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RESEARCH ARTICLE

Clinical and epidemiological factors related to mortality due to septic shock in a pediatric intensive care unit

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Abstract

Introduction: *Septic shock is a potentially life-threatening condition. The aim of this study was to identify clinical and epidemiological factors associated with mortality in pediatric patients admitted to a pediatric intensive care unit (PICU) with septic shock.* **Materials and methods:** *A retrospective comparative case series study was conducted with children aged 1 month to 14 years with septic shock from 2018 to 2020 in a PICU in Lima, Peru. Patients were divided into deceased and survivor groups based on their condition at discharge from the PICU.The influence of each variable on mortality was assessed using a logistic regression model.* **Results:** *A total of 174 patients were included in the study, with 51 (29.3%) fatalities. Deceased patients, compared to survivors, were older, had a higher incidence of oncological disease (31.4% vs. 14.6%; p = 0.011), more frequently presented with hemoglobin ≤ 9 g/dL (44% vs. 28%; p = 0.043), lactate > 2 mmol/L (70% vs. 44%; p = 0.002), platelets ≤ 150 (×10^3)/µL (77% vs. 42%; p < 0.001), and pH ≤ 7.1 (31% vs. 6%; p < 0.001). In the logistic regression model, factors related to mortality were having a pH ≤ 7.1 (odds ratio [OR] = 8.95; 95% confidence interval [CI]: 2.52-31.75) and platelets ≤ 150 (×10^3)/µL (OR = 3.89; 95% CI: 1.40-10.84).* **Conclusions:** *Factors associated with mortality in pediatric patients with septic shock were a pH ≤ 7.1 and platelets ≤ 150 (×10^3)/µL in the assessments conducted upon admission to the PICU.*

Keywords: *Shock. Septic. Risk factors. Mortality. Child. Critical illness (MeSH/NLM).*

Factores clínicos y epidemiológicos relacionados con la mortalidad por shock séptico en una unidad de cuidados intensivos pediátricos

Resumen

Introducción: *El shock séptico es una condición potencialmente mortal. El objetivo del estudio fue identificar factores clínicos y epidemiológicos relacionados con la mortalidad en pacientes que ingresaron por shock séptico a una Unidad de Cuidados Intensivos Pediátricos (UCIP).* **Métodos:** *Estudio retrospectivo tipo serie de casos comparativos con niños de 1 mes a 14 años hospitalizados por shock séptico del 2018 al 2020 en una UCIP de Lima en Perú. Los pacientes fueron divididos en fallecidos y vivos según su condición al alta de la Unidad. La influencia de cada variable sobre la mortalidad fue evaluada mediante un modelo de regresión logística.* **Resultados:** *Ingresaron 174 pacientes al estudio, fallecieron 51 (29.3%). Los fallecidos en comparación con los vivos fueron de mayor edad, tuvieron más casos oncológicos (31.4% vs. 14.6%; p = 0.011), presentaron con mayor frecuencia hemoglobina ≤ 9 g/dL (44% vs. 28%; p = 0.043), lactato > 2 mmol/L (70% vs. 44%;*

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p = 0.002), plaquetas ≤ 150 (×10³)/µL (77% vs. 42%; p < 0.001) y pH ≤ 7,1 (31% vs. 6%; p < 0.001). En la regresión logística ajustada los factores que se relacionaron con la mortalidad fueron tener un pH ≤ 7,1 (OR = 8.95; IC 95%: 2.52 a 31.75) y plaquetas ≤ 150 (×10³)/µL (OR = 3.89; IC 95%: 1.40 a 10.84). **Conclusiones:** *Los factores relacionados con la mortalidad en pacientes hospitalizados por shock séptico fueron tener un pH ≤ 7.1 y plaquetas ≤ 150 (×10³)/µL en los controles realizados al ingreso de la UCIP.*

Palabras clave: *Choque séptico. Factores de riesgo. Mortalidad. Niño. Enfermedad crítica (DeCS/BIREME).*

Introduction

Sepsis is a life-threatening condition, with septic shock being its most severe form of presentation[1,2]. It is estimated that a person dies of these causes every 6 s worldwide, with the pediatric population being one of the most affected[3-5]. Nearly half of the deaths from septic shock in children occur within the first 24 h after admission to pediatric intensive care units (PICUs)[6], making it a priority to understand the profile of the group at the highest risk of dying to act early.

Various publications have studied the clinical and epidemiological characteristics of children with septic shock upon PICU admission. However, these studies included patients with both sepsis and septic shock, knowing that they involve different degrees of severity and, consequently, different risks of death[7-9]. Furthermore, although children in developing countries are the most affected, most knowledge about this pathology comes from developed countries[10], with few publications from Latin America and none is representative of Peru[11-14]. Therefore, there is no profile that allows us to identify children with septic shock at higher risk of unfavorable outcomes in our context.

Consequently, our study aimed to identify clinical and epidemiological factors related to mortality in patients hospitalized for septic shock in a national reference PICU in Lima, Peru.

Materials and methods

Study design, population, and sample

A retrospective comparative case series study was conducted using information from patients hospitalized in the PICU of the Edgardo Rebagliati Martins National Hospital (HNERM) from January 1, 2018, to December 31, 2020. HNERM is located in Lima, Peru, is a national reference center, and is considered one of the largest in the country[15]. The pediatric hospitalization area has more than 100 beds, whereas the PICU had 9 beds during the research period. The population consisted of children from 1 month to 13 years, 11 months, and 29 days who were hospitalized in the PICU of HNERM with a diagnosis of septic shock. Non-probabilistic convenience sampling was used with consecutive cases during the study period.

The diagnosis of septic shock was considered following the recommendations of the American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock, which are patient with suspected or confirmed infection who presented some combination of hypothermia or hyperthermia, altered mental state, peripheral vasodilation or vasoconstriction, very rapid capillary refill or > 2 s, mottled or reticulated skin, and/or hypotension[16].

Certain conditions of the patients can increase the risk of death by themselves, so to reduce bias, patients with the following criteria were excluded: Do-not-resuscitate order, history of cardiorespiratory arrest up to 7 days before PICU admission, history of end-stage chronic renal failure receiving hemodialysis or peritoneal dialysis, and liver failure meeting transplant criteria.

The patients included in the study were divided into two groups based on their condition at discharge from the unit: deceased and non-deceased. Each group constituted a case series. Analysis was performed for each series and comparatively between both.

Variables

Information on qualitative variables was recorded, such as deceased status at discharge from the unit (the variable that determined which case series the patient belonged to), sex, presence of comorbidity, and history of oncological disease. Data on numerical variables were also obtained based on the first records upon PICU admission, including age, pediatric risk of mortality (PRISM III) score, hemoglobin, platelet count, creatinine, lactate, albumin, pH, and HCO_3.

Some numerical variables were categorized for convenience according to their degree of compromise to explore their influence on mortality. These variables

were age (< 1 year, 1 to < 5 years, 5 to < 9 years, and ≥ 9 years), hemoglobin (≤ 10 g/dL, ≤ 9 g/dL, ≤ 8 g/dL, and ≤ 7 g/dL), platelets ≤ 150 ($\times 10^3$)/µL, lactate > 2 mmol/L, albumin ≤ 3 g/dL, pH (≤ 7.3, ≤ 7.2, and ≤ 7.1), and HCO_3 ≤ 15 mEq/L.

It is worth mentioning that the PRISM III is a prognostic index that estimates the risk of dying in the PICU[17]. It evaluates 17 physiological variables, considering their worst value during the first 24 h of PICU admission[17]. The evaluated variables are systolic blood pressure, heart rate, temperature, pupils, mental status, alkalosis, acidosis, PaO_2, $PaCO_2$, total CO_2, glucose, potassium, creatinine, urea, prothrombin time or partial thromboplastin time, white blood cell count, and platelet count[17]. Finally, a statistical program converts the obtained score into a percentage[17]. The resident physicians of the HNERM PICU are responsible for performing the PRISM scores for admissions using a computerized program available at the unit.

The principal investigator collected the data and verified that each value had been recorded twice before doing the analysis.

Analysis

The collected data were transferred to a database created in Microsoft Excel 2016, where quality control was performed to identify and manage outliers. Subsequently, it was exported to the statistical package Stata 14.0 (StataCorp, TX, US). Descriptive and inferential statistics were performed, using frequency measures for qualitative variables and measures of central tendency and dispersion for quantitative variables. Quantitative variables were assessed by comparing means with the student t-test or Mann–Whitney U test according to the normality of the variable, which was evaluated by the Shapiro–Wilk test. For categorical variables, the assessment was done by comparing proportions, using the Chi-square test or Fisher's exact test, after calculating expected values. Finally, for those variables that were clearly different, a crude and adjusted logistic regression model was applied. The influence of each variable was evaluated using an odds ratio (OR), which was considered "exploratory." A $p < 0.05$ with a 95% confidence interval (CI) was considered significant.

Ethical aspects

As this was a descriptive and retrospective study based on data from patients' medical records, informed consent was not requested; however, the anonymity of the information was respected. The respective permissions were obtained from the Edgardo Rebagliati Martins National Hospital and the Universidad Peruana Cayetano Heredia ethics committees.

Results

From January 2018 to December 2020, 990 patients were admitted to the PICU of HNERM; 25 had a diagnosis of sepsis (2.5%), and 190 had septic shock (19.2%). Of the latter, 16 were excluded; 12 of them due to post-cardiac arrest status, three due to end-stage chronic renal failure, and one due to acute liver failure meeting transplant criteria. Finally, 174 patients were included in the analysis, of whom 51 (29.3%) died (Fig. 1).

Among the included patients, the median age was 1.6 years (interquartile range [IQR]: 0.5-8.4 years), the age group under 1 year was the most frequent at 43.1%, 54.6% were male, 19.5% had an oncological disease, and the median PRISM III score was 13% (IQR: 4% to 45%) (Table 1). Regarding laboratory values at PICU admission, 52% had platelets ≤ 150 ($\times 10^3$)/µL and 32% had hemoglobin ≤ 9 g/dL. In addition, 52% presented lactate > 2 mmol/L and 13% had pH ≤ 7.1 (Table 2).

When evaluating the most significant factors related to mortality at PICU discharge, it was observed that the deceased group, compared to the survivors, was older (median in years [IQR], 5 [0.8-10.2] vs. 1 [0.3-7.6]; $p = 0.008$), had more oncological cases (31.4% vs. 14.6%; $p = 0.011$), their risk of dying was higher (48% vs. 9%; $p<0.001$), more frequently presented hemoglobin ≤ 9 g/dL (44% vs. 28%; $p = 0.043$), lactate > 2 mmol/L (70% vs. 44%; $p = 0.002$), pH ≤ 7.1 (31% vs. 6%; $p < 0.001$), and bicarbonate ≤ 15 mEq/l (41% vs 13%; $p<0.001$). The median platelet count in the deceased group was 59 ($\times 10^3$)/µL and in survivors 169 ($\times 10^3$)/µL, with a statistically significant difference ($p < 0.001$). Similarly, when categorizing the platelet value, the deceased, compared to survivors, had a count ≤ 150 ($\times 10^3$)/µL more frequently (77% vs. 42%; $p < 0.001$) (Tables 1 and 2).

In the exploratory crude analysis, the main factors associated with mortality in patients hospitalized for septic shock were having a pH ≤ 7.1 with an OR of 7.31 (95% CI: 2.76-19.39) and presenting platelets ≤ 150 ($\times 10^3$)/µL with an OR of 4.59 (95% CI: 2.14-9.84) (Table 3). In the adjusted analysis, both factors maintained this relationship, with an OR of 8.95 (95% CI: 2.52-31.75) for a pH ≤ 7.1 and an OR of 3.89 (95% CI: 1.40-10.84) for platelets ≤ 150 ($\times 10^3$)/µL (Table 3).

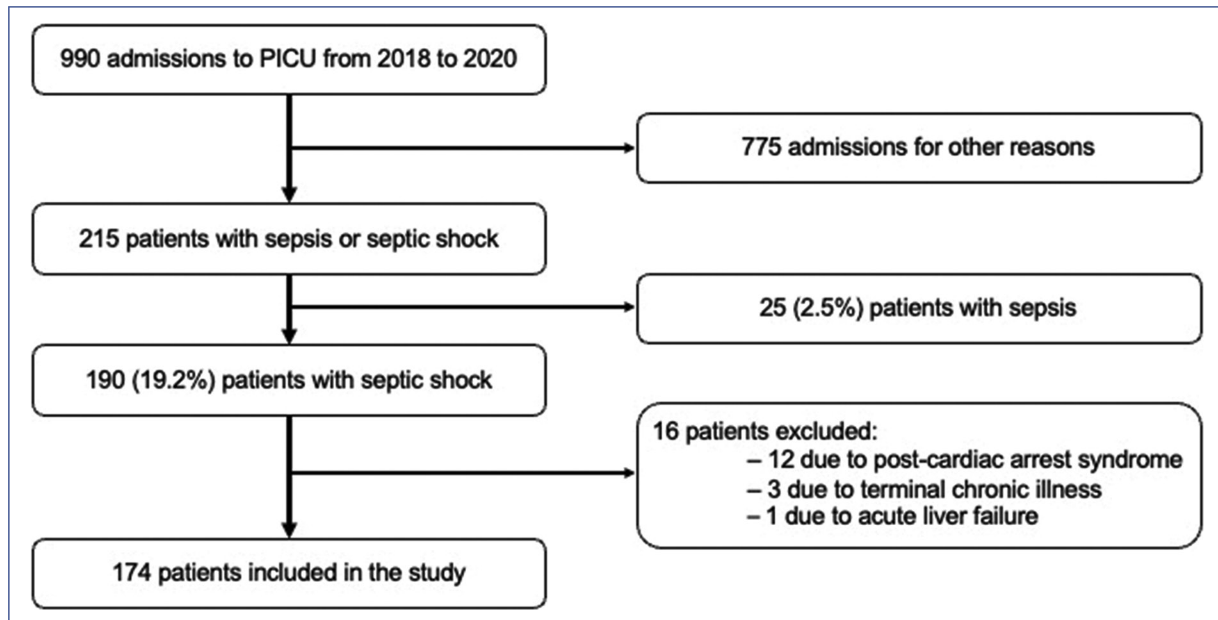

Figure 1. Flow diagram of the study patients. *PICU: Pediatric Intensive Care Unit.

Table 1. Epidemiological and clinical characteristics of patients with septic shock on admission to pediatric intensive care according to their condition at discharge

Variable	Total (n = 174) n (%)	Alive (n = 123) n (%)	Deceased (n = 51) n (%)	p-value#
Gender Female	79 (45.4)	56 (45.5)	23 (45.1)	0.959[b]
Age, years median [IQR]	1.6 [0.5-8.4]	1 [0.3-7.6]	5 [0.8-10.2]	0.008[a]
Age category < 1 year 1 year < 5 years 5 year < 9 years More than 9 years	 75 (43.1) 32 (18.4) 27 (15.5) 40 (23.0)	 61 (49.6) 21 (17.1) 16 (13.0) 25 (20.3)	 14 (27.5) 11 (21.6) 11 (21.6) 15 (29.4)	 0.058[b]
Comorbidity	107 (61.5)	74 (60.2)	33 (64.7)	0.575[b]
Oncologic disease	34 (19.5)	18 (14.6)	16 (31.4)	0.011[b]
PRISM* III (n = 159) median [IQR]	13 [4-45]	9 [2-26]	48 [18-82]	0.001[a]

IQR: interquartile range.
*PRISM: Pediatric Risk of Mortality expressed as a percentage (%).
#p values obtained with: [a]U Mann Whitney; [b]Chi-square.

Discussion

During the 3 years of the study, septic shock admissions to the HNERM PICU represented 19.2% of total admissions. This value is similar to the 19.8% reported by de Souza in a study conducted in 21 PICUs across five South American countries[11] and lower than the 48% found by Jaramillo in a study with 19 PICUs in Colombia[12]. These figures suggest that septic shock is a frequent health problem in our Hospital, as it is in the southern part of our continent.

29.3% of total septic shock admissions to the PICU died. This value is similar to what has been reported by other studies: 23.1%[11], 25%[7], and 34%[12]. In other words, in our Unit, approximately one in three admissions with this pathology died. This suggests that it is a frequent problem and implies high mortality.

Table 2. Laboratory characteristics of patients with septic shock upon admission to pediatric intensive care according to their condition at discharge

Variable	Total (n = 174) n (%)	Alive (n = 123) n (%)	Deceased (n = 51) n (%)	p-value[#]
Hemoglobin g/dl (n = 171) median [IQR]	10.1 [8.7-11.5]	10.2 [8.9-11.6]	9.3 [8.2-11.1]	0.035[a]
Hemoglobin ≤ 10 g/dL	84 (49)	56 (46)	28 (58)	0.132[b]
Hemoglobin ≤ 9 g/dL	55 (32)	34 (28)	21 (44)	0.043[b]
Hemoglobin ≤ 8 g/dL	28 (16)	17 (14)	11 (23)	0.149[b]
Hemoglobin ≤ 7 g/dL	13 (8)	6 (5)	7 (15)	0.050[c]
Platelets (×10^3)/µL (n = 171) median [IQR]	147 [52-240]	169 [75-288]	59 [34-149]	< 0.001[a]
Platelets ≤ 150 (×10^3)/µL	89 (52)	52 (42)	37 (77)	< 0.001[b]
Creatinine mg/dl (n = 167) median [IQR]	0.41 [0.28-0.67]	0.39 [0.26-0.56]	0.55 [0.36-0,78]	0.008[a]
Lactate mmol/L (n = 173) median [IQR]	2.2 [1.4-3.9]	1.9 [1.3-3.1]	4.1 [1,8-7.7]	< 0.001[a]
Lactate > 2 mmol/L	89 (52)	54 (44)	35 (70)	0.002[b]
Albumin g/dl* (n = 150)	2.9 ± 0.7	2.9 ± 0.6	2.8 ± 0.8	0.176[d]
Albumin ≤ 3 g/dL	86 (57)	58 (54)	28 (65)	0.222[b]
pH[§] (n = 172) median [IQR]	7.30 [7.17-7.36]	7.30 [7.22-7.37]	7,24 [7,09-7.34]	0.007[a]
pH[§] ≤ 7.3	92 (54)	62 (50)	30 (61)	0.199[b]
pH[§] ≤ 7.2	51 (30)	28 (23)	23 (47)	0.002[b]
pH[§] ≤ 7.1	22 (13)	7 (6)	15 (31)	< 0.001[b]
Bicarbonate mEq/L*	19 ± 5	19 [17-22]	18 [13-22]	0.028[a]
Bicarbonate ≤ 15 mEq/L	36 (21)	16 (13)	20 (41)	< 0.001[b]

IQR: interquartile range.
*Mean ± standard deviation.
[#]p-values obtained by: [a]Mann-Whitney U test; [b]Chi-square test; [c]Fisher's exact test; [d]t-test.
[§]pH: potential of hydrogen.

Table 3. Variables of patients with septic shock related to mortality: Crude and adjusted analysis

Variable	Crude Analysis			Adjusted Analysis[#]		
	OR	95 CI%	p-value	OR	95 CI%	p-value
Oncological disease	2.67	1.23-5.79	0.013	1.67	0.56-4.77	0.337
Hemoglobin ≤ 9 g/dL	2.04	1.02-4.07	0.045	1.62	0.67-3.90	0.282
Platelets ≤ 150 (×10^3)/µL	4.59	2.14-9.84	< 0.001	3.89	1.40-10.84	0.009
Lactate > 2 mmol/L	2.98	1.48-6.02	0.002	2,08	0.86-5.01	0.103
pH* ≤ 7.1	7.31	2.76-19.39	< 0.001	8.95	2.52-31.75	0.001

[#]By logistic regression adjusted for oncological disease, hemoglobin ≤ 9 g/dL, platelets ≤150 (×10^3)/µL, lactate > 2 mmol/L and pH ≤ 7.1.
*pH: potential of hydrogen.
OR: odds rato; CI: confidence interval.

Multiple studies found that children under 1 year were the most affected by septic shock[7,18,19]. We observed the same; those under 1 year represented 43.1% of total cases but without statistically significant differences between the groups of survivors and deceased. On the contrary, patients in the deceased group were

older than those who survived (5 and 1 year, respectively), with the difference being statistically significant. Other studies report different results regarding age, probably due to including septic patients[11] or having a small sample size[7]. 62% had a history of some comorbidity and 20% had cancer; we only found significant differences in mortality for the history of cancer. These results coincide with other publications[7,11,20], suggesting that cancer patients are vulnerable to developing septic shock.

On the other hand, we found differences in PRISM III scores; the deceased were at a higher risk for this outcome than the survivors, with values of 48% and 9%, respectively. Other studies also reported similar differences[7,20,21], reaffirming that the PRISM III evaluation helps approximate a patient's prognosis in septic shock.

Compared to the survivors, the deceased group more frequently presented lower platelet values, 59 ($\times 10^3$)/µL and 169 ($\times 10^3$)/µL, respectively, with statistically significant differences. Our results coincide with those reported by Kim in 65 Korean children with septic shock[20], where the deceased group had a mean of 56 ($\times 10^3$)/µL and the survivors 118 ($\times 10^3$)/µL. Furthermore, with Sayed et al.'s study in 60 Egyptian children with severe sepsis[22], the deceased group presented a median of 73 ($\times 10^3$)/µL and the survivor group, 265($\times 10^3$)/µL. These results suggest that the presence of thrombocytopenia in patients with septic shock could be a risk factor for mortality.

When evaluating anemia at different levels, we found a greater association with mortality when using a cut-off point of 9 g/dL. Although this situation would have been expected with a value lower than 7 g/dL, the small sample size probably influenced this not to be the case. We also observed increased creatinine and decreased pH and bicarbonate, with statistically significant differences between the survivor and deceased groups. Kim reported a similar trend in creatinine and pH values; however, the difference between both groups was not significant[20], probably because he evaluated 65 patients and we evaluated 174. It is possible that these laboratory results correspond to a more severe condition in the deceased group compared to the survivors, as demonstrated by the PRISM III value, 48% and 9%, respectively.

The lactate value was higher in the deceased group than in the survivors (4.1 mmol/L vs. 1.9 mmol/L). In addition, the deceased more frequently presented lactate > 2 mmol/L, and the difference was statistically significant. Other studies showed similar results[19-21,23]. Although we obtained a higher prevalence of albumin ≤ 3 g/dL in the patients who died, the difference was not significant. This result contradicts what Tiwari et al. reported in 2014[24], probably because he evaluated critically ill children with different diagnoses, and we only evaluated patients with septic shock.

An exploratory analysis was performed as this was a case series, not an analytical study. The results of this unadjusted logistic regression analysis show a significant association with mortality and oncological history, hemoglobin ≤ 9 g/dL, platelets ≤ 150 ($\times 10^3$)/µL, lactate > 2 mmol/L, and pH ≤ 7.1. However, when adjusting the model, only the presence of platelets ≤ 150 ($\times 10^3$)/µL and having pH ≤ 7.1 remained significant with mortality. The explanation for this result would be that only 34 cases with oncological history were recorded, distributed in the two groups, constituting a small sample for analysis. However, the 95% CI is not wide. A similar situation occurs with the presence of anemia.

To evaluate lactate, we equally considered the value from central venous and arterial samples, as studies demonstrate their adequate correlation[25-27]. However, some studies that did find an association between lactate and mortality only considered arterial samples[20]. Other publications also found no association, probably due to including patients with sepsis and septic shock or using different cut-off points[21,23].

The present study has limitations. It is a comparative case series study and not an analytical study. Therefore, we did not calculate the sample size; consequently, the statistical analysis could only be exploratory. Evaluating many variables and stratifying some decreased the number of cases in some subgroups. Being a retrospective study, it was only possible to have complete data for some variables, although most losses were < 5%. Patients from only one PICU were included, so it could not be extrapolated to other units. Due to the above, the results will serve to propose hypotheses to be evaluated in analytical studies.

Despite all the above, we maintain that our results are relevant. We included an important case series over 3 years of study. Various variables of interest were evaluated and further subdivided according to their level of compromise. Data loss was minimal. Although we only worked in one PICU, it is worth mentioning that it is one of the largest in the country, a national reference center with a high patient flow. Moreover, it was necessary to start with a descriptive study that constitutes the first work in Peruvian literature that includes a large number of pediatric patients exclusively with septic shock.

Conclusion

Finally, we conclude that the factors related to mortality in patients hospitalized for septic shock in the PICU of HNERM from 2018 to 2020 were having platelets ≤ 150 ($\times 10^3$)/µL and a pH ≤ 7.1. Both showed a strong association in the unadjusted model (OR 4.6 and 7.3, respectively), as well as in the adjusted model (OR 3.9 and 8.9). These results warrant an analytical study (case–control or cohort type) to confirm or not their association; therefore, we consider these results as having "exploratory" value.

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Conflicts of interest

The authors declare no conflict of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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