ONCOLOGÍA
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ORIGINAL ARTICLE

Specificity and sensitivity of procalcitonin and interleukin-6 in cancer patients with bacteremia and positive blood culture

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Conflicts of interest: The authors declare not to have any interest conflicts reses.

Received: Jauary 19, 2023
Accepted: March 31, 2023
Published: April 8, 2023
Editor: Dra. Lorena Sandoya

Cite:
Castro S, Caputi R. Specificity and sensitivity of procalcitonin and interleukin-6 in cancer patients with bacteremia and positive blood culture. Revista Oncología (Ecuador) 2023;33(1):40-48.

ISSN: 2661-6653

DOI: https://doi.org/10.33821/674

SOCIEDAD DE LUCHA CONTRA EL CÁNCER-ECUADOR.

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Abstract

Introduction: The utility of procalcitonin to predict bacteremia in cancer patients with fever has been reported, but few data exist on the utility of interleukin 6. This study aimed to establish the specificity and sensitivity of procalcitonin and interleukin in cancer patients with bacteremia and positive blood culture.

Methods: Cross-sectional, observational, retrospective and prospective study design, was carried out at the Hospital de SOLCA - Guayaquil. The study period was from January to December 2015. Patients of legal age and under 65 years of age with a diagnosis of oncological disease with a diagnosis of SIRS, sepsis, or septic shock were included. The variables were the presence of bacteremia, procalcitonin (PCT), interleukin-6 (IL-6), age, sex, and blood culture report. The sample was nonprobabilistic. Descriptive and inferential statistics were used. Two groups were analyzed: the presence and absence of bacteremia, and a diagnostic test for procalcitonin and interleukin-6 was performed in each group.

Results: A total of 169 patients participated, 69 with positive blood cultures (G1) and 100 controls without bacteremia (G2). Procalcitonin was 14.6 in G1 vs 0.54 ng/ml in G2 (P=0.0001). IL-6 was 1479.47 ng/ml in G1 vs 4.37 ng/ml in G2 (P< 0.001). The sensitivity (S) of PCT was 81.2%, the specificity (E) was 79%, and the area under the curve was 0.862. P<0.0001. The S of IL-6 was 98.6%, the E was 95%, and the area under the curve was 0.996 P<0.0001.

Conclusion: Interleukin-6 is a good test as a predictor of bacteremia in cancer patients due to its high specificity value and to establish that if you have bacteremia, it is due to its high specificity.

Keywords:
MESH: Sepsis, Neoplasms, Calcitonin-Related Alpha Polypeptide, Interleukin-6.

DOI: 10.33821/674

Introduction

Sepsis in an oncologic patient represents a significant risk factor for the outcome of death, so early diagnosis allows prompt actions that reduce mortality. An observational study evaluated the utility of procalcitonin (PCT), interleukin 8 (IL-8), interleukin 6 (IL-6), and C-reactive protein (CRP) in the diagnosis of bacteremia in cancer patients and analyzed 79 patients with febrile

syndrome, concluding that procalcitonin has better sensitivity and specificity than interleukins and PCR to the point that it can provide more information in the diagnosis of bacteremia in cancer patients [1].

The utility of procalcitonin to predict bacteremia in cancer patients with fever has been reported in a previous study where 134 adult patients were analyzed, reporting that PCT levels were higher in those patients with bacteremia than in the group without bacteremia. PCT Serical levels of 0.20 ng/ml were established as the cut-off point, with a negative predictive value of 95.8% to rule out bacteremia [2].

The objective of the present investigation was to establish the correlation of procalcitonin and interleukin in cancer patients with bacteremia and positive blood culture, which made it possible to identify groups with a high susceptibility to presenting bacteremia and its complications, such as sepsis, septic shock or SIRS, allowing its detection and timely treatment. In addition, information on this pathology in great demand in the hospital was updated, and the main characteristics of the patients, the sensitivity and specificity of the biomarkers, and their association with the blood culture results were analyzed.

Materials and methods

Study design

The present study is cross-sectional. The source is prospective.

Scenery

The study was carried out in the internal medicine department of the Hospital de la Sociedad de Lucha Contra el Cáncer (SOLCA) in Guayaquil, Ecuador. The study period was from January 1, 2015, to December 31, 2015.

Participants

Patients of legal age and younger than 65 years with a diagnosis of oncological disease with a diagnosis of SIRS, sepsis, or septic shock were included. Patients with hematological malignancies such as acute and chronic leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma were included, with complete reports of procalcitonin and interleukin-6 values. Cases with incomplete data were removed for analysis. Patients receiving treatment with antibiotics or immunosuppressive drugs at the time of blood collection; patients with severe trauma, severe burns, or recent surgery; patients seen outside the study period; patients with an incomplete clinical history; or patients without procalcitonin laboratory reports were excluded. and serum interleukin-6.

Variables

The variables were the presence of bacteremia, procalcitonin, interleukin, age, sex, and blood culture report.

Data sources/measurements

The source was direct; surveys and measurements were carried out on the patients upon admission to the hospitalization period. Additionally, a review of clinical records was performed.

The information was treated confidentially; no personal data were included to allow the identification of the study subjects.

Biases

To avoid possible interviewer, information, and memory biases, the principal investigator kept the data at all times with a guide and records approved in the research protocol. Observation and selection bias was avoided by applying the participant selection criteria. All the clinical and paraclinical variables of the period above were recorded. Two researchers independently analyzed each record in duplicate, and the variables were recorded in the database once their concordance was verified. Serum PCT levels up to 0.5 ng/ml were considered within the normal range.

Study size

The sample was nonprobabilistic, census type, where all possible cases of the study period were included.

Quantitative variables

Descriptive and inferential statistics were used. The results were expressed on a scale of means and standard deviation. Categorical data are presented in proportions.

Statistical analysis

Noninferential and inferential statistics are used. For the descriptive analysis, measures of central tendency and dispersion were calculated according to the measurement scale of each variable. Qualitative variables are presented as absolute numbers and percentages; quantitative variables are presented as medians and standard deviations.

Inferential analysis: two groups with bacteremia versus the absence of bacteremia are analyzed, a diagnostic test for procalcitonin and interleukin six is performed in each group, and the ROC curve and the area under the curve are presented. The statistical significance level was $P < 0.05$. The statistical package used was SPSS 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp).

Results

Participants

A total of 169 patients participated in the study, 100 controls without bacteremia and 69 cases with positive blood cultures.

General characteristics of the sample

Of the total number of study patients (69), the age group between 41-60 was the most frequent, with 59% (41). The average age was 45.56 years, with a range between 19 and 78 years of age. The male sex predominated at 65% (45), while the female sex represented 35% (24).

A total of 169 patients were studied, of which 69 belonged to the group with true bacteremia and 100 to the group without bacteremia. The bacteremic patients (cases) had

higher serum levels of procalcitonin than the 100 controls with sterile blood cultures (14.643 vs. 0.540 ng/ml, P = 0.0001); similar results were found with the determination of interleukin-6, where higher levels were reported. Elevated values of the biomarker in the group with true bacteremia were 1479.47 vs. 4.37 ng/ml in the group without bacteremia. Significant differences were found when comparing PCT and IL-6 values (P<0.001) between patients with and without bacteremia.

Diagnostic tests

The diagnostic tests are presented in Table 1; IL-6 performed better in the diagnostic tests.

Table 1. Diagnostic tests for the presence of positive blood cultures.

	Blood culture				
	Positive n=69	Negative n=100	Sensitivity	Specificity	Reliability
PCT > 0.5 ng/mL	56 (81.2%)	21 (79%)	81.2%	79%	80%
IL -6 Elevated	68 (98.6%)	5 (5%)	98.6%	95%	96.44%

The ROC curve is presented to determine an appropriate cutoff point for each diagnostic test (procalcitonin and interleukin-6) (Figure 1). The area under the curve (AUC) was calculated (Table 2) for PCT- and IL-6-positive blood cultures individually. Interleukin-6 had a greater area under the curve with a cutoff point of 6.4 pg/ml as the point that had the best balance between sensitivity and specificity. Procalcitonin has a smaller area under the curve than IL-6, with a cutoff point of 5.3 ng/ml as the one with the best balance between sensitivity and specificity.

Table 2. Discriminative power of procalcitonin and interleukin-6 in cancer patients

	Area	typ. error	asymptotic sig	asymptotic 95% CI	
				Lower limit	Upper limit
PCT	0.862	0.031	<0.0001	0.801	0.923
IL-6	0.996	0.003	<0.0001	0.991	1

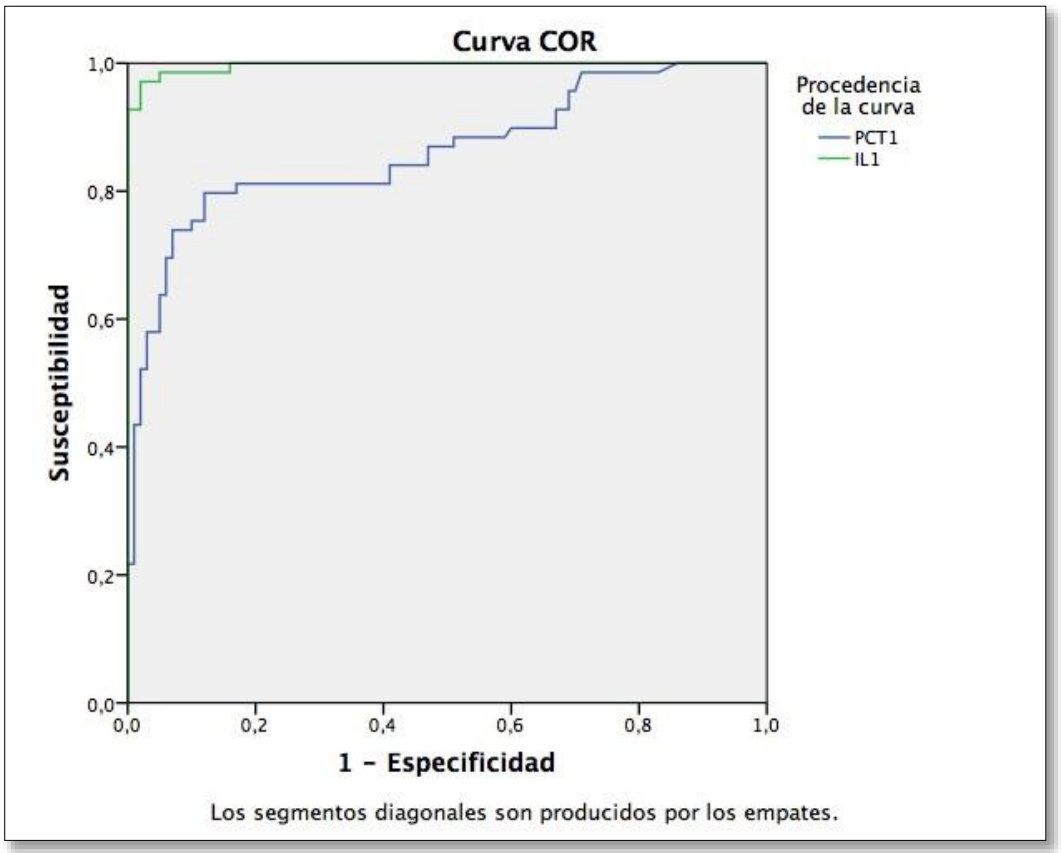
Discussion

When comparing PCT and IL-6 individually and in combination, interleukin-6 was found to be the best predictor of positive blood culture in cancer patients, with a sensitivity of 98.60% and a specificity of 95%. On the other hand, although PCT also showed high sensitivity (81.2%) and specificity (79%), IL-6 is still superior in excluding bacterial sepsis. Therefore, although the early evaluation of bacteremia requires the correlation of interleukin-6 with other laboratory markers such as PCT, IL-6 remains the best biomarker to diagnose or exclude bacterial sepsis in cancer patients.

Despite these promising results with IL-6, other authors, such as Naffaa et al. [3], found that PCT is significantly better than interleukin-6 in predicting positive blood culture bacteraemia since in multivariate logistic regression analysis, only procalcitonin was associated with blood culture positivity (odds ratio, 12.15 (CI 95% 1.29-114.0). The use of

procalcitonin cutoff points of 1.35 and 2.14 ng/mL made it possible to identify 100% and 90% of positive blood cultures. It reduced the need for blood cultures by 47.5% and 57.5%, respectively. Thus, the authors' results demonstrate that compared to IL-6, procalcitonin better predicts blood culture positivity in patients with sepsis and reduces the need for blood cultures in almost half of the patients with sepsis.

Figure 1. ROC curve of sensitivity and specificity of procalcitonin and IL-6.



The results of the present study revealed that interleukin-6 has a greater area under the curve with a cutoff point of 6.4 pg/ml as the point with the best balance between sensitivity and specificity. At the same time, procalcitonin has a lower area under the curve than IL-6, with a cutoff point of 5.3 ng/ml as the one with the best balance between sensitivity and specificity. Previous studies have investigated the utility of using procalcitonin as a positive predictive marker for bacteremia or sepsis with variable results regarding its clinical suitability.

In patients without bacteremia or systemic infections, procalcitonin levels are 0.1 ng/mL or less. With less than 0.1 ng/mL used as the cutoff, procalcitonin had an NPV of 96.3% to rule out bacteremia compared to the gold standard. Liaudat et al. (2013) [4] studied procalcitonin as an early marker of sepsis in a population of 41 hospitalized patients (8% prevalence of bacteremia) and found a high NPV, depending on the cutoff value for procalcitonin level (99% for 0.2 ng/ml and 95% for 0.5 ng/ml). In a study of 300 hospitalized febrile patients, Bossink et al. (2013) [5] reported an NPV of 90% using a cutoff value of 0.5 ng/mL for procalcitonin.

The results of the present investigation demonstrated that using 0.5 ng/ml procalcitonin as the cutoff point, the highest rate of sensitivity and specificity was obtained. With IL-6, with a cutoff point of 6.4 pg/ml, the sensitivity and specificity were higher than those found with procalcitonin, demonstrating greater predictive power for bacteremia. Kim D (2013) [6] determined whether PCT and PCR are good early diagnostic markers for bacteremia in 286 patients with neutropenia. He identified bacteremia in 38 (13.3%) patients. Median PCT (2.8 ng/mL vs. 0.0 ng/mL, *P*< 0.0001) and CRP (15.9 mg/dL vs. 5.6 mg/dL, *P = 0.002)* values were significantly higher in the bacteremia group than in the group without bacteremia.

In this study, the bacteraemic patients (cases) had higher serum levels of procalcitonin than the 100 controls with sterile blood cultures (14.643 vs. 0.540 ng/ml, P =0.0001). Similar results were found with the determination of interleukin- *6,* where higher levels of the biomarker in the group with true bacteremia were 1479.47 vs. 4.37 ng/ml in the group without bacteremia. Significant differences were found when comparing PCT and IL-6 values (P<0.0001) between patients with and without bacteremia. Similar results were reported by Kim D (2013) [6], with mean PCT values (2.8 ng/ml vs. 0.0 ng/ml, *P*= 0.0001) being significantly higher in the group with bacteremia than in the group without bacteremia. In multivariate analysis, elevated PCT (*P*< 0.01) was a diagnostic marker of bacteremia in patients with febrile neutropenia [7-10].

A substantial limitation of the study is the small sample size, attributed to the limited availability of PCT and IL-6 measurements in the hospital. Therefore, the concentrations of both biomarkers were determined once statistical significance was reached. To validate these results, other large-scale prospective studies could be performed in the future.

Conclusions

Interleukin-6 is a good test as a predictor of bacteremia in cancer patients due to its high specificity value and to establish that if you have bacteremia, it is due to its high specificity.

Editor's note

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Abbreviations

IL-6: Interleukin 6.
PCT: Procalcitonin.
PCR: C-reactive protein.

Administrative information

Additional Files

None declared by the authors.

Acknowledgments

Not applicable.

Author contributions

Sergio Rafael Castro Suarez: Conceptualization, formal analysis, research, project administration, original draft writing,
Rafael Caputi Oyague: Conceptualization, methodology, supervision, validation, visualization, writing - review and edition.
All authors read and approved the final version of the manuscript.

Financing

The studies, images, and medicines constituted the regular activity of the service and were not an additional cost for the patients. The authors financed the administrative costs of the research.

Availability of data and materials

Data are available upon request to the corresponding author. No other materials are reported.

Statements

Ethics committee approval

The study protocol was approved by the bioethics committee of the University of Guayaquil, document number CPFCMUG-066-ANTEP, dated June 19, 2017.

Consent for publication

It is not required when images, resonances, or tomographic studies of specific patients are not published.

Conflicts of interest

The authors declare that they have no conflicts of competence or interest.

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