Procalcitonin, C-Reactive Protein, Albumin, and Blood Cultures as Early Markers of Sepsis Diagnosis or Predictors of Outcome: A Prospective Analysis

Clinical Pathology
Volume 12: 1–7

DOI: 10.1177/2632010X19847673

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ABSTRACT

PURPOSE: Sepsis is a condition with high mortality rates and its diagnosis remains a challenge. We assessed epidemiological, clinical data, multiple biomarker profiles, and blood culture with respect to sepsis diagnosis and predictors of outcome.

METHODS: In total, 183 patients who were suspected of having sepsis and underwent blood culture collection were followed up for 7 days. Sepsis-related Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores were calculated daily; biomarkers and blood culture test results were evaluated.

RESULTS: In total, 78 (43%) had sepsis, 50 (27%) had septic shock, and 55 (30%) had no sepsis. Blood culture was positive in 28% and 42% of the sepsis and septic shock groups, respectively ($P < .001$). Regarding clinical profiles and biomarker values, there were no differences between the sepsis and non-sepsis groups, but significant differences were observed in the septic shock group. Multivariate logistic regression models revealed that age, serum albumin level, APACHE II, and SOFA 1st day scores were the independent variables for death.

CONCLUSIONS: The challenge in the diagnosis of sepsis continues as clinical and laboratory differences found between the groups were due to septic shock. Older aged patients with lower albumin levels and higher APACHE II and SOFA 1st day scores have a greater probability of mortality.

KEYWORDS: sepsis, biomarkers, procalcitonin, C-reactive protein, epidemiology

RECEIVED: February 22, 2019. **ACCEPTED:** April 9, 2019.

TYPE: Original Research

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by grants from FINEP – Financiadora de Estudos e Projetos – Ministério da Ciência e Tecnologia (grant number # 01.12.0519.00); Universidade Federal do Paraná – UFPR; and Conselho Nacional de Pesquisa – CNPq. LMDC, DC, LAP, and SMR were supported by fellowships from CNPq.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Worldwide, sepsis is a condition with high mortality rates, and despite advances in medicine, it remains very serious. In addition, it is associated with cognitive, physical, and psychological deficits in survivors.[1] Seeking to standardize diagnosis and therapy of sepsis, since 1991, various consensus have emerged to guide clinical interventions and improve outcomes. In the latest guideline reported in 2016, it was suggested new definitions for sepsis and for septic shock.[2–4]

In Brazil, data on sepsis burden are scarce since information is obtained from non-official databases. Previously, the PROGRESS study (2002-2005) showed a mortality rate of 65%, which is higher than the global rate of 49.6%.[5] After this study, a group of Brazilian and Argentinian researchers created the Latin American Sepsis Institute (ILAS) to compute data, produce scientific material, and regulate sepsis care in these countries. Subsequently, in association with the Brazilian Research in Intensive Care Network, the ILAS concluded a study that helped quantify the sepsis situation in Brazil. The Sepsis Prevalence Assessment Database (SPREAD) consisted of a 1-day point prevalence study with follow-up of patients with sepsis in ICU in Brazil. From 2632 randomly selected patients, 794 had sepsis (30.2/100 ICU beds). The ICU sepsis incidence was 36.3/1000 patient-days, and the mortality rate was 55.7%.[6]

Despite the high sepsis frequency, its diagnosis remains a challenge, and clinical profile, bacterial identification, and inflammatory markers have been used for early diagnosis and correct clinical management. Among inflammatory markers, procalcitonin (PCT), a peptide precursor of calcitonin, which increases in inflammatory and infectious process, has been considered an early diagnostic marker.[7] C-reactive protein (CRP) and serum albumin levels have also been suggested as predictors of therapeutic response and outcomes in sepsis.[8–10]

In this study, we report the epidemiological, clinical, and laboratory profiles of a hospitalized patient cohort from a tertiary care academic hospital and investigate whether PCT, CRP, and albumin serum levels and blood culture results could predict sepsis diagnosis and outcome.

Material and Methods

Study design and patients

This was a longitudinal Cohort study carried out at a tertiary care center in Curitiba, Southern Brazil. Patients were included from April 2015 to December 2015 and were followed up for 7 days. The Institutional Review Board approved this study (IRB: # 03377612.5.0000.0096), and all included patients provided written informed consent. Data collection was performed using a predesigned form and patients were enrolled using a convenience sampling method.

Patients over 18 years old who were hospitalized with suspicion of sepsis and who had a blood culture sample collected were included in the study. Samples for blood culture, PCT and CRP determinations were collected by peripheral venous puncture at the same time. Sepsis-related Organ Failure Assessment (SOFA) score[11] and Acute Physiology and Chronic Health Evaluation (APACHE) II score[12] were calculated daily by the same researcher until the seventh day of follow-up. The comorbid illness components of the Charlson comorbidity score were prospectively abstracted from the medical records.[13]

During the follow-up, clinical data, laboratory data, organic dysfunction score (SOFA), inflammatory activity, perfusion tests, and disease outcomes were evaluated. At the end, the patients were classified as sepsis (Group 1), septic shock (Group 2), and no sepsis (Group 3), according to the third international consensus guideline (Sepsis-3).[4]

Laboratory data

Blood samples were obtained by standard venipuncture, and routine assays were performed to assess hemogram, renal and hepatic functions, CRP, albumin, and PCT. For blood culture, two samples were collected for aerobic and anaerobic culture, and another sample was collected from the catheter to test for venous catheter infections. Conventional blood culturing was performed using an aliquot of 5 to 10 mL whole blood, which was inoculated into BACTEC_H aerobic and anaerobic bottles (Becton Dickinson, Sparks, MD). BACTEC Plus bottles were used for patients under antibiotic therapy, and standard bottles were used for untreated patients. Two sets of blood samples from two different sites were collected at the same time. The bottles were then incubated in a BACTEC FX (Becton Dickinson) automated blood culture system. An aliquot that was taken from the bottles flagged positive for Gram stain and was cultured on solid media for subsequent analysis. Identification of microorganisms was performed in the VITEK automated system (BioMérieux, Hazelwood, MO).

Serum PCT levels were measured using enzyme-linked fluorescent assays LIAISON® B.R.A.H.M.S PCT® II GEN (Thermo Fisher Scientific, B.R.A.H.M.S GmbH, Hennigsdorf), with a lower reference limit of 0.05 ng/mL. Serum CRP levels were measured using an immunoturbidimetric assay, the Multigent CRP Vario assay (Abbott Laboratories Inc, Abbott Park, IL), and the lower reference limit for the assay was 0.05 mg/dL. The quantitation of albumin in human serum or plasma was carried out using the Albumin BCG assay by Bromocresol Green methodology (Abbott Laboratories Inc), and the reference range for adults was 3.5 to 5.0 g/dL.

Statistical analysis

Statistical analysis was performed using R Development Core Team, Version 3.4.0.[14] Categorical variables are expressed as numbers and percentages, whereas continuous variables are expressed as medians and interquartile ranges (IQRs). Although multiple episodes of sepsis are possible, we only included the first episode from each patient. The primary endpoint of this study was sepsis diagnosis and the secondary endpoint was patient outcome on discharge from hospital.

Covariates were examined in a univariate analysis to determine their association with sepsis/septic shock diagnosis and with mortality. Using a stepwise conditional procedure, multivariate logistic regression models were conducted to identify independent predictors of both endpoints. Odds ratio (OR) and 95% confidence intervals were calculated for the variables with significant difference. *P*-values $< .05$ were considered statistically significant.

Through receiver operating characteristic (ROC) analyses, the associations between the biochemical markers' predictive performance, sepsis diagnosis, and outcome were assessed. For those variables with significant associations, the cutoff value and the area under the curve (AUC) were determined.

Results

Patients characteristics

A total of 221 samples were taken from 183 patients; some of them presented more than one episode of suspected sepsis. Among the 183 patients, 106 (58%) were male, and the median age was 54 years (IQR 37-69). The majority of patients' possibility of survival in 10 years was above 90%, and 143 (78%) patients had some comorbidity. A total of 118 (64%) patients were in the ICU. The medians of APACHE II and SOFA 1st day scores were 16 (IQR

Table 1. Demographic, clinical, and laboratory findings in study groups (n = 183).

	GROUP 1	GROUP 2	GROUP 3	UNIVARIATE ANALYSIS
	SEPSIS, N = 78 (%)	SEPTIC SHOCK, N = 50 (%)	NON-SEPSIS, N = 55 (%)	*P*-VALUE
Sex				
Male	44 (56)	29 (58)	33(60)	NS
Age (years), median (IQR)	60 (36–69)	53.5 (43.7–70)	49 (37–69)	NS
Length of hospital, in days, median (IQR)	23 (13–33.5)	16 (7.7–43.2)	20 (10–37)	NS
Charlson probability of 10–year survival[a]				
99% to 90%	47 (60)	29 (58)	29 (52)	NS
77% to 53%	17 (22)	12 (24)	13 (24)	
21%	14 (18)	9 (18)	13 (24)	
Leukogram (cells/μL), median (IQR)	10020 (6990–12470)	9760 (6305–18560)	8960 (5703–13278)	NS
Leukogram (cells/μL)				
<3800	8 (11)	8 (16)	6 (11)	NS
3801 to 10999	35 (49)	20 (41)	28 (52)	
>11000	28 (40)	21 (43)	20 (37)	
Platelets ($\times 10^3$/μL), median (IQR)	204 (102–301)	165 (62–264)	200 (109.5–296)	NS
Case fatality	24 (31)	34 (68)	14 (25)	**<.0001**[b]
Serum albumin (g/dL), median (IQR)	2.6 (2.3–3.2)	2.2 (1.8–2.7)	2.8 (2.6–3.3)	**<.0001**[b]
Serum CRP (mg/L), median (IQR)	10.7 (4.9–16.2)	16.3 (7.2–21.7)	8.6 (4–14)	**<.05**[b]
Serum PCT (ng/mL), median (IQR)	0.4 (0.1–2.1)	4.28 (0.79–32.7)	0.36 (0.1–0.9)	**<.0001**[b]
Serum PCT (ng/mL)				
⩽0.5	40 (52)	8 (16.5)	31 (57)	**<.0001**[b]
	0.51 to 1.9	15 (19)	14 (28.5)	14 (26)
	⩾2	22 (29)	27 (55)	9 (17)
APACHE II score, median (IQR)	14 (10–19)	22 (18–27)	13 (8–21)	**<.0001**[b]
SOFA 1st day, median (IQR)	3 (1–5)	8.5 (7–11)	4 (1–6)	**<.0001**[b]
Acquired infection				
Hospital	45 (58)	29 (58)	—	NS
Community	33 (42)	21(42)		
Blood culture				
Positive	22 (28)	21 (42)	—	**<.0001**
Negative	56 (72)	29 (58)		

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CRP, C-reactive protein; IQR, interquartile range; NS, non significant; PCT, procalcitonin; SOFA, Sepsis-related Organ Failure Assessment.
Significant values are in bold.
[a]A total of 40 patients do not have any comorbidities.
[b]Significant differences only for Group 2.

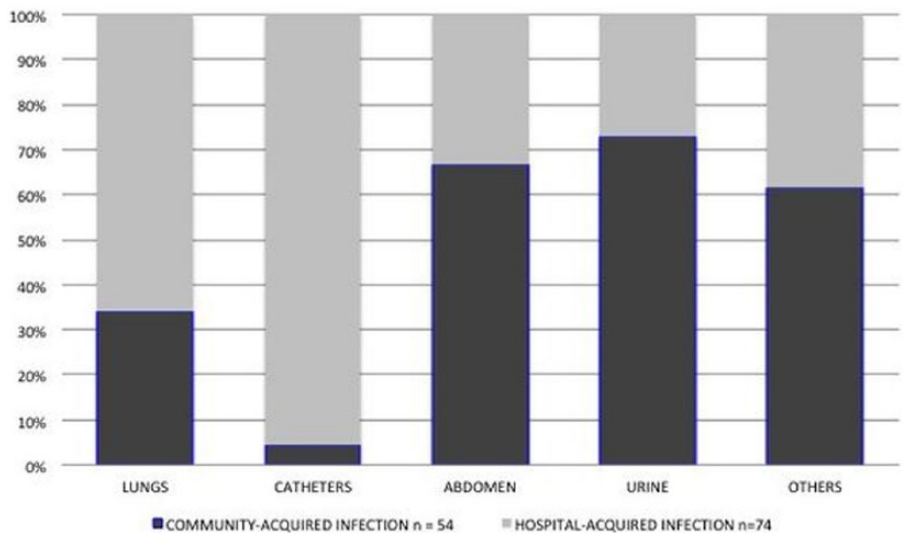

Figure 1. Infection sources of community- and hospital-acquired infections.

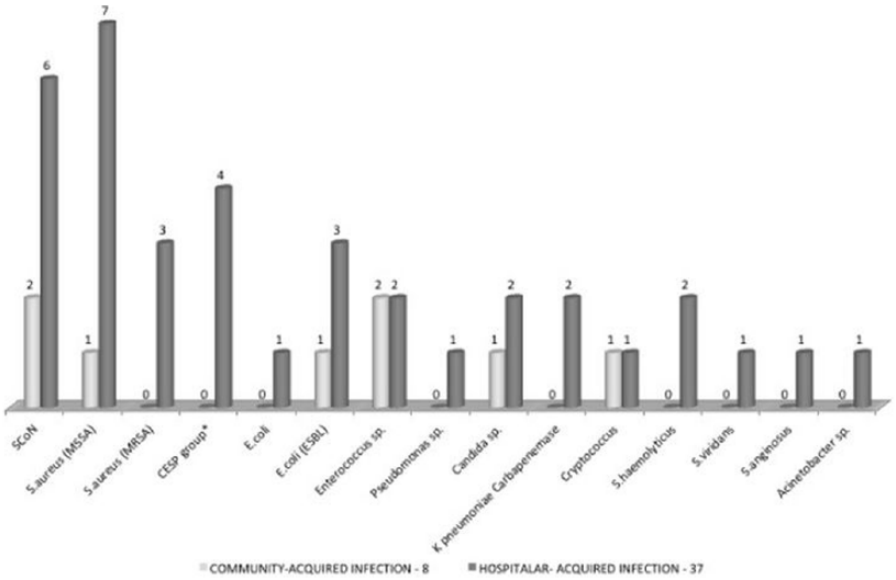

Figure 2. Pathogens identified in blood cultures.
*SCoN indicates coagulase-negative *Staphylococcus* sp.; *Staphylococcus haemolyticus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; ESBL, extended spectrum beta-lactamase.
CESP group:[15] *Enterobacter cloacae* (n = 1), *Serratia marcescens* (n = 2), and *Citrobacter koseri* (n = 1).

11-22) and 4 (IQR 2-8), respectively. Patients were divided into three groups: sepsis (78 cases/43%), septic shock (50 cases/27%), and non-sepsis (55 cases/30%). Demographic, clinical, and laboratory findings between the groups are compared in Table 1.

Sepsis resulted from hospital- or community-acquired infections in 74 (58%) and 54 (42%) cases, respectively. For hospital-acquired infections, the main sources of infections were lung- (45%) and catheter- (30%) related infections. Among community-acquired infections, the main sources of infections were lung- (31%) and abdomen- (22%) related infections (Figure 1). The origin of primary sepsis and septic shock was the lung and catheter, respectively.

Blood culture was positive in 43 patients with 22 (28%) occurring in the septic group and 21 (42%) occurring in the septic shock group ($P < .001$). Positive cultures were more common in cases of hospital- than in community-acquired infections, being Gram-positive bacteria the most frequent. Other pathogens that were found are depicted in Figure 2.

Clinical scores, biological markers, and sepsis diagnosis

Overall mortality was 39%, and the mortality rate for sepsis patients, septic shock patients, and non-septic patients was 31%, 68%, and 25%, respectively. Fatality case number, serum albumin, CRP, PCT levels, positive blood culture, and APACHE II and SOFA 1st day scores were significantly different in Group 2 (septic shock) patients compared with those in Groups 1 and 3 (Table 1). No statistical difference was found between Group 1 and Group 3, and no clinical or laboratory finding was shown to help in identifying these two groups.

Table 2. Demographic, clinical, and biomarker findings in predicting outcome in studied patients (n = 183 patients).

VARIABLE	DISCHARGE, N = 111 (%)	DEATH, N = 72 (%)	UNADJUSTED ANALYSIS	ADJUSTED ANALYSIS		
			P-VALUE	*P*-VALUE	OR	95% CI
Age, years, median (IQR)	48 (31–66)	62.5 (52–72.7)	<**.001**	**.003**	1.03	1.01 to 1.05
Charlson comorbidity index*						
99% to 90%	68 (61)	37 (51)	.174	—	—	—
77% to 53%	26 (24)	16 (22)				
21%	17 (15)	19 (27)				
APACHE II score, median (IQR)	13 (8–19)	21 (15–25)	<**.001**	**.037**	1.07	1.0 to 1.15
SOFA 1st day, median (IQR)	3 (1–5)	7 (3–10)	<**.001**	**.026**	1.15	1.01 to 1.31
Serum albumin (g/dL), median (IQR)	2.8 (2.4–3.3)	2.4 (1.9–2.8)	<**.001**	**.001**	0.5	0.28 to 0.86
Serum CRP (mg/L), median (IQR)	9.9 (4.3–15.9)	28.1 (19–37.7)	.068	—	—	—
Serum PCT (ng/mL), median (IQR)	0.4 (0.1–2)	1.4 (0.4 (7.2)	<**.001**	.623	—	—
Serum PCT (ng/mL)						
⩽0.5	59 (54)	20 (28)	**.002**		0.341	
0.51 to 1.9	22 (20)	21 (30)				
⩾2	28 (26)	30 (42)				
Blood culture						
Positive	20 (18)	23 (32)	**.029**		0.244	
Negative	91 (82)	49 (68)				
Platelets ($\times 10^3/\mu L$), median (IQR)	205 (109–304)	175 (65–244)	**.035**	.345		
Final classification						
Sepsis	54 (49)	24 (33)	<**.01**		0.118	
Septic shock	16 (14)	34 (47)				
Non-sepsis	41 (37)	14 (20)				

Abbreviation: APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; CRP, C-reactive protein; IQR, interquartile range; OR: odds ratio; PCT, procalcitonin; SOFA, Sepsis-related Organ Failure Assessment.
Significant values are in bold.

Clinical scores, biological markers, and outcomes

The univariate relationship between demographic data, clinical scores, and each biochemical marker and outcome are shown in Table 2. The levels of PCT and serum albumin were associated with fatality case rate. A multiple logistic regression model adjusted for age, albumin, PCT, platelets, positive blood culture, APACHE II, SOFA scores, and final classification was performed to predict the outcome. The independent variables found were age, albumin level, APACHE II, and SOFA scores.

The ROC curve calculated the PCT, CRP, and albumin levels with respect to death outcome (adjusted for age, gender, comorbidities, APACHE II, SOFA 1st day, and final classification), and the AUCs obtained were 0.66 (0.58-0.75), 0.59 (0.49-0.69), and 0.67 (0.58-0.75), respectively, for death prediction (Figure 3).

Discussion

This study focused on clinical-epidemiological and biomarkers profiles of patients admitted to the tertiary public hospital in southern Brazil for a period of 1 year. Regarding the epidemiological characteristics, predominance of male was in agreement with that reported in previous local and worldwide studies,[16,17] but the median age was lower than that observed in most centers and private hospitals in Brazil. The same was observed in the 2004 Brazilian Sepsis Epidemiological Study, which showed a younger median age of the public hospitals compared with the private hospitals.[15-20]

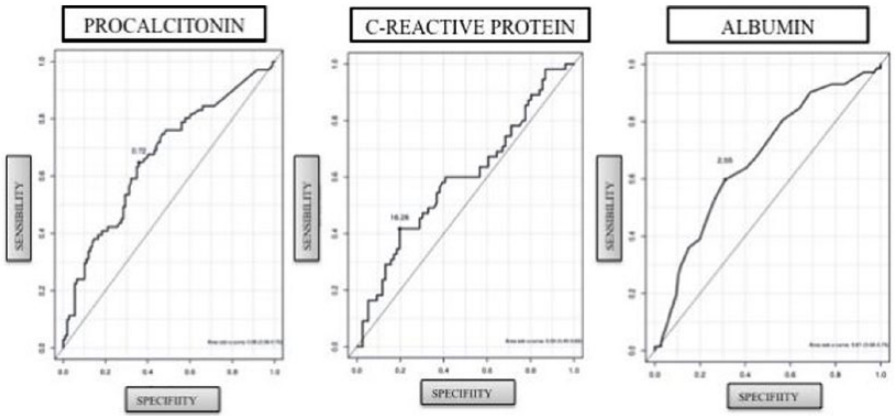

Figure 3. Receiver operating characteristic (ROC) curves for procalcitonin, CRP, and albumin to predict fatality.

The presence or absence of comorbidities did not influence the outcome, and no association was found between sepsis severity and baseline disease. These data are divergent when analyzing other epidemiological studies. In the study conducted in Australia and New Zealand, there was a significant decrease in sepsis fatality rate between the beginning (35% in 2000) and the end of the analysis (18% in 2012). It was observed that septic patients who were younger and without comorbidities had a lower mortality rate (4.6%), which shows that the presence of comorbidities may influence the outcome.[16] Another retrospective study carried out in Catalunya from 2008 to 2012 also showed a relationship between mortality and the presence of comorbidities.[21]

In this study, 78% patients presented some comorbidity with no difference between the groups. However, most patients (n = 147; 80%) had a Charlson comorbidity score ⩽4 (that means a low risk of death in 10 years). It could be an explanation why we do not found a correlation between mortality and the Charlson comorbidity score. Excluding these patients to assess the impact of the presence of comorbidities would make the sample in each group very small, and the findings could not be adequately assessed.

Regarding infection sites, the lungs were the main infection sites as described previously. However, this similarity did not occur with respect to the second most frequent site of nosocomial infection, which was catheter-related infection. Usually, these infections generally account for less than 4% in most studies. This difference is probably due to difficult to implement protocols for catheter insertion, maintenance, and early withdrawal of the venous catheters. Since this is a preventable infection, efforts to introduce technical protocols should be intensified.[5,6,15,19–22]

Considering the biomarkers, all differences found were in the septic shock group, probably due to hemodynamic changes present. However, no significant difference between patients with and without sepsis was found. As septic shock is a very well characterized clinical entity, it would not require biomarkers for its differential diagnosis.

Concerning the difference in albumin levels between groups, it may be a marker of severity and also would not aid in the diagnosis. Magnussen and colleagues[23] evaluated 1844 adults with community-acquired bacteremia and found that hypoalbuminemia was a better predictor of early mortality than the SOFA severity score. Similar to the present study, Yin et al observed higher mortality among septic patients with lower albumin levels and higher APACHE II and SOFA scores. In this study, the cut-off value of albumin was 2.9 mg/dL, ie, patients with albumin levels lower than 2.9 mg/dL had a worse outcome.[9]

The CRP levels had poor application to the initial diagnosis of sepsis, it seems that its evaluation sequentially should be recommended, and a decline from the 3rd and 5th day is associated with a better prognosis of the disease,[24] but these data were not evaluated in this study.

In 2015, a meta-analysis comprising 12 studies on PCT and sepsis showed its correlation with increased risk of mortality. High single values or non-clearance would indicate a higher risk of death.[25] Likewise, in the present analysis, there was a correlation between PCT levels and mortality, but it was not confirmed when the adjusted analysis was performed. However, this marker was not related to the diagnosis of sepsis.[25] It would serve as collaborator in the differential diagnosis of sepsis, but could not be used as unique criteria.[26]

A comprehensive extensive review of more than 178 different biomarkers showed that individually, all are limited in the differentiation between sepsis and another inflammatory state. Even the most widely used as PCT and CRP were not useful.[27] A simple blood sample evaluated with multiple biomarkers and cross-results with data from electronic medical records could contribute to the diagnosis of sepsis, as well as its prognosis.[28] However, defining such biomarkers, their time and frequency of collections are still challenges in clinical practice.

The definition of the etiological agent and the focus of the infection are also essential in the management of the patient. They allow the optimization of antimicrobial therapy, aside from other types of therapeutic interventions such as drainage of infection sites.

The predominance of Gram-positive bacteria (27%) was in agreement with current studies that have shown an increase in their isolation in sepsis in the last 25 years.[17,20,29,30] Blood

cultures were considered contaminated if there were more than two microorganisms growing in a sample or if there was growth of non-coagulase-producing staphylococcus (CoNS) in the sample. However, despite the increase in the number of infections by this organism in recent years, it is still very common as a contaminant in blood culture samples. All CoNS cases were extensively reviewed and only those situations where this pathogen was considered the causal agent of infection were included.

Previous studies reported that PCT levels greater than 2 ng/mL would be related to a higher number of positive blood cultures, but this was not observed in this study. Even with the dichotomization of the values, this difference was not significant.[31,32]

Between 2004 and 2009, 1001 patients admitted to a university hospital in Singapore for severe sepsis were evaluated. It was found that patients with negative blood cultures had lower APACHE II and SOFA values and lower mortality. In the current study, this difference was also significant, higher scores of APACHE II and SOFA 1st day were present when blood culture was positive. However, these results did not differentiate the microorganisms.[33]

This study has limitations. One limitation is that the inclusion of patients was done via convenience sampling, as the suspected cases of sepsis were identified by the attending physician. In addition, the dosages of the investigated biomarkers were not performed serially, which could have increased the chance of obtaining some correlation between the findings and sepsis diagnosis. However, the data obtained will contribute in increasing the knowledge of the burden of this syndrome in the region.

Sepsis is a clinical condition triggered by an infectious process, and its rapid identification and early therapy have a significant impact on mortality reduction. There is still no specific biomarker for sepsis diagnosis nor for the prediction of its outcome, and it seems that sequential dosages of multiple biomarkers could be useful, but it needs to be further evaluated.

Author Contributions

Methodology, formal analysis, investigation, draft writing: ACSON. Statistical analysis: RLP. Evaluation of patients: RMF. laboratory tests: DC and LAP Conceptualization, method design, result analysis, writing – review & editing, project administration and funding acquisition: LGO, LMDC and SMR.

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