: 81.8% and 74% ($p = 1$), respectively. In addition, 91.6% of the patients with APACHE II scores >22 developed thrombocytopenia, while only 51.2% of the group with APACHE II

scores ≤22 developed this condition (RR 1.75; 95% CI 1.05 - 2.92; $p = 0.0320$) (Table 2). Of the patients with APACHE II scores >22, Group 1 had an 81.8% mortality rate, while no deaths were observed in Group 2 ($p = 0.25$). Among the patients with APACHE II scores ≤22, the mortality rate of the thrombocytopenic patients was 74% versus 42.8% for the nonthrombocytopenic patients ($p = 0.0741$) (Table 1).

When the patients were categorized according to thrombocytopenia quartiles, the mortality and platelet counts were inversely proportional; however, these results were not statistically significant, likely due to the small number of patients with lower counts (Table 1).

Twenty Group 1 patients had pneumonia as their primary site of infection, and 80% of these patients died, versus 85.7% and 57.1% of those with abdominal or other primary infection sites, respectively ($p = 0.5262$). A total of 33 patients (58.9%) were admitted with sepsis, and among the thrombocytopenic patients, 15 (44.1%) already had platelet counts lower than 150.000/mm³ at admission. Table 1 summarizes the data discussed above.

DISCUSSION

Most critically ill patients with a systemic inflammatory response have coagulation disorders,^(14,15) and thrombocytopenia is the most frequent finding. In the majority of the studies,^(2,8-10,14) thrombocytopenia is

Table 2 - Population characteristics according to platelet counts

	Group 1	Group 2	Total	p value	RR (95% CI)
Number of patients	34 (60.7)	22 (39.3)	56 (100)	0.1416	
Age (years)	66.5 (22 - 88)	54.5 (12 - 82)	59.5 (12 - 88)	0.0234	
Male	16 (57)	12 (43)	28 (50)	0.7844	
Length of hospital stay (days)	7 (2 - 45)	6.5 (2 - 50)	7 (2 - 50)	0.7874	
Mortality	26 (74.2)	9 (25.8)	35 (62.5)	0.0163	
Sepsis focus					
Pneumonia	20 (64.5)	11 (35.5)	31 (55.4)	0.7086	
Abdominal	7 (50)	7 (50)	14 (25)		
Others	7 (63.6)	4 (36.4)	11 (19.6)		
Platelet count (x 10 ³ /mm ³) at admission	136 (37 - 840)	266.5 (195 - 526)	208.5 (37 - 840)	<0.0001	
Platelet count (x 10 ³ /mm ³) Nadir	94.5 (6 - 149)	233 (151 - 393)	131 (6 - 393)	<0.0001	
Admission score					
APACHE II	20 (4 - 37)	12 (2 - 23)	17.5 (2 - 37)	0.0014	
APACHE II >22	11 (91.6)	1 (8.4)	12 (21.4)	0.0320	1.75 (1.05 - 2.92)
APACHE II ≤22	23 (51.2)	21 (48.8)	44 (78.6)		

APACHE II - Acute Physiology and Chronic Health Evaluation; CI - confidence interval; RR - relative risk. Results expressed as a number (%) or median (minimum-maximum).

identified as a marker of poor prognosis in critically ill patients overall and an important predictor of death in severe sepsis.⁽¹⁶⁾

The cause of thrombocytopenia in critically ill patients may be difficult to determine and is usually multifactorial. Basically, thrombocytopenia stems from reduced platelet production, increased platelet consumption and platelet destruction or sequestration. Platelet consumption is likely to be the main cause in septic patients, as the coagulation system activation is exacerbated, leading to systemic microcirculation deposition of macrothrombi, which consumes large amounts of platelets and coagulation factors.^(2,8-10,14,17,18)

In this study, the overall mortality of septic patients was high, above the literature reported rates (35 - 55%).⁽¹⁹⁻²¹⁾ However, the mortality rate in septic shock may be as high as 70%.^(20,21) American and European studies report 13.5% to 53.6% mortality rates,⁽²²⁻²⁵⁾ while Brazilian studies report rates between 21.8% and 46.4%.^(22,26) It was not possible to assess the progression of platelet counts for the six excluded patients. The mortality rate assessed in this study was related to patients hospitalized for more than 24 hours, but not earlier. The demographics regarding gender, median age and APACHE II scores are compatible with the reported literature.⁽²¹⁾ A statistically significant association between thrombocytopenia and death was observed in this study as well as poorer prognosis for patients with >50% drops in platelet counts and, in particular, in patients with sustained thrombocytopenia.

The relative risk of thrombocytopenia was 1.87, which is compatible with that reported in the literature (1.5-4.2).^(9,10) The progression of platelet counts was also effective for predicting death. The mortality among patients with >50% drops in platelet counts was significantly higher, which is also compatible with the reported literature.^(2,9)

In this study, comparative data of patients who recovered normal platelet counts and those who remained thrombocytopenic showed the highest statistical significance. All of the thrombocytopenic patients who failed to recover their platelet counts died, and all of the surviving thrombocytopenic patients had recovered their counts. Akca et al.⁽¹⁰⁾ have shown that thrombocytopenia, at any time, is associated with increased mortality and that sustained thrombocytopenia, i.e., showing no recovery, is associated with an additionally increased risk of death. Therefore, assessing one single platelet count is not as valuable for predicting death as the observation of progressively dropping platelet counts in sepsis.⁽¹⁰⁾ Conversely, the normalization and stabilization of platelet counts reflect reduced generation of thrombin, meaning improved prognosis.⁽¹⁸⁾

Correlating thrombocytopenia and the admission prognosis score, it was evident that the higher a patient's severity is at admission, independently of a sepsis diagnosis, the higher the incidence of thrombocytopenia is during the hospitalization. In both groups, i.e., patients with APACHE II scores >22 ($p = 0.25$) and patients with APACHE II scores ≤ 22 ($p = 0.0741$), the thrombocytopenic patients had higher mortality rates compared with the nonthrombocytopenic patients. However, this difference was not statistically significant. When the APACHE II score (either >22 or ≤ 22) was used as predictive factor of death among the thrombocytopenic patients, the mortality rates were not significantly different. Notwithstanding, this finding emphasizes that thrombocytopenia is a determinant of poorer prognosis, independent of the admission illness severity. Vanderschueren et al.⁽²⁾ have shown that, more than a cause of death in the ICU, thrombocytopenia is a risk factor reflecting a homeostatic disorder, independent of the disease severity or number of organ dysfunctions.

Recent studies have shown increased incidences of thrombocytopenia in patients with pneumonia compared with patients with other infective sites and higher mortality rates.^(27,28) However, the sepsis etiology had no influence on the development of thrombocytopenia or on the thrombocytopenic patients' outcomes. These data failed to show statistical significance, likely due to the small numbers of patients when categorized into different subgroups. A diagnosis of sepsis or thrombocytopenia at admission had no significant influence on mortality compared with patients who developed sepsis or thrombocytopenia during the hospitalization. Therefore, platelet counts should not be used as a single assessment for prognosis at admission.

An attempt to use 25 as the cutoff level for the APACHE II scores resulted in too few patients above this level, rendering a statistical comparison unfeasible. Therefore, a cutoff point of 22 was elected, preserving the clinical relevance of a high APACHE II score. Although the statistical relevance was defined by the ROC curve of a cutoff of 13, no significant divergence was found between the results for the 13 and 22 cutoff points. Therefore, the level 22 was chosen for this study, considering its higher clinical relevance.

As a limitation, we understand that this study would benefit from a larger sample size, which would allow a comparison of the mortality rates of different quartiles of thrombocytopenia as well as an assessment of the subcategories of septic patients, evaluating the more frequent and severe development of thrombocytopenia

in severe sepsis or septic shock patients. The severity of sepsis in this sample of patients is unknown, which limits our survival analysis. Using a larger sample size, more significant p values would be likely, especially for the comparison of the admission prognosis scores, which would allow the use of the 25 cutoff level for the APACHE II score, acknowledged in the literature as the ideal cutoff point for differentiating patients more or less likely to die during the hospitalization. In addition, a prospective trial would be recommended to ensure that the necessary daily data are obtained. Missing data may prevent recognition of the actual nadir or recovery and the last platelet count, therefore affecting the results.

There is growing evidence that platelets play a complex role in sepsis. Interfering with platelet function could be a good way to treat sepsis.⁽⁸⁾ When treating thrombocytopenic septic patients, intensive care physicians should continuously attempt to identify and treat the causes of thrombocytopenia, with the aim of reducing mortality.^(2,8) The need for considering a differential diagnosis in critically ill thrombocytopenic patients should be stressed, especially a diagnosis of disseminated intravascular coagulation (DIC), always taking into account the severity of thrombocytopenia, systemic signs of inflammation, activated prothrombin time, fibrinogen levels and bleeding events.

Considering the results of this study and that platelet counting is a simple and affordable method, thrombocytopenia should be assessed daily as an important prognostic factor in sepsis.

CONCLUSION

Thrombocytopenia was shown to be an indicator of poor prognosis in this sample. In addition, drops of >50% and failure to recover the platelet counts were further determinants of unfavorable outcomes.

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RESUMO

Objetivo: Demonstrar associação da trombocitopenia e do comportamento das plaquetas, com a mortalidade em pacientes sépticos.

Métodos: Foram selecionados os pacientes que apresentaram critérios de sepse na admissão ou em qualquer momento no curso da internação e excluídos os que ficaram menos de 24h internados. A trombocitopenia foi definida como contagem plaquetária abaixo de 150.000/mm³ e a recuperação, definida como retorno da contagem para níveis acima de 150.000/mm³ após trombocitopenia. Observaram-se variáveis de prognóstico na admissão (APACHE II), contagem plaquetária durante os dias de internação e desfecho.

Resultados: Dos 56 pacientes, 34 desenvolveram trombocitopenia no curso da sepse (Grupo 1). A mortalidade nesse grupo foi de 76,4%, e entre os não trombocitopênicos (Grupo 2) de 40,9%, (RR 1,87; IC 95% 1,12 – 3,12; $p = 0,0163$). Em 44,1% dos pacientes do Grupo 1, houve queda > 50% das plaquetas em relação à admissão, e desses, 93,3% evoluíram para óbito (RR 1,48; IC 95% 0,93 – 2,36; $p = 0,0528$). Entre os pacientes do Grupo 1 que apresentaram recuperação na contagem plaquetária, 53,3% sobreviveram, e dos que mantiveram trombocitopenia sem recuperação, 100% evoluíram para óbito (RR 2,14; IC 95% 1,35 – 3,39; $p = 0,0003$). Entre os pacientes com APACHE II > 22, os trombocitopênicos apresentaram mortalidade de 81,8% ($p = 0,25$) contra nenhuma morte entre os não trombocitopênicos, enquanto no grupo com APACHE II ≤ 22, a mortalidade dos trombocitopênicos foi de 74% ($p = 0,0741$) contra 42,8% dos não trombocitopênicos.

Conclusão: A trombocitopenia, bem como seu comportamento evolutivo com queda >50% ou não recuperação, mostraram-se fatores de mau prognóstico no grupo de pacientes sépticos estudado.

Descritores: Trombocitopenia; Sepse; Prognóstico

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