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Thrombocytopenia versus SOFA to Predict Mortality in Patients with Sepsis in the Intensive Care Unit of a Tertiary Hospital in Guatemala

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Articles

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Trombocitopenia versus SOFA para predecir mortalidad en pacientes con sepsis in la Unidad de Cuidados Intensivos de un hospital de tercer nivel de Guatemala

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Abstract: The most common coagulation disorder in the intensive care unit is thrombocytopenia. Considering the fundamental role of platelets in hemostasis and as markers of disseminated intravascular coagulation, a significant decrease in platelet counts is alarming in the context of septic patients, and it is known to be a predictor of death. The objective was to compare the ability of the platelet count with the Sequential Organ Failure Assessment (SOFA) to predict death in patients with severe sepsis or septic shock. A longitudinal study was conducted with a sample of 29 consecutive cases evaluated during January to December 2015 in the Intensive Care Unit of the General Hospital of Diseases (HGE) of the Guatemalan Social Security Institute. Platelet and SOFA counts were performed at the first and the fifth day of hospitalization, documenting the outcome of the patients. 51.7 % of the patients were men and 48.3% were women, with an average age of 62.0 (16.9) years, median SOFA admission of 10 units ($Q1$=4, $Q3$=14) and platelet median on admission of 196000 ($Q1$=100000, $Q3$=250000). The univariate association between thrombocytopenia and death was significant (p = .021, RR = 2.45, CI 95% [1.21, 4.99]). According to a Bootstrap test, there is no significant difference between the predictive capacity of SOFA and the platelet count (p = .965). It was concluded that the presence of thrombocytopenia is a simple predictor of death in patients with severe sepsis or septic shock, with similar capacity to SOFA.

Keywords: Organ Dysfunction Scores, Platelet Count, Sepsis, Septic Shock.

Resumen: *El trastorno de coagulación más frecuente en la unidad de cuidados intensivos es la trombocitopenia. Teniendo en cuenta el papel fundamental de las plaquetas en la hemostasia y como marcadores de la coagulación intravascular*

disemina, una disminución significativa en el recuento de plaquetas alarmante en el contexto de pacientes sépticos, y se sabe que es un predictor de muerte. El objetivo fue comparar la capacidad del recuento de plaquetas con la puntuación Sequential Organ Failure Assessment (SOFA) *para predecir la muerte en pacientes con sepsis grave o choque séptico. Se realizó un estudio longitudinal con una muestra de 29 casos consecutivos evaluados durante enero a diciembre de 2015 en la Unidad de Cuidado Intensivo del Hospital General de Enfermedades (HGE) del Instituto Guatemalteco de Seguridad Social. Se realizó recuento de plaquetas y SOFA al primero y al quinto día de hospitalización, documentando el desenlace de los pacientes. El 51.7 % de los pacientes eran hombres y el 48.3 % mujeres, con edad promedio (desviación estándar) de 62.0 (16.9) años, mediana de SOFA al ingreso de 10 unidades (Q1=4, Q3=14) y mediana de plaquetas al ingreso de 196,000 (Q1=100,000, Q3=350,000). La asociación univariante entre trombocitopenia y muerte fue significativa (p = .021; RR = 2.45, IC95% [1.21, 4.99]). Según una prueba Bootstrap, no existe diferencia significativa entre la capacidad predictiva de SOFA y recuento plaquetario (p = .965). Se concluyó que la presencia de trombocitopenia es un predictor sencillo de muerte en pacientes con sepsis grave o choque séptico, con capacidad similar a SOFA.*

Palabras clave: *Puntuaciones en la Disfunción de Órganos, Recuento de Plaquetas, Sepsis, Choque Séptico.*

Introduction

Thrombocytopenia is a clinic syndrome that is very frequently present in the Intensive Care Unit. It is present in approximately 35 to 40% of critical patients, and it is defined as a platelet count under 150,000 platelets/µL, even though it is suggested that the proper cut-off point to identify thrombocytopenia clinically significant should be 100,000 platelets/µL. Thrombocytopenia can represent not only a diagnostic clue of the cause of the underlying disease or the case complication, but it can also be used as a powerful predictor of an adverse result. Three stages of thrombocytopenia are recognized: Mild 100,000-150,000 platelets/µL, Moderate 50,000-100,000 platelets/L, and Severe <50,000 platelets/µL (Erkurt, 2012; Knöbl, 2016; Levi, 2016; Smock & Perkins, 2014).

Now a days, platelets, besides participating in coagulation and thrombus formation, are considered as essential agents of immune response, reaction to infection and altered tissue integrity. They also assist inflammation, pathogens death, and tissue repair. The association between thrombocytopenia and a clinic response does not stablish a causal relationship. The mechanism that possibly causes thrombocytopenia dictates the consequences that the patient will have (Antier *et al*., 2014; Dewitte *et al*., 2017; Marco-Schulke *et al*., 2012). It is estimated that in an Intensive Care Unit, 35.45% of patients develop thrombocytopenia, and 5-20% develop severe thrombocytopenia (Greinacher & Selleng, 2010).

Sepsis is a complex syndrome characterized by a disorder in immune, endocrine and metabolic response to infection that can turn out in a Multi Organ Failure (MOF), shock and death; that is, a non-homeostatic response

from the guest to the infection that leads to organ dysfunction potentially deadly (Dewritte *et al*., 2017; Greco, Lupia, Bosco, Vizio, & Montrucchio, 2017).

In sepsis, a depletion of fibrinolytic and fibrinogen agents occurs, as well as blood clot formation and hemorrhages associated to intravascular coagulation disseminated in response to alterations in coagulation cascades and cytokines released by endothelial and mononuclear cells (Guclu, Durmaz, & Karabay, 2013), and generally the platelet count in septic patients decreases during the first four days of intensive care (Levi, 2005). Severe thrombocytopenia is a strong negative prognostic marker in patients with sepsis; first, acting as a intravascular coagulation marker, and getting a higher value when sequential counts are performed during the course of the sepsis (Boechat, Silveira, Faviere, & Macedo, 2012; Greco *et al*., 2017).

SOFA score has been used since its introduction to objectively assess the long-term organ dysfunction level and to assess the morbidity of septic patients in the Intensive Care Unit (ICU). Nowadays, its usage has reached non-septic patients assessment and morbidity prediction. SOFA assesses the functioning of the respiratory, circulatory, renal, hematological, hepatic, and central nervous system (Minnie, Abu-Hanna, & de Jonge, 2008).

The objective of this research was to compare the platelet count capacity using SOFA score to predict death in patients with severe sepsis or septic shock, which is why a platelet count and a SOFA were performed with 29 patients on their first and fifth day of hospitalization, documenting their outcome.

Materials and Methods

Research Scheme

The study was longitudinal, prospective and analytical; and it was a cohort study. The population was comprised by patients in a severe sepsis or septic shock state, admitted to the Intensive Care Unit of the General Hospital of Diseases, Guatemalan Institute of Social Security.

The non-probabilistic and consecutive sample consisted of all the patients in severe sepsis or septic shock state admitted from January to December, 2015.

The inclusion criteria taken into account were: Man and women over 18 years old, admitted to the Critical Care Unit for more than 24 hours, in a severe sepsis or septic shock state, defined according to the criteria of the Society of Critical Care Medicine in the assessment performed by the residents II and III of Internal Medicine on call, and that did not die before the fifth day. The exclusion criteria were: Patients with congenital or acquired congenital disorders, patients using anticoagulation, patients with congenital or acquired liver disease or hematological diseases records.

Procedure for Data Collection

The demographic and clinic data, as well as the data from the

interventions performed from the clinic report was collected using a technical datasheet. In addition the SOFA score was calculated.

Data Procedure and Analysis

The data was tabulated in an Excel spreadsheet and later analyzed in the statistics software of free distribution R. The categorical variables were summarized with counts and percentages; and the numeric variable, with means and standard deviation, if distribution was normal, and with medians and quartiles, if distribution was not normal. The Shapiro-Wilk test was used to assess the normality of data.

A significance level of 5% was used in all hypothesis tests. To assess the association between categorical variables, we used contingency tables. So, the statistic of Pearson's chi-squared or the Fisher's Exact Test were calculated according to the expected frequencies. The association's strength was calculated by means of the Relative Risk (RR) and its corresponding confidence interval. The Student's *t*-test or the Mann-Whitney test were used to compare numeric variables in two groups.

We calculated the correlation of Spearman between quantitative or ordinal variables, and the *p* value of corresponding the hypothesis test was reported. We calculated the area under the ROC curve of the predictive capacity of the platelets at the beginning and at the fifth day, searching as a cut-off point, whichever presented the highest sensibility and specificity simultaneously. We calculated a 95% confidence interval in the area under the curve. It was considered a good predictor if the area under the curve was higher than .70. The ROC and SOFA curves were compared, as well as the platelet count at the fifth day, using a Bootstrap test.

Results

During the period from January to December 2015, we assessed 29 patients diagnosed with sepsis and septic shock, admitted in the Intensive Care Unit of the General Hospital of Diseases (HGE) of the Social Security (Table1). Out of these patients, 51.7% were man, and 48.3% were women. The average (standard deviation) age was 62.0 (16.9) years old, SOFA median at the admission of 10 units ($Q1 = 4$, $Q3 = 14$) and the median of the platelets at the admission of 196,000 ($Q1 = 1000,000$, $Q3 = 250,000$). In the fifth day, 14 patients died (43.3%). In Table 1, the characteristics of alive and deceased patients were compared, and it can be observed that the *p* values of the corresponding inferential tests, as well as the relative risk.

Table 1.
Comparison of the characteristics of alive and deceased patients

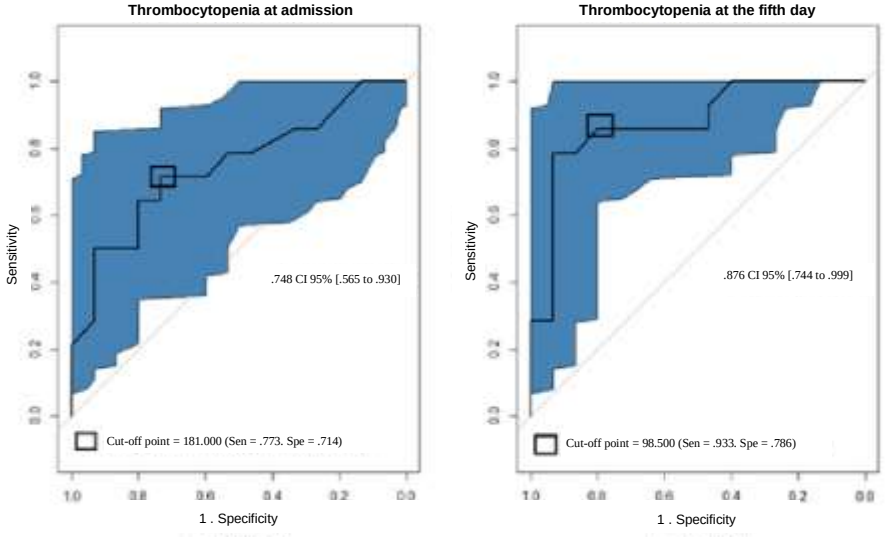
Patients' characteristics		**Condition at discharge**		***p Value***	**Relative Risk**
		Alive	**Deceased**		
		f (%)	f (%)		
Sex	Male	6 (40%)	9 (60%)	.191	1.68
	Female	9 (64.3%)	5 (35.7%)		
Age	Mean (SD)	56.7 (20.2)	67.7 (10.5)	.078	NA
Diagnosis at admission	Septic Shock	3 (18.8%)	13 (81.3%)	< .001	10.56
	Severe Sepsis	12 (92.3%)	1 (7.7%)		
Diabetes	Yes	9 (42.9%)	12 (57.1%)	.215	2.28
	No	6 (75.0%)	2 (25.0%)		
High Blood Pressure	Yes	8 (38.1%)	13 (61.9%)	.035	4.95
	No	7 (87.5%)	1 (12.5%)		
Mechanical Ventilation	Yes	1 (7.7%)	12 (92.3%)	<.001	7.38
	No	14 (87.5%)	2 (12.5%)		
Platelets at admission	Median (Q1, Q3)	(8E5, 1.91E5)	(8E5, 2.93E5)	.024	NA
Platelets at fifth day	Median (Q1, Q3)	(9E5, 0.96E5)	(1E5, 2.40E5)	< .001	NA
SOFA score admission	Median (Q1, Q3)	4 (2.5, 7.0)	(10.0, 15.5)	.002	NA
SOFA score at the fifth day	Median (Q1, Q3)	5 (4.0, 6.0)	(12.5, 20.0)	< .001	NA
Usage of Norepinephrine	Yes	4 (23.5%)	13 (76.5%)	< .001	9.22
	No	11 (91.7%)	1 (8.3%)		

Table 2 shows the lethality in terms of thrombocytopenia at the admission and at the fifth day, with its corresponding calculation of *p* value and relative risk.

Graphic 1 shows the area under the curve of platelets at the admission and at fifth day as predictors of mortality; and Table 3, the risk of lethality depending on the platelet level, based on the cut-off points of the ROC curve.

Table 2.
Lethality in terms of thrombocytopenia at admission and at fifth day

Thrombocytopenia		**Condition**				***P* Value**
		Deceased		**Alive**		
		Frequency	**Percentage**	**Frequency**	**Percentage**	
Admission	No	5	29.$	12	70.6	.025
	Yes	9	75.0	3	25.0	
Fifth day	No	2	18.2	9	81.8	.021
	Yes	12	66.7	6	33.3	
Relative risk thrombocytopenia at admission = 2.82 CI 95% [1.01, 7.88]						
Relative risk thrombocytopenia at the fifth day = 2.45 CI 95% [1.21, 4.99]						



Graphic 1. Comparison of ROC curves of thrombocytopenia at admission and at the fifth day as dead predictors.

Graphic 1 includes the area under the curve of each ROC curve, as well as its corresponding confidence intervals of 95%.

Table 3.
Lethality depending on platelet classification based on the cut-off points of the ROC curve.

Mortality risk depending on platelets		**Condition at discharge**				***p* Value, Fisher's exact test**
		Deceased		**Alive**		
		Frequency	**Percentage**	**Frequency**	**Percentage**	
At admission	181,000 or more	4	26.7	11	73.3	0.027
	< 181,000	10	71.4	4	28.6	
At the fifth day	98,500 platelets or more	3	17.6	14	82.4	<.001
	< 98,500 platelets	11	91.7	1	8.3	
Relative risk < 181,000 platelets at admission = 2.57 CI 95% [1.06 to 6.20]						
Relative risk < 98,500 platelets at the fifth day = 9.99 CI 95% [1.49 to 65.37]						

Through a Spearman's rank correlation coefficient, we found association between SOFA and the platelets at admission, result of which was -.356 (*p* = .058). The results between SOFA and the platelets at the fifth day were -.345 (*p* = .067); and the results between platelets at admission and SOFA at the fifth day were -.522 (p = .004). We also found that SOFA and mortality are significant, both at admission (area under curve = .833, CI 95% [.672, .995], *p* = .002) and at the fifth day (area under curve = .871, CI 95% [.729, .999] *p* = .001).

The *p* value of the Bootstrap test for two ROC curve of .965 indicates that there was not any significant difference between the predictive capacity of SOFA and the platelet count of the fifth day.

Discussion

This study was developed to compare the predictive capacity of mortality of thrombocytopenia presence versus SOFA scale at the first and fifth day. In this study, 29 patients with sepsis and septic shock participated. In addition, we assessed the association with age, gender, and patient's comorbidity such as diabetes mellitus and high blood pressure, and mechanical ventilation requirement while staying in ICU.

The sex distribution in the group of the patients that died showed that men had a higher death incidence (60.0% versus 35.7%); however, such difference was not significant (*p* = .191). The patients that died were older (age mean = 67.7) than the patients alive (age mean = 57.7), and the difference was not significant (*p* = .078).

Regarding the diagnosis, 13 patients presented severe sepsis; and 16, septic shock. The patients with septic shock were the ones who presented a higher lethality risk (81.3%). This difference regarding the patients with severe sepsis was significant ($p < .001$). Diabetes and high blood pressure increase the lethality risk; however, only the high blood pressure was significant at significance level of 5% ($p = .035$). Out of the patients with diabetes and high blood pressure, 57.1% and 61.9% died, respectively.

Regarding the procedures, there was a high percentage of patients that required vasopressors and died. This association was significant ($p < .001$). It was also observed that most of patients that received mechanical ventilation died (92.3%). This association was significant ($p < .001$).

SOFA showed to be a better predictor than platelets, as it is displayed in the values of the area under the curve. This could be explained by SOFA being based on a larger evidence that provides assessment of six physiological systems (Minne *et al*., 2008). However, in this study, we considered relevant that something simpler, such as the platelet count, has a great power to predict mortality. A meta-analysis carried out aiming to assess SOFA performance to predict patients' mortality In the Intensive Care Unit concluded that other scores that assess the severity of the disease have a predictive capacity limited to the first 24 hours after admission, while the models based on SOFA scores do not present this limitation (Minne *et al*., 2008). In addition, we found a relationship between SOFA and the platelets count, according to the statistician Rho de Spearman, that could be classified as weak following the Mukaka revision (2012). On his behalf, Barton and Peat (2014) state that the required sample to detect a significant correlation with a weak effect should be higher that the total of patients of this study. The correlation was not significant, as opposed to the study of Marko-Shulke and contributors (2012) where significant differences were found in SOFA values in patients with and without thrombocytopenia.

In Table 2, it is presented the discharging condition based on thrombocytopenia. Out of the total of patients with thrombocytopenia at admission, 75.0% ($p = .025$) died, and out of the patients with thrombocytopenia, on the fifth day, 66.7% ($p = .021$) died. According to the calculated relative risk, and regarding the patients without thrombocytopenia, a patient with thrombocytopenia at admission had 2.82 times the risk of dying, and a patient with thrombocytopenia at the fifth day presented 2.45 times the risk of dying. This was a risk slightly higher than the one found in the study of Boechat and contributors (2012), which was carried out in Brazil. This study reported a relative risk of 1.87. However, when comparing the confidence intervals of said study (1.12 to 3.12) with this new study, we could not find any significant difference. In addition, this authors report a relative risk of 1.48 for patients whose platelet levels fell more than half the initial value, and a relative risk of 2.17 for patients that acquired thrombocytopenia and whose platelet levels did not increase during the illness.

Thrombocytopenia classification is also important. It has been observed a higher mortality in patients with severe thrombocytopenia, due to the increase of bleeding risk. This also limits any therapeutic and diagnostic procedure. In this study, we did not detect severe thrombocytopenia in any patient; not at admission or at the fifth day. We did observe in the evaluation at the fifth day that 80% of the patients with moderate thrombocytopenia died.

We believed that platelet count at the fifth day would be the best measurement, since it has a higher sensibility and specificity. It is possible that the difference between the two measurements in the matter presents a small effect, and gets a significant difference with a larger sample. Table 3 shows that under 98,500 platelets, the risk of dying was 9 times, approximately, in relation with the patients that had a high platelet count. The cut-off point of the first evaluation of platelet count as a prognostic factor places it in a not-considered level of thrombocytopenia: 189,000 platelets. However, it is important to remember that at the beginning several procedures are performed to stabilize the patient. At the fifth day, it is expected that most of clinical disorders of the patients are relieved, reason why the platelet count at the fifth day was considered as a better predictor. Other authors have studied the platelet count as a mortality predictor, the platelet volume and the platelet distribution; so is the case of Guclu and contributor (2013).

As it was stated above, even though SOFA is the best predictor, there was no significant difference between the predictive capacity of SOFA and the platelet count at the fifth day, according to the Bootsrap test.

One of the limitations of this study was the limited population that was included. However, this was a study that could have continuity increasing the population for the study, and so increase the statistical power.

The early approach to a patient with severe sepsis, based on the Surviving Sepsis Guidelines, has showed the decrease of the rate of the mortality and complications in patients (Rhodes *et al.*, 2017). This is the reason why medical staff must have the capacity of identifying and approaching septic patients. In this study, it was demonstrated that the platelet count at the fifth day is a good predictor that differs a little from the information provided by SOFA at the fifth day. Therefore, it is considered as an effective tool to predict death in patients with severe sepsis and septic shock.

At the end of this study, we considered as relevant the use of platelet count at the fifth day as a mortality predictor, substituting SOFA, which, due to its complexity, requires more resources. Thus, it is concluded that using SOFA at the first day combined with platelet count at the fifth day is an appropriate method for death prediction in patients with sepsis and septic shock in the Intensive Care Unit. It is also concluded that this can help to save resources.

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