Procalcitonin levels in children with bloodstream infections caused by different species: a cohort study

José Iván Castillo Bejarano
University Hospital "Dr. José Eleuterio González" https://orcid.org/0000-0003-4270-2687
Agustín De Colsa Ranero
Instituto Nacional de Pediatria
Oscar Tamez Rivera
Instituto Nacional de Pediatria
Andrés Guillen Lozoya
Hospital Universitario Dr Jose Eleuterio Gonzalez
Napoleón González Saldaña
Instituto Nacional de Pediatria
Alfonso Huante Anaya
Instituto Nacional de Pediatria
Ismael Herrera Benavente
Universidad Autonoma de San Luis Potosi - Facultad de Medicina
Abiel Mascareñas de los Santos (a_mascarenas@hotmail.com)
https://orcid.org/0000-0002-4057-9526

Research article

Keywords: Procalcitonin; Sepsis; Bacterial sepsis

DOI: https://doi.org/10.21203/rs.3.rs-25485/v3

Abstract

Background: Timely diagnosis and accurate identification of the causative microorganism in sepsis is crucial in order to offer directed treatment and increase survival rates. Previous studies have aimed to identify biomarkers that could potentially predict blood culture positivity in patients with bacteremia; however, most of the research has been performed in adult populations. The aim of this study were to analyze procalcitonin levels in confirmed bloodstream infections by species in children and assess its utility in immunocompromised patients. Methods: We included children who met the diagnostic criteria for sepsis, with PCT levels collected within a 72-hour period prior to obtaining a blood culture. Kruskal-Wallis test was used to compare differences among groups. Receiver-operating characteristic curves were used to evaluate PCT cut-offs. Results: 120 patients were included, mean age of 55 months. Subjects with immunodeficiency mean PCT was 26.68 mcg/L, compared to 8.78 in immunocompetent hosts. Subjects with Gram-negative bacilli (GNB) had the highest mean PCT levels (18.2 ± 34.2). The difference among microorganisms was significant. Sensitivity and specificity were 78% and 53% for Gram-positive cocci, 60.9% and 33.3% for GNB, and 75% with 25% for yeasts. Subgroup analysis showed 87.5% sensitivity and 16.7% specificity of PCT for predicting GNB blood culture in immunodeficiency children. Conclusions: PCT could be considered as a surrogate biomarker in immunocompromised children and a viable tool to differentiate etiology by species. Key words: Procalcitonin; Sepsis; Bacterial sepsis

1. Background

Sepsis is a leading cause of morbidity and mortality worldwide (1). Timely and accurate identification of the causative microorganism is crucial in order to increase survival rates by offering targeted treatment. Previous studies have explored the use of biomarkers that could potentially predict blood culture positivity in patients with bacteremia; however, most of the available evidence has focused on adult populations (1,2).

Procalcitonin (PCT) is a 116-amino acid prohormone synthetized and secreted predominantly by the thyroid C-cells; however, during an infection, any parenchymal tissue is capable of secreting PCT (3-5). High levels of PCT are observed in critically-ill infected patients (7-10). It has been reported that elevated PCT levels predict blood culture-confirmed bacteremia in adults, with a 75% sensitivity and 72% specificity (9). Likewise, a high negative predictive value (95.4%) of normal PCT levels for predicting bacteremia has also been described (10). In addition, PCT may be used as a discriminating tool that differentiates among possible bacterial etiologies, particularly Gram-negative bacilli (GNB) and Gram-positive cocci (GPC) (11). A knowledge gap exists in the diagnostic yield of PCT levels in children with bloodstream infections, particularly in those who are immunocompromised. The objectives of this study were to analyze PCT levels in children with confirmed bloodstream infections and assess their utility for differentiating among bacterial species in immunocompetent and immunocompromised patients.

2. Methods

Medical records of all subjects admitted to the National Institute of Pediatrics (INP) in Mexico City from 2011 to 2018 were reviewed. Subjects younger than 18 years of age who met the diagnostic criteria for sepsis, with PCT levels collected within 72 hours before obtaining a blood culture were included in the analysis. Subjects with polymicrobial blood cultures and/or with the isolation of commensal bacteria (coagulase-negative *Staphylococci*, Gram-positive bacilli, and *Micrococcus* spp) in a single peripheral blood culture were excluded. Blood cultures with commensal bacteria were only included in central line-associated bloodstream infections (CLABSI), and if the same microorganism was documented in two or more peripheral blood cultures. Samples were processed by the automated blood culture system BD BACTEC™. Bacterial identification and susceptibility testing were performed by BD Phoenix™100. PCT levels were obtained using the Thermo Scientific Fisher™ system, with a cut-off value of 0.5 mcg/L.

2.1 Definitions

Sepsis was defined as the presence of systemic inflammatory response syndrome (SIRS) in addition to a documented infection via blood culture according to the Society of Critical Care Medicine(4).Children who met two or more of the following criteria were diagnosed with SIRS: fever ≥38ºC, hypothermia <36ºC, tachycardia > 90 beats per minute, tachypnea >20 breaths per minute, hypocapnia $PaCO_2$ <32 mmHg, and leukocytosis/leukopenia adjusted by age. To avoid the overestimation of infectious episodes, a second infectious event in the same subject was defined as sepsis after a minimum of six days of hemodynamic stability without antibiotics. Patients with immunodeficiencies, including solid organ transplantation, hematopoietic stem cell transplantation (HSCT), primary immunodeficiency, solid tumors, nephrotic syndrome, Down's syndrome, severe malnutrition, hematologic immunodeficiency (i.e. leukemia, hemophagocytic lymphohistiocytosis), and drug-induced immunodeficiency were eligible for inclusion in the study.

2.2 Statistical analysis

For the statistical analysis, a chi-squared test was used to analyze categorical variables. Kruskal-Wallis test was used to compare differences among groups. Receiver-operating characteristic (ROC) curves were used to evaluate PCT cut-offs. Statistical significance was assumed if the null hypothesis could be rejected at $p < 0.05$. Statistical analysis was performed using SPSS v.21 (IBM Corp., USA).

3. Results

3.3 Demographic characteristics

A total of 41,836 blood cultures were obtained from January 2011 to April 2018, of which 5,059 cultures (12.09%) were positive. PCT levels were available for 311 subjects; 191 of these were excluded due to polymicrobial (n=2), contaminated (n=68), and duplicated (n=121) blood cultures. The final sample included 120 subjects with sepsis and documented PCT levels within 72 hours before blood culture collection (Figure 1). The mean age was 55 months, 54% were male, and 44.2% had an immunodeficiency. The mean PCT level was 15.3 mcg/L.

3.4 PCT levels in immunocompromised children.

Mean PCT level in immunodeficient children was 26.68 mcg/L, compared to 8.78 mcg/L in immunocompetent hosts ($p < 0.05$). PCT level distribution is shown in Table 1. The most frequent immunodeficiencies were hematologic (53.8%), primary immunodeficiency (9.6%), and solid tumors (9.6%). Subjects with hematologic immunodeficiency had the highest PCT mean level (31.4 mcg/L), followed by HSCT recipients (16.9 mcg/L); however, no statistical significance was observed.

Table 1 PCT levels by type of immunodeficiency

Type of ID[1,2]	n (%)	Median PCT level (mcg/L)	P value
SOT[2]	2 (3.8)	2.4	**0.15**
PID[2]	5 (9.6)	3.8	
Hematology	28 (53.8)	31.4	
HSCT[2]	2 (3.8)	23.8	
Solid tumor	5 (9.6)	9.3	
Nephrotic syndrome	3 (5.8)	16.9	
Down syndrome	3 (5.8)	1.14	
Severe malnutrition	3 (5.8)	1.9	
Drugs	1 (1.9)	180	

[1)] Kruskal-Wallis analysis

[2)] Immunodeficiency (ID), Primary Immunodeficiency (PID), Solid Organ Transplant (SOT), Hematopoietic Stem Cell Transplantation (HSCT)

3.5 PCT levels by microorganism

Mean PCT levels by microorganisms are shown in Table 2. The most commonly isolated microorganisms were GNB (65.8%), followed by GPC (24.2%) and yeasts (10%). Subjects with Gram-negative bacterial sepsis had the highest mean PCT levels (18.2± 34.2 mcg/L), compared to GPC (13.1 ± 36 mcg/L) and yeasts (1.9 ± 1.69 mcg/L). We found a statistically significant difference in mean PCT levels among the major microorganism groups ($p < 0.001$). The bacteria with the highest PCT mean levels were Beta-hemolytic streptococcus (39.3 mcg/L), *Klebsiella pneumoniae* (28.4 mcg/L), and *Streptococcus pneumoniae* (25.8 mcg/L).

Table 2 PCT levels corresponding to pathogens isolated

Pathogen	n (%)	Median PCT level (mcg/L)	Range
Gram-negative bacteria	**79**	**18.2**	**0.3–243.4**
Acinetobacter spp	3 (2.5)	3.4	0.99–8.16
Burkholderia cepacia	2 (1.7)	0.1	0.09–0.21
Enterobacter cloacae	7 (5.8)	14.2	0.18–45.8
E. coli	18 (15)	16.9	0.26–93.6
Klebsiella spp	25 (20.8)	28.4	0.46–243.4
Salmonella spp	3 (2.5)	13.7	0.43–34.9
Stenotrophomonas maltophiliia	6 (5)	7.9	0.03–40
Pseudomonas aeruginosa	15 (12.5)	15.1	0.33–76.6
Gram-positive bacteria	**29**	**13.1**	**0.03–180**
Enterococcus spp	3 (2.5)	1	0.4–2.2
Staphylococcus aureus	8 (6.7)	0.8	0.7-3
Coagulase negative *staphylococcus*	11 (9.2)	17.3	0.1–180
Staphylococcus lugdunensis	2 (1.7)	5.1	0.03–101
Beta-hemolytic s*treptococcus*	3 (2.5)	39.3	7.3–65
Streptococcus pneumoniae	2 (1.7)	25.8	1.2–50.4
Fungi	**12**	**1.9**	**0.2–5.5**
Candida spp	12 (10)	1.9	0.2–5.5

3.6 PCT sensitivity and specificity by microorganism

ROC curves were used to evaluate the diagnostic efficacy of PCT for predicting a positive blood culture. Using a cut-off value of 0.5 mcg/L, we found a sensitivity of 58% and specificity of 35%, with an area under the curve (AUC) of 0.639 (95% CI, 0.519 – 0.760). Higher values were observed in immunocompromised subjects with 82% sensitivity and 53% specificity (AUC 0.635, 95% CI. 0.457-0.812). Sensitivity and specificity by microorganism group were 78% and 53% for GPC, respectively (AUC 0.581, 95% CI, 0.402-0.761), compared to 60.9% and 33.3% for GNB (AUC 0.640, 95% CI, 0.429 - 0.851). For yeasts, we found a 75% sensitivity and 25% specificity (AUC 0.734, 95% CI, 0.444 - 1).

Subgroup analysis showed an 87.5% sensitivity and 16.7% specificity of PCT for predicting blood culture-demonstrated GNB infection in immunocompromised patients (AUC 0.906, 95% CI, 0.748 – 1), and a 78.8% sensitivity and 22.2% specificity for GPC infection (AUC 0.744, 95% CI, 0.542 - 0.946).

4. Discussion

Although PCT as a biomarker for sepsis has been described in previous studies. current knowledge of PCT levels to predict blood culture results is scarce, especially in children (12-13). A 2015 meta-analysis showed that PCT is highly accurate in differentiating bacterial and viral meningitis in children with 96% sensitivity (12). In our study included 311 consecutive patients, over a 7-year study period, PCT was effective to predict blood-culture results in cases that underwent a sepsis episode, particularly in immunocompromised children.

According to our data, mean PCT levels in cases with GNB infections were significantly higher than those with GPC and *Candida* spp infections. In our study, we found a 75% sensitivity and 53% specificity using PCT as a predictor of GNB infection in children. Previous studies in adults showed similar results (14-16). The median PCT levels in the adult population with GNB infection has been reported in 26.1 ng/ml, 25.1 ng/ml, and 7.47 ng/ml, comparable to our results with an 18.2 mcg/Lvalue (18-20). A previous report in the adult population of Shuhua et al (20), regarding sensitivity and specificity, with an optimal cut-off value of 3.11 ng/mL, led to 63.9% and 93.3% values, respectively. Yan et al (1) and Watanabe et al (17), described a similar sensitivity from GNB infection with 72.5% and 74.5% results, respectively. A subgroup analysis of our study demonstrates87.5% sensitivity using PCT for predicting GNB infection in immunocompromised children (AUC 0.906, 95% CI, 0.748 – 1), this finding has not been reported in children.

The role of PCT as a predictor of GPC in blood cultures, mainly in infections caused by *Staphylococci* was evaluated by Shomali et al, reporting higher mean PCT levels in infections by *S. aureus* compared to coagulase-negative S*taphylococci* (0.85 mcg/L versus 0.26 mcg/L, respectively) (21). In our study when we compare the PCT levels between *Staphylococcus aureus* and coagulase-negative *Staphylococci*, we found higher PCT levels in bloodstream infections by coagulase-negative S*taphylococci* (17.3 vs 0.8 ng/mL), a different result than Shomali et al study. This difference may be attributed to a higher isolation rate of coagulase-negative staphylococci in our hospital.

Studies that analyze PCT levels as a biomarker for invasive fungal infection by *Candida* spp are scarce and show conflicting data (22-25). According to median PCT levels in *Candida* spp infection, a median of 0.6 ng/ml, 0.5 ng/ml, 1 ng/ml and 0.5 ng/ml were reported by Shuhua et al (20), Miglietta et al (26), Oussalah et al (27) and Leli et al (29), respectively. In another work by Thomas-Rüddel et al (18) a higher median of 4.7 ng/ml was described. Consistent with previous studies in the adult population, we report lower PCT levels in fungal infections compared to bacterial events. In a previous study by Cartegiani et al (25), using PCT levels to predict a *Candida* spp bloodstream infection, 86.8% sensitivity was described. These results were similar to our work, with a 75% sensitivity. Although the identification of *Candida*

species was not performed in our study, previous authors have not found any difference regarding PCT levels in infections by different *Candida* species.

Current knowledge of PCT role in immunocompromised children is scarce (30-34). Previous reports in children with cancer showed that PCT is an effective biomarker of sepsis during a fever and neutropenia episode; however, none of them evaluate the role of PCT to predict blood culture results (30,34). We report an 87.5% sensitivity of PCT for predicting blood culture-proven GNB infection, making PCT a useful resource in clinical practice. PCT levels were also increased in different types of immunosuppression. According to mean PCT levels, we found a statistically significant difference between immunocompromised (26.68 mcg/L) and immunocompetent (8.78 mcg/L) children with sepsis ($p < 0.05$). A different result than Al-Nawas B in the adult population.

Our study has several limitations. A prospective design would aid in having better control of the variables and include a larger sample, to avoid heterogeneity of the cases. Likewise, PCT measurements were not serial, which would have allowed us to analyze PCT behavior concerning variables such as time, isolated microorganism, treatment, and outcome.

5. Conclusions

Our study found that PCT could be a viable tool to predict blood-culture proven sepsis, particularly in immunocompromised patients with GNB infection. The use of PCT could be considered as a surrogate biomarker of bacterial infection, and PCT levels could offer a general prediction of the possible microbial etiology (GNB, GPC, and yeasts). Further prospective studies are needed to expand the available evidence on the use of PCT as a predictive value for blood culture-proven by species infection in children.

List Of Abbreviations

PCT - Procalcitonin

GNB - Gram-negative bacilli

GPC - Gram-positive cocci

CLABSI - Central line-associated bloodstream infections

SIRS - Systemic inflammatory response syndrome

HSCT - Hematopoietic stem cell transplantation

ROC - Receiver-operating characteristic

AUC - Area under the curve

Declarations

Ethics approval and consent to participate: The authors confirm our study was submitted to and approved by the Academic Group of the National Institute of Pediatrics, Mexico, with the code: **GA/094/18.** No informed consent was obtained due to the nature of the retrospective data according to the Academic Group of the National Institute of Pediatrics, Mexico. The data used in this study were anonymized before its use.

Consent for publication: Not applicable

Availability of data and materials: Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Competing interests: The authors declare that they have no competing interests

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors´ contributions:CBJIconception and analysis of data; CRA interpretation of the data, TRO analysis, and writing, GLA statistical analysis, GSN design of the work, HAA creation of software used in the work, HBI have substantively revised the work, MSAH work coordination, and analysis.

Authors´information: Not applicable

Acknowledgments: Not applicable

References

1. Yan ST, Sun LC, Jia HB, Gao W, Yang JP, Zhang GQ. Procalcitonin levels in bloodstream infections caused by different sources and species of bacteria. Am J Emerg Med. 2017;35(4):579–83.
2. Liu HH, Zhang MW, Guo JB, Li J, Su L. Procalcitonin and C-reactive protein in early diagnosis of sepsis caused by either Gram-negative or Gram-positive bacteria. Ir J Med Sci. 2017;186(1):207–12.
3. Fran Balamuth, Scott L. Weiss, Mark I. Neuman, Halden Scott, Patrick W. Brady, Raina Paul, Reid W.D. Farris, Richard McClead, Katie Hayes, David Gaieski, Matt Hall S, S. Shah; Elizabeth R. Alpern. Pediatric Severe Sepsis in US Children's Hospitals. Pediatr Crit Care Med. 2014;15(9):798–805.
4. Singer, M. et al., Bellomo R, Bernard GR, Chiche J, Craig M, Hotchkiss RS, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801–10.
5. Hawiger J, Veach RA, Zienkiewicz J. New paradigms in sepsis: From prevention to protection of failing microcirculation. J Thromb Haemost. 2015;13(10):1743–56
6. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: A systematic review and meta-analysis. Clin Infect Dis. 2004;39(2):206–17.

7. Casado Flores J, Blanco Quirós Procalcitonina: un nuevo marcador de infección bacteriana. An Pediatría. 2001;54(1):69–73.
8. Cha JK, Kwon KH, Byun SJ, Ryoo SR, Lee JH, Chung J, et al. Clinical value of procalcitonin for suspected nosocomial bloodstream infection. Korean J Intern Med. 2017
9. Riedel S, Melendez JH, An AT, Rosenbaum JE, Zenilman JM. Procalcitonin as a marker for the detection of bacteremia and sepsis in the emergency department. Am J Clin Pathol. 2011;135(2):182–9.
10. Sager R, Kutz A, Mueller B, Schuetz P. Procalcitonin-guided diagnosis and antibiotic stewardship revisited. BMC Med . 2017;1–11.
11. Díez-Padrisa N, Bassat Q, Morais L, O'Callaghan-Gordo C, Machevo S, Nhampossa T, et al. Procalcitonin and C-reactive protein as predictors of blood culture positivity among hospitalized children with severe pneumonia in Mozambique. Trop Med Int Heal. 2012;17(9):1100–7.
12. Lanziotti VS et al. Use of biomarkers in pediatric sepsis: a literature review. Rev Bras Ter Intensiva. 2016; 28 (4): 472-82.
13. Pontrelli G et al. Accuracy of serum procalcitonin for the diagnosis of sepsis in neonate and children with systemic inflammatory syndrome: a meta-analysis. BMC Infectious Diseases. 2017; 17: 302.
14. Kim MH, Lim G, Kang SY, Lee WI, Suh JT, Lee HJ. Utility of procalcitonin as an early diagnostic marker of bacteremia in patients with acute fever. Yonsei Med J. 2011;52(2):276–81.
15. Liu HH, Zhang MW, Guo JB, Li J, Su L. Procalcitonin and C-reactive protein in early diagnosis of sepsis caused by either Gram-negative or Gram-positive bacteria. Ir J Med Sci. 2017;186(1):207–12.
16. Charles PE, Ladoire S, Aho S et al. Serum procalcitonin elevation in critically ill patients at the onset of bacteremia caused by either Gram negative or Gram positive bacteria. BMC Infect Dis. 2008; 8:38.
17. Watanabe Y; Oikawa N; Hariu M, Fuke R; Seki M. Ability of procalcitonin to diagnose bacterial infection and bacteria types compared with blood culture findings. International Journal of General Medicine. 2016; 9: 325-331.
18. Thomas-Rüddel D et al. Influence of pathogen and focus of infection on procalcitonin values in sepsis patients with bacteremia or candidemia. Critical Care. 2018; 22: 128.
19. Bassetti et al. Comparision between procalcitonin and C-reactive protein to predict blood culture results in ICU patients. Critical Care. 2018; 22.
20. Shuhua Li; Heng Rong; Qinliang G; Yifei C; Zhang G; Jiong Y. Serum procalcitonin levels distinguish Gram-negative bacterial sepsis from Gram-positive bacterial and fungal sepsis. Journal of Research in Medical Sciences. 2016; 21: 39.
21. Shomali W et al. Can procalcitonin differentiate Staphylococcus aureus from coagulase-negative staphylococci in clustered gram-positive bacteremia?. Diagnostic Microbiology and Infectious Diseases. 2013; 76: 158-61.
22. Martini A, Gottin L, Menestrina N, Schweiger V, Simion D, Vincent J-L: Procalcitonin levels in surgical patients at risk of candidemia. J Infect 2010,60(6):425–430.

23. Brodská H, Malíčková K, Adámková V, Benáková H, Sťastná MM, Zima T: Significantly higher procalcitonin levels could differentiate Gram-negativesepsis from Gram-positive and fungal sepsis. Clin Exp Med2012:1–6.
24. Montagna M, Coretti C, Caggiano G: Procalcitonin: a possible marker ofinvasive fungal infection in high risk patients? J Prev Med Hyg 2011,52(1):38.
25. Cortegiani A, Russotto V, Montalto F, Foresta G, Accurso G, Palmeri C, et al. Procalcitonin as a marker of Candida species detection by blood culture and polymerase chain reaction in septic patients. BMC Anesthesiol. 2014;14(1):9.
26. Miglietta et al. Procalcitonin, C-reactive protein and serum lactacte dehydrogenase in the diagnosis of bacterial sepsis, SIRS and systemic candidiasis. Le infezioni in Medicine. 2015; 3: 230-237.
27. Oussalah et al. Diagnostic accuracy of procalcitonin for predicting blood culture results in patients with suspected bloodstream infection. Medicine. 2015; 94 (44): 1-8
28. Leli C, Ferranti M, Moretti A, et al. Procalcitonin levels in Gram-positive, Gram-negative, and fungal bloodstream infections. Dis Markers. 2015;2015:701480.
29. Charles PE, Ladoire S, Aho S et al (2008) Serum procalcitonin elevation in critically ill patients at the onset of bacteremia caused by either Gram negative or Gram positive bacteria. BMC Infect Dis 8:38
30. Fleischhack G, Cipic D, Juettner J, Hasan C, Bode U. Procalcitonin-a sensitive inflammation marker of febrile episodes in neutropenic children with cancer. Intensive Care Med. 2000;26 Suppl 2:S202-11.
31. Fleischhack G, Kambeck I, Cipic D, Hasan C, Bode U. Procalcitonin in paediatric cancer patients: Its diagnostic relevance is superior to that of C-reactive protein, interleukin 6, interleukin 8, soluble interleukin 2 receptor and soluble tumour necrosis factor receptor II. Br J Haematol. 2000;111(4):1093–102.
32. Staehler M, Hammer C, Meiser B, Reichart B (1997) Procalcitonin: a newmarker for differential diagnosis of acute rejection and bacterial infection in heart transplantation. Transplant Proc 29:584-585
33. Al-Nawas B, Shah PM (1996) Procalcitonin in patients with and without immunosuppression and sepsis. Infection 24:434—436
34. Arif T, Phillips RS. Updated systematic review and meta-analysis of the predictive value of serum biomarkers in the assessment and management of fever during neutropenia in children with cancer. Pediatric Blood & Cancer. 2019; 66 (10): e27887.

Figures

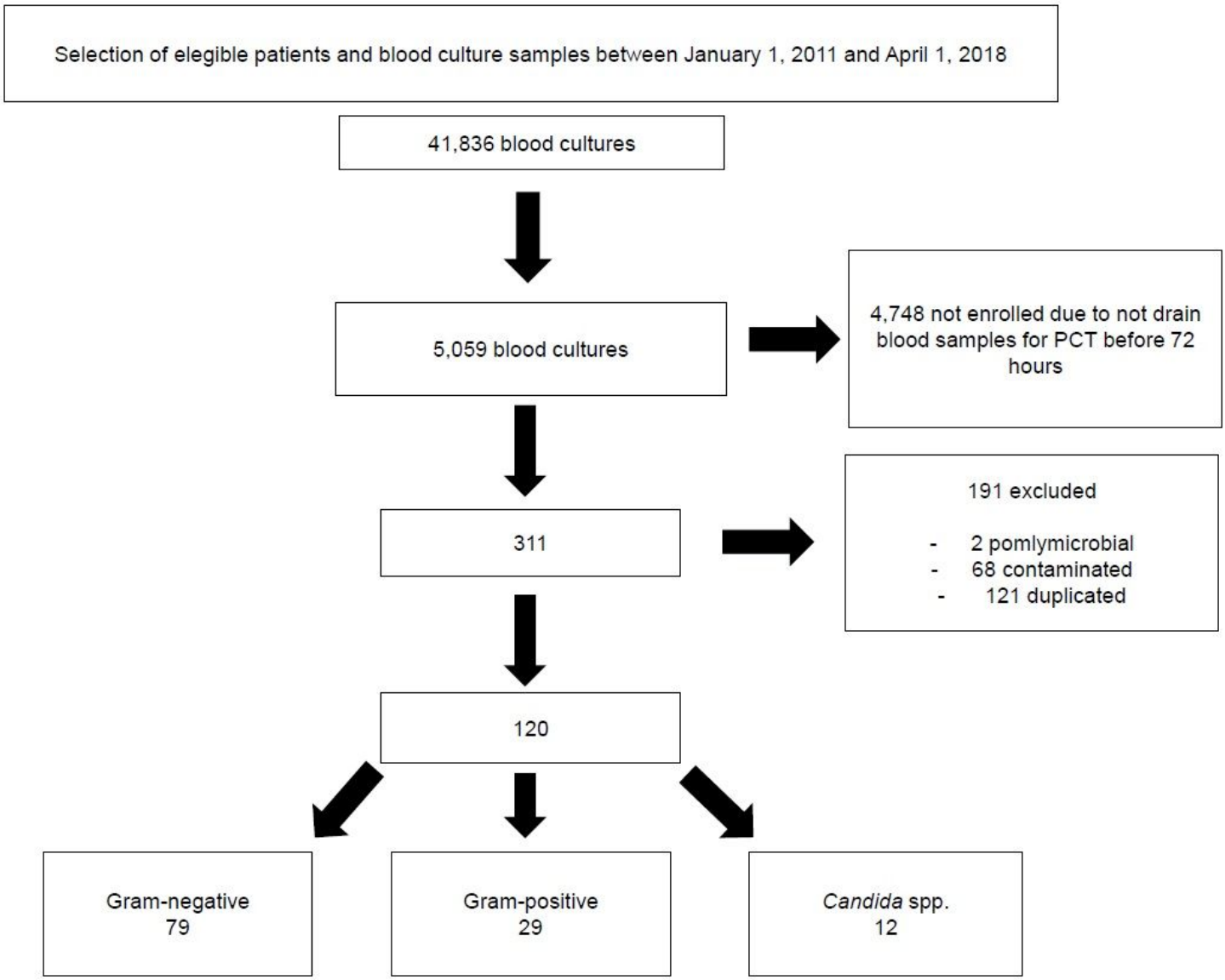

Figure 1

Selection of elegible patients and blood culture samples between January 1, 2011 and April 1,2018

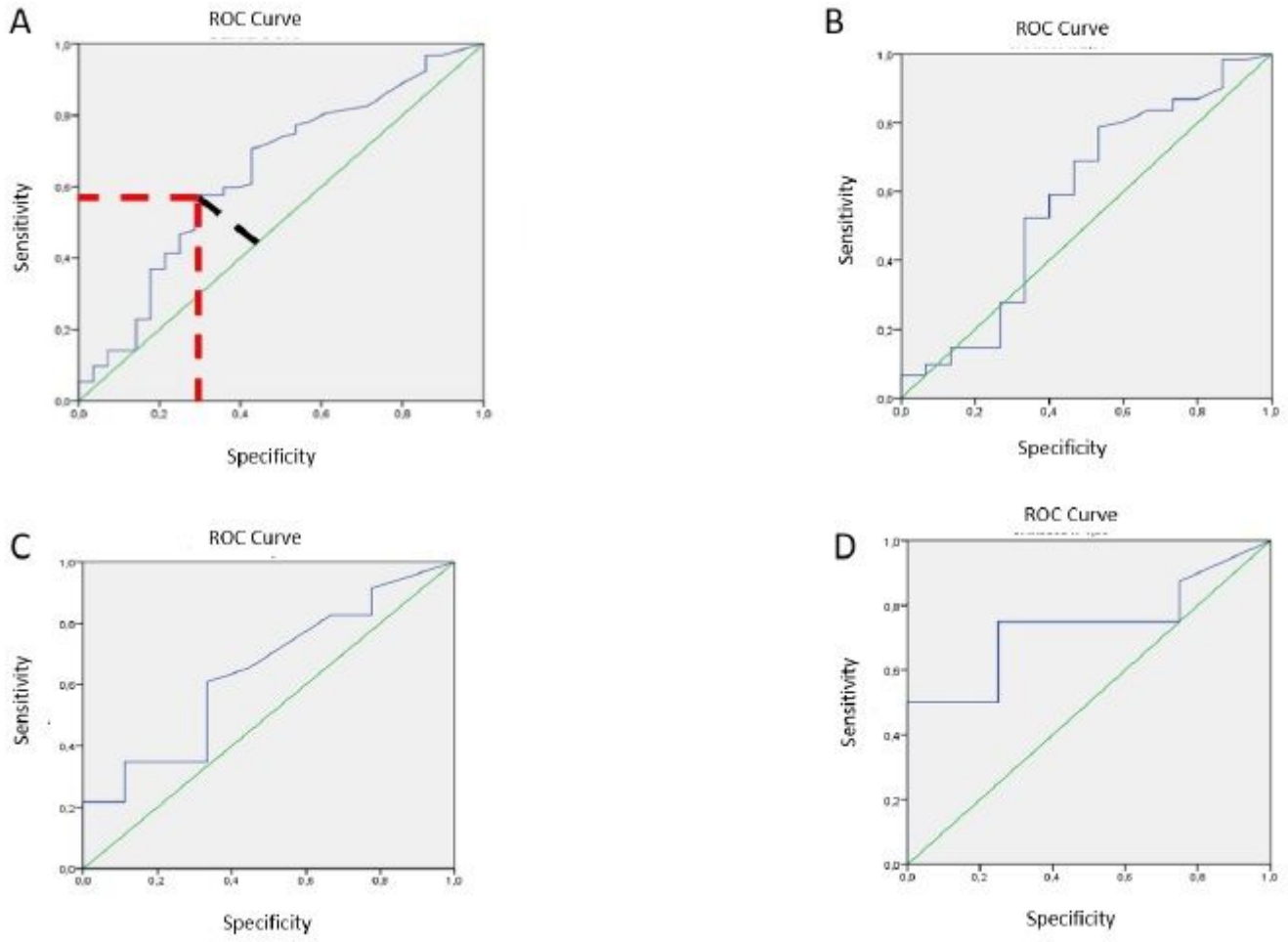

Figure 2

A) ROC curve of PCT, AUC 0.639 (95% CI, 0.519 – 0.760). B) ROC curve of PCT for CGP AUC: 0.581 (95% CI, 0.402 – 0.761). C) ROC curve for BGN, AUC: 0.640 (95% CI, 0.429 – 0.851). D) ROC curve for molds, AUC: 0.734 (95% CI, 0.444 – 0.1).