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Is procalcitonin correctly used in medical and surgical departments only in cases with severe bacterial infections? Correlations with the severity scores used in the ICU.

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Abstract

The use of procalcitonin (PCT) in the diagnosis of severe bacterial infections has been tested and proven by numerous international studies. We intend to evaluate how PCT is used in patient admission in various medical and surgical departments and the correlations between PCT and severity scores used for patients in critical state. The death rate correlated with the PCT values above 10 ng/ml and thrombocytopenia, APACHE II score and with a mean SOFA score of 8. For a cutoff value of 0.5 ng/ml in our study the sensitivity of the PCT was 86% with 91% specificity. Placing PCT in a key step in the schemes of the management of patients suspected of sepsis is an important factor in determining the strategy that should be followed, the antibacterial and immunological therapy and the treatment costs implication. Procalcitonin remains so far the best pro-inflammatory marker used in the management of patients with severe bacterial infections.

Keywords: Severe bacterial infections, Sepsis, Procalcitonin, C-reactive protein.

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Abbreviations: PLT: Platelets; CRP: C-reactive protein; OR: Odds Ratio; ICU: Intensive Care Unit.

Introduction

The use of procalcitonin (PCT) in the diagnosis of severe bacterial infections has been tested and proven by numerous international studies. In this study we intend to evaluate how PCT is used in patient admission in various medical and surgical departments and the correlations between PCT and severity scores used for patients in critical state. Based on this idea, we conducted a prospective observational study, from January 2008 to December 2013, in which we have enrolled all patients in whom the PCT serum level has been determined. The study was conducted in the Academic Emergency Hospital Sibiu, Romania, where 406 patients were enrolled. We analyzed the motivation for the PCT determination, the initial diagnosis, the presumption of severe bacterial infection, the PCT correlations with the presumptive diagnosis, the values of other proinflammatory markers, and the correlations of the studied markers and the evolution of confirmed cases with the sepsis.

Materials and Methods

The study focused on 406 patients who were hospitalized between January 2008 and December 2013, patients in whom the PCT value was determined at the time of admission or later during hospitalization. The PCT level detection was decided in the absence of a protocol for the use of this test in an effort to determine whether the antibiotic therapy should be initiated and to differentiate bacterial infections from other infectious or noninfectious causes responsible for the clinical picture. The PCT levels were determined using the immuno-chromatographic assay for the semi-quantitative detection of PCT through the BRAHMS PCT-Q system developed by Thermo Scientific; the tests are quick, with an incubation period of 30 minutes, requiring no calibration or other measuring devices. The test uses a monoclonal mouse anti-catacalcin antibody conjugated with colloidal gold (tracer) and a polyclonal sheep anti-calcitonin antibody (solid phase). The PCT values were compared to the values of other usual markers (WBCs, C-reactive protein, erythrocyte sedimentation rate, and fibrinogen) considering the value of $\geq$ 0.5 ng/ml as significant for initiating or continuing antibiotic administration.

The collected data was processed in Microsoft Excel 2013 and then statistically analyzed using IBM SPSS, version 19. The quantitative variables were expressed as a mean ± SD (standard deviation) or as a median. The qualitative variables were summarized numerically and as percentage. The quantitative variables were compared using the Student`s t-test or the chi-square test. We also performed comparisons between variables

using Kruskal-Wallis test. For each correlation that was made, the Pearson's r-value and the Sig. (2-tailed) value were determined. To assess the association between two variables (an exposure and an outcome) the odds ratio was also measured. We used the Kaplan-Meier analysis for the survival rate at 30 days and the ROC curve (Receiver operating characteristic) for sensitivity and specificity of PCT. Overall, $p<0.05$ was considered significant.

Results and Discussion

From the 406 patients that were included in our study, 210 were male patients (51.7%) and 196 (48.3%) female patients with a sex ratio (males to females) of 1.07.

The most common diagnosis to require a PCT dosage was the hematological malignancy associated with fever in 95 patients (23.39%), followed by sepsis, 53 (13.05%), acute bacterial pneumonia with or without suspicion of sepsis 17 (4.18%) cases. 17 cases with fever syndrome, 14 cases (3.44%) with anemic syndrome in context of fever and infective endocarditis, respectively, and 5 cases of renal abscess. The remaining diagnoses of the samples to have been referenced to the laboratory did not suggest the existence of any infection, such as: cardiovascular disease in 25 cases, 21 cases with acute pancreatitis, 7 cases with malignant tumors, 15 cases with the diagnosis of surgery or major trauma, end-stage renal disease and prematurity or fetal distress each in 9 cases, osteoarthritis is 7 cases, collagen-related diseases in 6 cases, acute kidney failure in 3, liver failure in 2 cases and one case with acute pulmonary edema, prostate adenoma, operated renal tumor, cerebral hematoma, congestive heart failure, cardiogenic shock, renal transplant rejection, ruptured abdominal aortic aneurysm and hemoperitoneum, respectively. 78 requests were not associated with a diagnosis when the samples were sent to the laboratory.

227 samples (55.9%) had values of the PCT <0.5 ng/ml, 80 patients (19.7%) between 0.5 and 2 ng/ml, 65 patients (16%) between 2 and 10 ng/ml and in only 34 patients (8.37%) the levels of PCT were recorded >10 ng/ml. Of all the cases investigated, 179 patients (44.08%) had levels of procalcitonin ≥ 0.5 ng/ml and associated the presence (probable or documented) of infection together with systemic manifestations of infections [1], therefore, they were diagnosed with sepsis.

The primary site of infection was the respiratory system in 51 patients (28.49%), followed by the gastrointestinal tract - 48 cases (26.81%), 28 cases (15.64%) presented the primary site of infection the skin or the soft tissues and for 14 cases (7.82%) the diagnosis of urosepsis was confirmed. For 4 cases the starting point was uterine and in 34 cases the initial site of the infection could not be ascertained. Our data are similar to the ones published in the literature excepting for the urinary starting point of the infection, which is most often the 3rd possible cause of sepsis, followed by skin or soft tissue. Figure 1 presents the cases related to the source of infection, data compared with other data from 4 different studies [2-5], in which Maxim is the maximum number of patients for which that source was found in the 4 studies, Minim is the minimum number found in the studies and Median represents the median number of cases in our study.

In terms of etiology, in 74 cases (41.34%) the microbial agent was identified either from blood cultures, bacteriological examination of the sputum or urine culture, most frequently *Acinetobacter baumannii* being isolated in 20 cases, followed by *Enterococcus* spp. (*E. faecalis* and *E. faecium*) in 16 cases, 14 cases with *Enterobacter* spp., 6 cases with *Escherichia coli*, 8 cases with *Klebsiella pneumoniae*, 4 cases with *Streptococcus* spp. and 6 cases with *Staphylococcus aureus*. In 25 cases (13.96%) an association of bacteria in terms of etiology was identified (*Acinetobacter* spp. + *Enterobacter* spp., *Acinetobacter* spp. + *Staphylococcus aureus*, *Enterococcus* spp. + *Klebsiella pneumoniae*, *Enterobacter* spp. + *Pseudomonas aeruginosa*). *Candida* spp. was responsible for 10 (5.58%) cases. For 70 cases (39.12%), no etiological agent was able to be identifiable from the biological products to have been harvested.

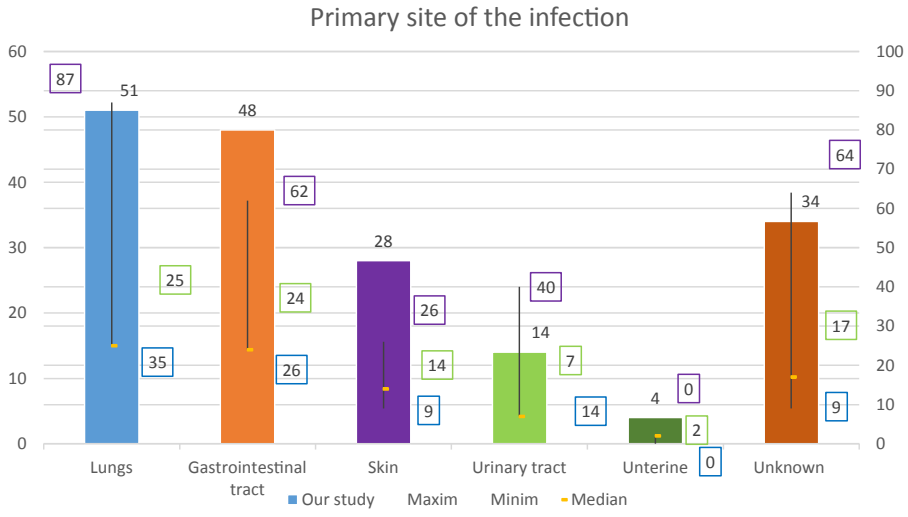

***Figure 1**: The primary site of the infection in sepsis*

Diagnosing sepsis using the PCT serum level of ≥ 0.5 ng/ml was most commonly used in the Intensive Care Unit - 85 patients (47.48%) followed by the Hematology Department - 27 patients (15.08%) and the Neonatal Intensive Care Unit - 9 cases (5.02%).

Of these cases, 50 patients (27.93%) were diagnosed with septic shock, 57 (31.84%) with severe sepsis and 72 (40.22%) with sepsis.

Analyzing the PCT serum levels as compared to the other serum markers in patients with sepsis versus patients without sepsis, we obtained the following data, which are presented in Table 1.

From the initial study group (n=406), 35.18% of patients had thrombocytopenia (PLT ≤ 150000 /mm^3) and 10.18% had thrombocytosis (PLT ≥ 400000/mm^3). The lowest count for PLT that was determined was 0/mm^3 and the highest was 840000/mm^3.

From the group of patients with sepsis 67 (37.43%) had thrombocytopenia (PLT ≤ 150000/mm^3) and 23 (12.84%) had thrombocytosis (PLT ≥ 400000/mm^3). The lowest value determined was 66/mm^3 and the highest was 840000/mm^3. 6 patients had platelet counts above 650000/mm^3, three of them being hematological patients.

From the patients with thrombocytopenia, 26 had a serum level of PCT above 2 ng/ml and 20 of them more than 10 ng/ml. Thrombocytopenia was statistically correlated with the increased levels of PCT (p=0.037) and more frequently corresponded to the cases with severe sepsis or septic shock. For this hypothesis the Pearson's r-value was 0.41. There is a positive correlation between the two variables with a reasonable strength of association (a moderate uphill, positive, relationship).

Decreased platelet counts were associated with serum levels of PCT ≥ 0.5 ng/ml, a statistically significant correlation with a p=0.038. There is a weak downhill (negative) linear relationship with an r-value of -0.25 between the two variables. An OR of 2.09 suggests that decreased platelets count is associated more frequently with increasing levels of PCT. An association between the

***Table 1**: Base line characteristics of the two groups (patients with sepsis and without sepsis)*
Level 1: PCT=0.5 ng/ml, 2: PCT=0.5-2 ng/ml, 3: PCT=2-10 ng/ml, 4: PCT>10 ng/ml.

Characteristic	Value				Mean		Median		Standard deviation ±		p-value
	minimum		maximum								
	NS	S	NS	S	NS	S	NS	S	NS	S	
Hematocrit (HCT)	10.3	15.3	71.2	54	36	33.29	35	32.3	7.25	7.06	np
No. of erythrocytes (mil/mm^3)	1.25	1.67	8.5	5.24	4.07	3.63	4.08	3.58	0.949	0.94	0.09
Hemoglobin (HGB, mg/dl)	3.6	5.3	21.2	19.5	11.9	11.02	11.9	10.8	2.07	3.05	np
Platelets /mm^3	0	66	527000	840000	236506	207258	223000	171000	126523	166599	0.038*
Leukocytes /mm^3	750	1540	45500	39790	9236	14538	7750	13090	6145	8647	L↑ 0.00 L↓ 0.86
Neutrophils /mm^3	269	200	21617	38430	5950	10651	4480	9311	4775.35	7285	0.00
Monocytes /mm^3	0	0	4340	3640	749	973	669	781	620	781.58	np
Eosinophils /mm^3	0	0	1130	2380	115	159	48	39	173.017	357	np
Basophils /mm^3	0	0	203	203	18	18	10	10	27	30.11	np
Lymphocytes	0	0	6400	6400	1694	1502	1450	1210	1212.9	1197.11	↓ 0.69
ESR mm/h	2	1	147	136	57	67	53	61	39	32.84	0.046
CRP mg/l	1	0.3	420	369	85	159.38	48	123	97	108	0.00
Fibrinogen mg/dl	145	100	736	775	392	488	375	514	117	155.95	0.00

*S=septic patients, NS=non-septic patients, *p*= for an α hypothesis and an increased level of PCT;* p=0,038 for the decreased number of platelets associated with a elevated level of PCT, np= the *p* value for this characteristic was not measured because that characteristic was not considered as an hypothesis and to be associated with an increased level of PCT; L= leukocytes; L↑ >9000/mm^3 L↓ <4000/mm^3;

number of erythrocytes (both decreased and increased) and serum levels of PCT has not been demonstrated in our study (p=0.09); we have issued this hypothesis because we noticed that anemia was present in some of the patients with sepsis. The increased number of leukocytes correlates statistically with the increasing level of PCT (p=0.00), which was already known; also for this hypothesis an OR of 6.99 suggests that leukocytosis is associated with increased levels of PCT. An r-value of 0.82 suggests that there is a positive correlation between the two variables (an increased number of leukocytes and PCT) with a strong strength of association (a strong uphill, positive, linear relationship). In our study a decreased number of white blood cells does not correlate with increased serum level of PCT (p=0.86). The OR of 1.06 suggests that leukopenia is more frequent (with 6% more often) in patients with sepsis. Pairing neutrophilia over 80% of white blood cells and increased PCT levels correlates statistically (p=0.00, r-value of 0.80 that suggests a strong uphill, positive, linear relationship and an OR = 3.03). Increased erythrocyte sedimentation rate (ESR) is often associated with the increased levels of PCT (p=0.046), with an r-value of 0.39 (that suggests a moderate uphill, positive relationship) and an OR of 2.97.

The level of the C-reactive protein and fibrinogen has also been statistically analyzed; the increase level of PCT correlates from a statistical point of view with an increased level of this markers (p=0.00), with an OR of 18.41, respectively 4.46 and an r-value of 0.80, respectively 0.50. The increase of the CRP and fibrinogen does not involve the increase of the PCT while the increase of PCT involves increasing fibrinogen and C-reactive protein. There is a positive correlation between the increased PCT level and an increased level of CRP with a strong strength of association. There is also a correlation between the increased PCT level and an increased level of fibrinogen with a moderate uphill (positive) relationship.

For the patients with sepsis, the lowest value of leukocytes was 1540/mm^3 and the highest value was 39790/mm^3; the neutrophil count ranged between 200/mm^3 and 38430/mm^3.

The distribution level of CRP, ESR and fibrinogen is done on a large beach except for a hiatus of values for the fibrinogen and ESR levels between 110-160.

In assessing the severity and the death rate in our study, we used the APACHE II score. For the patients with serum PCT levels ≥ 10 ng/ml. APACHE II scores ranged from 18 to 46 points and the possible risk of death between 20.5%-96.1%.

For the patients with serum PCT levels between 2-10 ng/ml, APACHE II score ranged from 15 to 30 points and the possible risk of death between 21% and 76%. There are clear differences between the severity of cases and the risk of death in patients with serum PCT levels ≥ 10 ng/ml and those with serum PCT levels of 2-10 ng/ml.

For the patients with serum PCT levels between 0.5-2 ng/ml, the APACHE II score ranged from 18 to 26 points and the possible risk of death between 21.2% and 59.7%. Most patients in this group were hospitalized in the Cardiology ward, their diagnosis requiring determining the PCT level of infective endocarditis.

For the patients with serum PCT levels of 0.5 ng/ml, APACHE II score ranged between 9 and 21 points and the possible risk of death was within the range of 9.9% and 38.9%. Associating with PCT the APACHE II score, we can say that the serum procalcitonin provides indirect information about the severity and risk of death of the patient.

Overall, the severity score ranged from 9 to 46 points and possible risk of death between 9.9% and 96.1% with an average of 27.5 points (Figure 2).

The rate of death recorded in patients with thrombocytopenia and a PCT level >10 ng/ml was 45%. Among the patients with thrombocytopenia and a PCT level above the normal value, the death rate was 23.40%, accounting for 11 deaths, patients aged over 57 years with an average age of 66.5 years.

The analysis of the clinical parameters on subgroups highlights no differences in the severity of sepsis, except in patients with a serum PCT levels over 10 ng/ml, with an average SOFA score of 8.

We also noticed that the serum PCT levels increase with the severity of sepsis and` with the occurrence of organ failure that can be used for identifying the patients with a high risk or a guarded prognosis (Table 2 and APACHE II score) without being able to improve the death rate in these cases, as it was also demonstrated in other studies [6,7].

In addition to the pathology for which the patients were hospitalized (sepsis, severe sepsis and septic shock), most patients had a background disorder as well. The Charlson Comorbidities score, which analyzes the risk of death for a period of 10 years for the patients with sepsis, showed values ranging from 1 to 12 points.

The estimated death rate was evaluated using the Kaplan Meier statistical analysis based on the serum

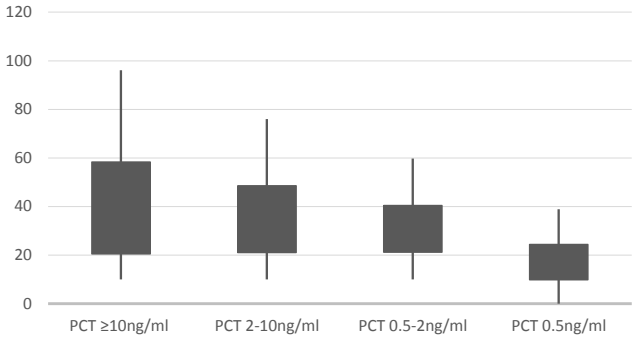

***Figure 2**: Graphic representation of the APACHE II score and the PCT level*

***Table 2** : Vital signs at admission in patients with sepsis*

Vital sign	
BP_S the lowest value (mean ± SD), mm Hg	67 ± 18
HR the highest value (mean ± SD), beats per minute	122 ± 37
RespR the highest value (mean ± SD), breaths per minute	31 ± 12
Temperature the highest one (mean, interval), t°C	38.1 (36.4-39.7)
The lowest level of oxygen saturation (SpO_2) ± SD, %	92.6 ± 6.6
SOFA score (median, interval)	6 (2-11)

BP_S= systolic blood pressure, HR= heart rate, RespR= respiratory rate, SOFA= Sequential Organ Failure Assessment Score

levels of procalcitonin, the C-reactive protein serum level, the age and type of disease of the patients who had been hospitalized.

From the total number of patients with sepsis (n=179), 43 patients died (24.02%).

There are significant differences between the death rate and the serum levels of procalcitonin (Figure 3), the death rate for the serum PCT levels of 0.5 ng/ml was 12.19%, for PCT of 0.5-2 ng/ml it was 10%, for PCT 2-10 ng/ml it was 44.11% and for PCT >10 ng/ml the death rate was 47.05%.

From the total number of patients without sepsis (n=227), 19 patients died during the hospitalization period,

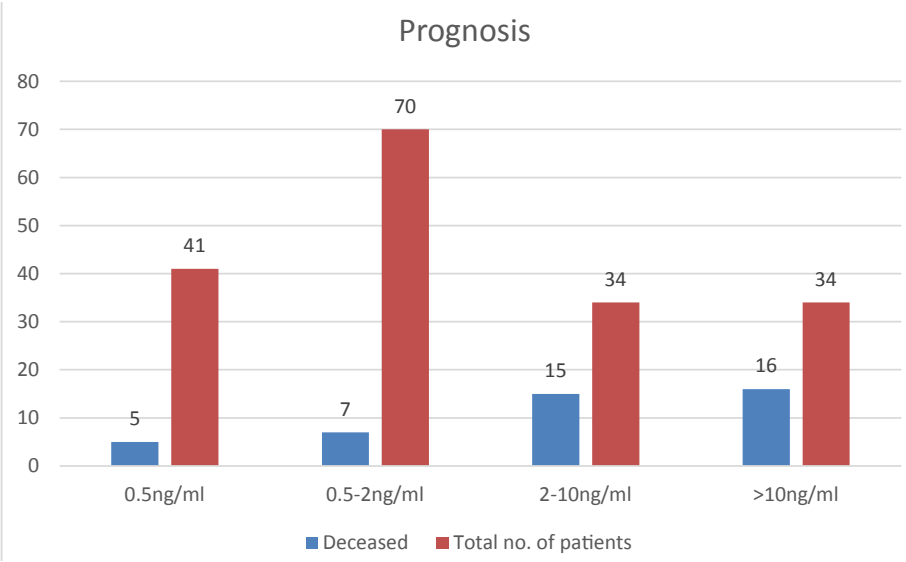

***Figure 3**: Graphic representation of the prognosis of patients with sepsis according to the PCT serum levels*

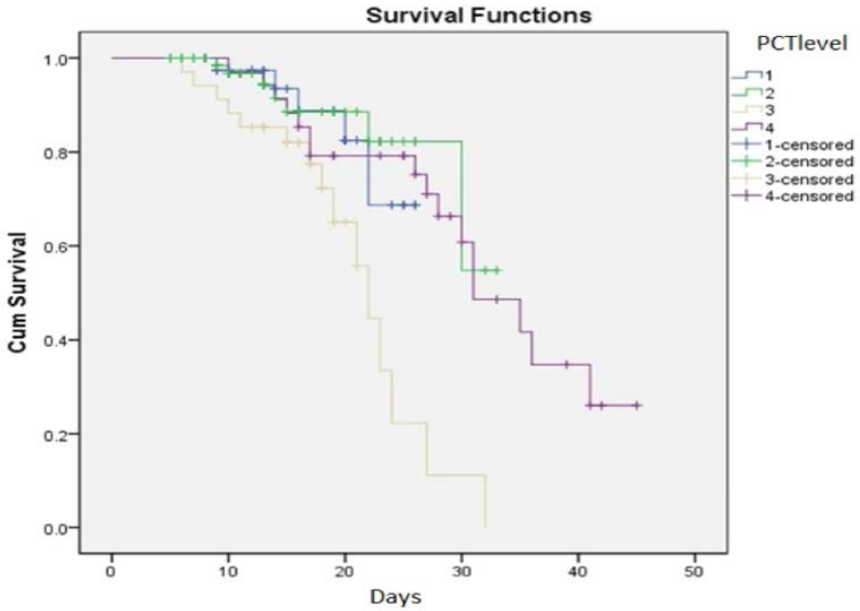

***Figure 4**: The Kaplan-Meier survival rate analysis within 55 days.*
*And add as a legend: *serum PCT level: 1: PCT 0.5ng/ml, 2: PCT 0.5-2ng/ml, 3: PCT 2-10ng/ml, 4: PCT>10ng/ml*

accounting for 8.37%. Overall, from the initial number of patients enrolled in the study, 62 patients died during hospitalization, accounting for 15.27% of cases.

The Kaplan-Meier survival analysis, in which the PCT serum level had been set as an influencing factor, was used in order to estimate the death rate and this is what it revealed: for the patients with a PCT level of 0.5 ng/ml, the estimated survival rate at 30 days was 73%, for the ones with a PCT level of 0.5-2 ng/ml the analysis estimates a survival rate of 83% at 30 days and 55% at 35 days; for patients with PCT levels between 2-10 ng/ml, the survival rate was 58% at 25 days and for patients with PCT levels >10 ng/ml, the estimated survival rate at 45 days was 35%. In our study, as well as in other data found din literature [8], the PCT demonstrated its importance in identifying critical patients with higher mortality rate. On the other hand, there are also studies in which the PCT value does not correlate with a high risk of mortality [9]. Reducing the duration of administration of antibiotics by monitoring PCT is supported by a number of studies [10-17].

We analyzed the receiver operating characteristic curve (ROC curve) that highlights an area under the curve of .911 (with a 95% confidence interval [CI] between 0.880 and 0.943); we can say that the determination of serum **procalcitonin** is the "gold standard" for the diagnosis of patients with sepsis, severe sepsis and septic shock. For a cutoff point of ~ 0.5 ng/ml the sensitivity of the test is 86% and the specificity is 91%.

Similar data were published in *Critical Care* by Canan Balcl (Usefulness of procalcitonin for diagnosis of sepsis in the Intensive Care Unit) which suggests a sensitivity of 85% and a specificity of 91% [18]. Other meta-analyses place these values in the neighborhood of 80%.

Conclusion

Measuring the PCT serum level was important in the diagnosis of fever associated with hematological malignancies, in cases of sepsis, infective endocarditis and acute pneumonia. The primary site of infections for our sepsis cases was the respiratory system followed by gastrointestinal tract, skin or soft tissue infections and urinary tract infections. Among the pathogens *Acinetobacter baumannii* was most frequently isolated alone or in assosiation with other pathogens, followed by *Enterococcus* spp., *Enterobacter* spp. and *Candida* spp. was responsible for 5.58% of the cases. Higher Serum levels of PCT were associated with thrombocytopenia, leukocytosis with neutrophilia, increased CRP and fibrinogen level. The death rate correlated with the PCT values above 10 ng/ml and thrombocytopenia, APACHE II score and with a mean SOFA score of 8. For a cutoff value of 0.5 ng/ml in our study, the sensitivity of the PCT was 86% with 91% specificity. Routine determination of serum procalcitonin levels in sepsis improves patient management, for example by preventing unexpected use of ultra-board-spectrum antibiotics and backup antibiotics, well known for multidrug resistant strains selection. Placing procalcitonin in a key step in the schemes of the management of patients suspected of sepsis is an important factor in determining the strategy that should be followed, the antibacterial and immunological therapy and the treatment costs implication. Procalcitonin remains so far the best pro-inflammatory marker used in the management of patients with severe bacterial infections.

Conflict of Interest

The authors have no conflicts of interest to declare.

Author Contributions

RMB made substantial contribution to conception and design of the manuscript. RMB also performed the analysis and interpretation of data. VB was involved in drafting the manuscript, acquisition of data and interpretation of data. All authors read and approved the final manuscript**.**

Consent Section

Written informed consent was obtained from the patients on their admission to the hospital when their consent was requested for all their laboratory investigations that would be performed. The study was accepted by the Ethics Committee of the hospital and also by the University, the study is part of RMB bachelor`s degree thesis, and they encourage publishing the article. No other additional consent was required for the study as this was prospective observational one.

References

1. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM. Surviving Sepsis Campaign: International
2. Guidelines for Management of Severe Sepsis and Septic Shock: 2012. Crit Care Med 2013; 41: 580-637.
3. Brun-Buisson C, Doyon F, Carlet J, Dellamonica P, Guion F, Lepoutre A. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units. French ICU Group for Severe Sepsis. JAMA 1995; 274: 968-974.
4. Bernard GR, Wheeler AP, Russell JA, Schein R, Summer WR, Steinberg KP. The effects of ibuprofen on the physiology and survival of patients with sepsis. The Ibuprofen in Sepsis Study Group. N Engl J Med 1997; 336: 912-918.
5. Angus DC, Birmingham MC, Balk RA, Scannon PJ, Collins D, Krause JA. E5 murine monoclonal antiendotoxin antibody in gram-negative sepsis: a randomized controlled trial. E5 Study Investigators. JAMA 2000; 283: 1723-1730.
6. Fisher CJ Jr, Dhainaut JF, Opal SM, Pribble JP, Balk RA, Slotman GJ. Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome. Results from a randomized, double-blind, placebo-controlled trial. Phase III rhIL-1ra Sepsis Syndrome Study Group. JAMA 1994; 271: 1836-1843.
7. Jensen JU, Hein L, Lundgren B, Bestle MH, Mohr TT, Andersen MH. Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and

improve survival in the intensive care unit: a randomized trial. Crit Care Med 2011; 39: 2048-2058.

8. Jensen JU, Lundgren B, Hein L, Mohr T, Petersen PL, Sndresen LH. The Procalcitonin And Survival Study (PASS) - a randomised multi-center investigator-initiated trial to investigate whether daily measurements biomarker Procalcitonin and pro-active diagnostic and therapeutic responses to abnormal Procalcitonin levels, can improve survival in intensive care unit patients. Calculated sample size (target population): 1000 patients. BMC Infect Dis 2008; 8: 91.
9. Jensen JU, Heslet L, Jensen TH, Espersen K, Steffensen P, Tvede M. Procalcitonin increase in early identification of critically ill patients at high risk of mortality. Crit Care Med 2006; 34: 2596-2602.
10. Prkno A, Wacker C, Brunkhorst FM, Schlattmann P. Procalcitonin-guided therapy in intensive care unit patients with severe sepsis and septic shock--a systematic review and meta-analysis. Crit Care 2013; 17: R291.
11. Shehabi Y, Sterba M, Garrett PM, Rachakonda KS, Stephens D, Harrigan P. Procalcitonin algorithm in critically ill adults with undifferentiated infection or suspected sepsis. A randomized controlled trial. Am J Respir Crit Care Med 2014; 190: 1102-1110.
12. Hohn A, Schroeder S, Gehrt A, Bernhardt K, Bein B, Wegscheider K. Procalcitonin-guided algorithm to reduce length of antibiotic therapy in patients with severe sepsis and septic shock. BMC Infect Dis 2013; 13: 158.
13. Assink-de Jong E, de Lange DW, van Oers JA, Nijsten MW, Twisk JW, Beishuizen A. Stop Antibiotics on guidance of Procalcitonin Study (SAPS): a randomised prospective multicenter investigator-initiated trial to analyse whether daily measurements of procalcitonin versus a standard-of-care approach can safely shorten antibiotic duration. BMC Infect Dis 2013; 13: 178.
14. Kollef MH. Will procalcitonin reduce antibiotic use in intensive care? The Lancet 2010; 375: 435-436.
15. Kopterides P, Siempos II, Tsangaris I, Tsantes A, Armanganidis A. Procalcitonin-guided algorithms of antibiotic therapy in the intensive care unit: a systematic review and meta-analysis of randomized controlled trials. Crit Care Med 2010; 38: 2229-2241.
16. Heyland DK, Johnson AP, Reynolds SC, Muscedere J. Procalcitonin for reduced antibiotic exposure in the critical care setting: a systematic review and an economic evaluation. Crit Care Med 2011; 39: 1792-1799.
17. Schuetz P, Chiappa V, Briel M, Greenwald JL. Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. Arch Intern Med 2011; 171: 1322-1331.
18. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet 2010; 375: 463-474.
19. Balcl C, Sungurtekin H, Gurses E, Sungurtekin U, Kaptanogul B. Usefulness of procalcitonin for diagnosis of sepsis in the intensive care unit. Crit Care 2003; 7: 85-90.

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