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

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Research article

Keywords: Procalcitonin; Sepsis; Bacterial sepsis

Posted Date: April 30th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-25485/v1

Abstract

Background: Timely diagnosis and accurate identification of the causative microorganism in sepsis is crucial in order to offer targeted 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 aims of this study were to analyze procalcitonin (PCT) levels in confirmed bloodstream infections by species in children and assess their utility in immunocompromised patients.

Methods: Medical records of children younger than 18 years admitted from 2011 to 2018 were reviewed. Subjects who met the diagnostic criteria for sepsis, with PCT levels collected within a 72-hour period prior to obtaining a blood culture were included. Kruskal-Wallis test was used to compare differences among groups. Receiver-operating characteristic curves were used to evaluate PCT cut-offs.

Results: A total of 120 patients were included. Mean age was 55 months. Mean PCT levels in immunosuppressed patients was 26.68 mcg/L, compared to 8.78 in the immunocompetent group. Subjects with bacteremia by Gram-negative bacilli (GNB) had the highest mean PCT levels (18.2 ± 34.2) ($p < 0.001$). Sensitivity and specificity were 78% and 53% for Gram-positive cocci (GPC), 60.9% and 33.3% for GNB, and 75% and 25% for yeasts, respectively. Subgroup analysis showed 87.5% sensitivity and 16.7% specificity of PCT for predicting documented GNB bacteremia in immunodeficient children.

Conclusions: PCT may be considered as a surrogate biomarker in immunocompromised children, and a viable tool to differentiate etiology by species.

1. Background

Sepsis is a leading cause of morbidity and mortality in the pediatric population (1). Timely diagnosis and accurate identification of the causative microorganism is crucial in order to offer targeted 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 (1, 2).

Procalcitonin (PCT) is a 116-aminoacid prohormone synthetized and secreted by the thyroid C-cells (3–5). High levels of PCT are observed in critically ill infected patients (7–10). It has been reported that PCT levels higher than 3.61 ng/mL predict blood culture-confirmed bacteremia in adults, with a 75% sensitivity and 72% specificity (9). Likewise, previous studies have described a high negative predictive value (95.4%) of normal levels of PCT for predicting bacteremia (10). Furthermore, it has been suggested that PCT levels could be helpful in differentiating among bacterial species in adults, with Gram-negative bacilli (GNB) causing a greater increase of PCT levels compared to Gram-positive cocci (GPC) (11). The objectives of this study were to analyze PCT levels in confirmed bloodstream infections by species in children and assess their utility in 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 a 72-hour period prior to obtaining a blood culture were included in the analysis. Subjects with polymicrobial blood cultures and/or with 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. SIRS was defined according to the Society of Critical Care Medicine (4). Subjects 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. In order to avoid 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, 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 a 72-hour period before blood

culture collection (Fig. 1). Mean age was 55 months, 54% were male, and 44.2% had an immunodeficiency. 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 microorganism 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 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

The current knowledge about PCT as a biomarker for sepsis in children has been described in previous studies (12–13). Elevation of PCT levels usually occurs earlier during the course of infection, even before the elevation of other biomarkers, peaking at 24–36 hours (12). Pontrelli et al (13) showed a moderate accuracy for the diagnosis of sepsis in neonates with a PCT cut-off of 2.0-2.5 ng/mL (14). A 2015 meta-analysis showed that PCT is highly accurate in differentiating bacterial and viral meningitis in children with 96% sensitivity (12). PCT leves in blood culture positivity by different microorganism groups in children is scarce, especially in immunocompromised hosts.

Our results show a statistically significant difference between mean PCT values for each microorganism group. Mean PCT levels in children with GNB infections were significantly higher than those with GPC and fungal infections. These findings are consistent with previous studies performed in adults (14–16). Yan et al (1) reported a 72.4% sensitivity and 51% specificity of PCT as a predictor of blood culture positivity in adults, using a 0.495 mcg/L PCT cut-off value. Watanabe et al (17), reported a 74.5% sensitivity and 59.1% specificity of PCT for predicting blood culture-proven bacteremia. In our study we found a 75% sensitivity and 53% specificity of PCT as a predictor of GNB infection, using a PCT cut-off value of 0.5 mcg/L.

Thomas-Rüddel et al (18) reported a median PCT significantly higher in GNB compared to GPC (26 ng/ml vs 7.1 ng/ml, $p < 0.001$). The AUC in the ROC analysis was 0.69 (0.67–0.72) for differentiating GNB from GPC or candidemia, and 0.73 (0.71–0.74) for the prediction of GNB compared to all other blood culture results. Bassetti M et al (19), reported similar findings with a median PCT concentration of 25.1 ng/ml in GNB bacteremia compared to 8.9 ng/ml in GPC. The AUC was 0.7 (0.62–0.77) among GNB and 0.46 (0.39–0.53) among GPB. In a previous study, Shuhua et al (20) found a median PCT level of 7.47 ng/ml in GNB compared to 0.48 ng/ml in GPC. An optimal cut-off value of 3.11 ng/mL for PCT in discriminating GNB sepsis from fungal sepsis, led to a sensitivity of 63.9% and specificity of 93.3%.

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 we found higher PCT levels in bloodstream infections by coagulase-negative s*taphylococci* (17.3 vs 0.8 ng/mL). This difference may be attributed to a higher isolation rate of coagulase-negative staphylococci in our hospital.

Studies that analyze PCT as a biomarker for invasive fungal infection by *Candida* spp are scarce and show conflicting data (22–25). In our study, mean PCT levels in *Candida* spp infections were 1.9 mcg/L, with a 75% sensitivity and 25% specificity. Previous studies by Cortegiani *et al* (25) report higher sensitivity and specificity of PCT for predicting fungal infection by *Candida* spp, with 86.8% and 87.4% respectively. Identification of *Candida* species was not performed in our study; however, previous authors

have not found any difference regarding PCT levels in infections by different *Candida* species. Thomas-Rüddel et al (18) reported a median PCT level of 4.7 ng/ml, compared to 2.1 ng/ml by Bassetti et al (19). Median PCT levels 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. Consistent with previous studies, we report lower PCT levels in fungal infections compared to bacterial events (26). It has been suggested that fungal infections could trigger an alternate inflammatory response route that does not involve PCT, explaining its modest rise.

Studies on PCT in immunocompromised patients are scarce (30–34). A recent systematic review and meta-analysis in children with chemotherapy-induced neutropenic fever showed that PCT levels > 0.5 ng/mL have a 67% sensitivity (CI 0.53–0.79), and 73% specificity (CI 0.66–0.77) for predicting microbiologically defined infections (34). In our study 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 ($p < 0.05$). We also 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.

Our study has several limitations. A prospective design would aid in having better control of the variables and include a larger sample. Likewise, PCT measurements were not serial, which would have allowed us to analyze PCT behavior in relation to 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 in order 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 was anonymized before its use.

Consent for publication: Not applicable

Availability of data and materials: Data sharing is not applicable 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: CBJI conception and analysis of data; CRA interpretation of the data, TRO analysis and writing, GLA statistical analysis, GSN design of the work, HAA creation of a software used in the work, HBI have substantively revised the work, MSAH work coordination and analysis.

Authors´ information: Not applicable

Acknowledgements: Not applicable

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Figures

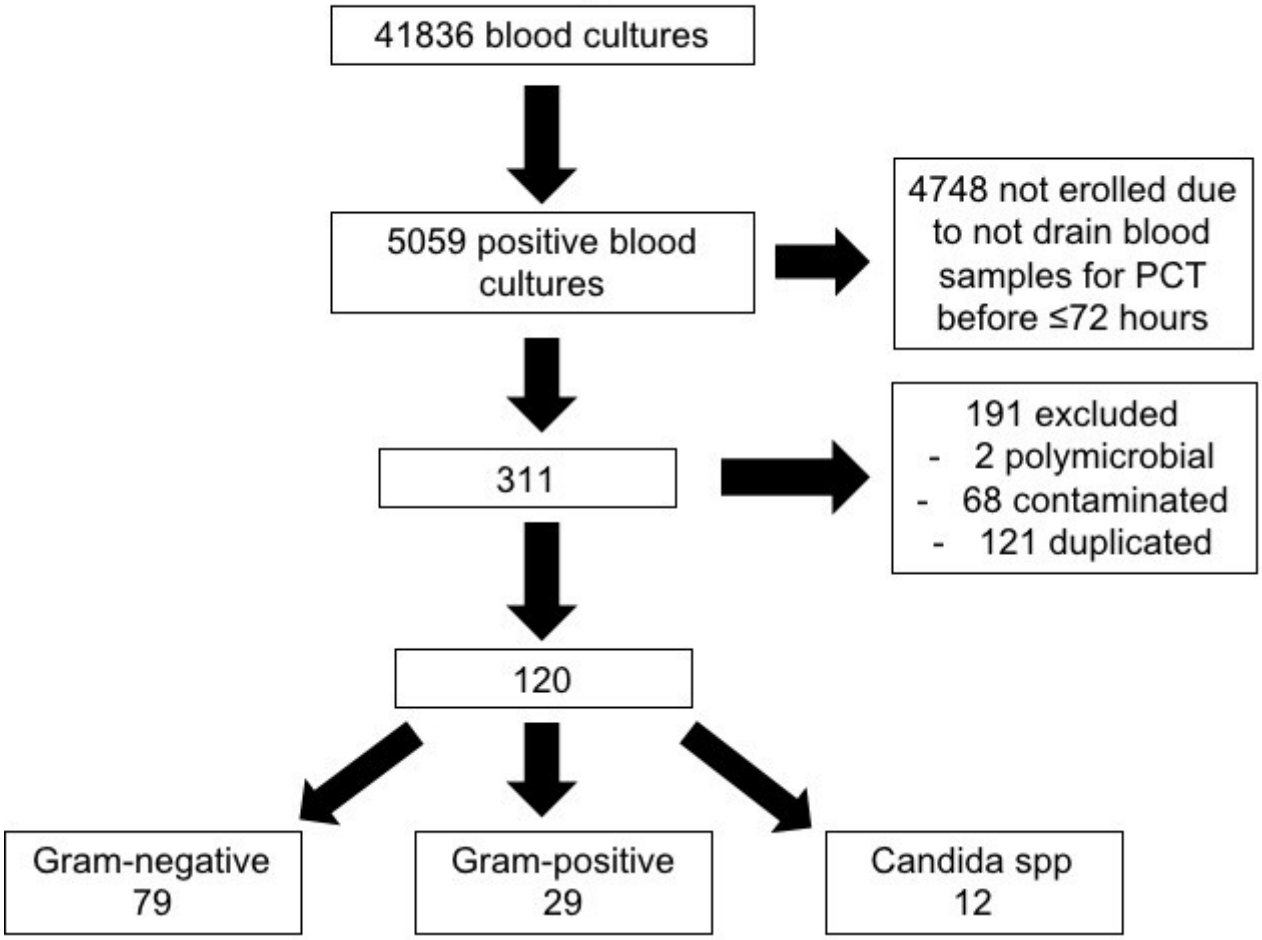

Figure 1

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

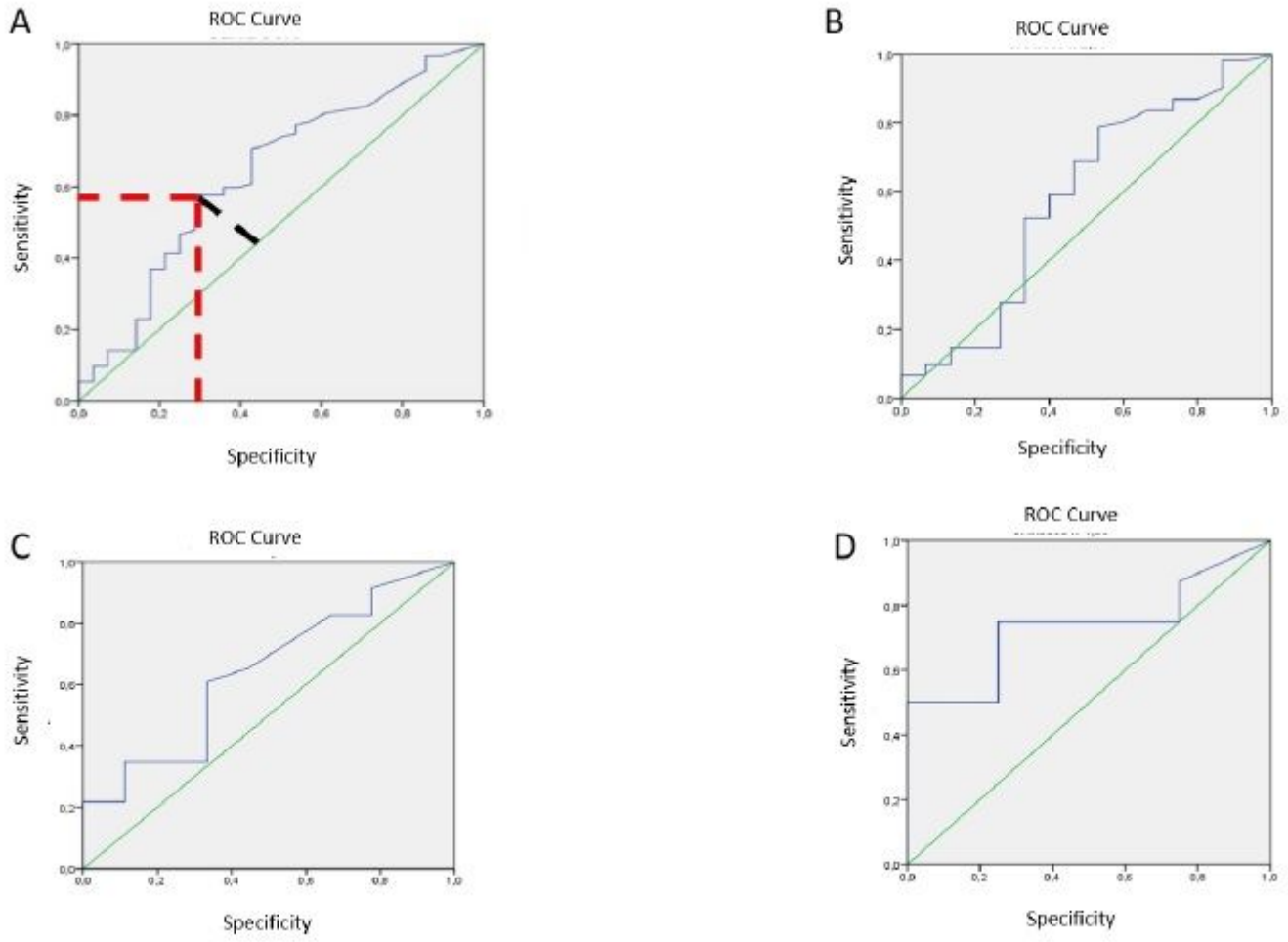

Figure 2

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).