Procalcitonin as a marker of infection in patients with sepsis: a prospective study

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Abstract
Background and Objective: Sepsis is characterized by multiple organ dysfunction due to inflammation. It is generally credited to pathogenic infection, but there are several cases of non-infectious sepsis. Procalcitonin is a small protein that signals increased inflammation during sepsis. This study aims to characterize the prognostic value of procalcitonin in predicting sepsis severity and discriminating infectious and non-infectious sepsis.
Methods: We performed a prospective non-Interventional study, including 75 participants suffering from sepsis. The patients were grouped according to disease severity and their procalcitonin levels measured. The biochemical and microbiological outcomes were analyzed with respect to procalcitonin levels. Results were analyzed by the chi - square test, Kruskal-Wallis test, or Mann-Whitney test. Further, the receiver operating characteristic curve (ROC) was plotted for procalcitonin levels and type of infection and the area under the ROC curve was calculated.
Results: Procalcitonin was found to be correlated with sepsis severity (p=1.80E-09). A significant relationship was observed between procalcitonin levels and the presence of infection (p=0.03996). The area under the ROC curve of procalcitonin for determining presence of infection was 65.18%. At cut-off of 0.6494 (ng/mL) the sensitivity and specificity was found to be 69.81% and 63.63%. Moreover, the presence of methicillin resistant *Staphylococcus aureus* conferred increased procalcitonin than methicillin sensitive variety (p= 0.0098).
Conclusion: We show that procalcitonin is a predictor of sepsis severity. It can be used to predict the type of infection in patients of sepsis in a critical care setting.

Keywords: Procalcitonin, Sepsis, Gram-negative bacteria, Gram-positive bacteria

Introduction
Procalcitonin is the peptide precursor of calcitonin, a hormone involved in calcium homeostasis. Procalcitonin is almost undetectable in serum of healthy persons, but increases in response to inflammation caused by infection. Since procalcitonin levels recovers to normal once the infection subside, its levels in serum has been used to guide the duration of antibiotic use in inflammation caused due to pneumonia and lower respiratory tract infections.[1, 2] Recent advances suggest that serum procalcitonin can be used as a marker for sepsis and predicting mortality.[3-5]
Sepsis occurs when there is a dysregulated inflammation in response to an infection and could lead to multiple organ dysfunction syndrome. In 2017, there were nearly 48.9 million cases and 19.7% deaths due to sepsis worldwide.[6] Sepsis could present in varying degrees of severity based on the number of organ systems that are dysfunctional and range of inflammation.[7] Early phases of sepsis are identified by either infection or bacteremia; however, the infection may be undetectable in about half of sepsis patients.[8] Methods to reliably predict the severity and causative organism of sepsis are necessary to improve treatment outcome and decide appropriate antimicrobial agents to use.
In this study, we performed a prospective analysis on patients with sepsis and measured the effect of serum procalcitonin on treatment outcome. We also analyzed the predictive ability of this biochemical marker for the identification of causative infectious agent of sepsis.

Methods

Study design

We carried out a prospective non-Interventional study in the Intensive Care unit of a tertiary care center. Patients over the age of 18 years admitted to the intensive care unit (ICU) with a diagnosis of sepsis from December 2017 to May 2019 were included in the study. The approval of the institutional ethics committee was obtained prior to the initiation of the study and written informed consent was signed by all the participants or their relatives. Patients were excluded from the study if they were less than 18 years or suffered from major trauma, burns, or surgery. Patients with chronic infections necessitating long-term antibiotic usage or those with immunosuppression were also not included. Based on these criteria, a total of 75 patients with sepsis were enrolled.

Sample size calculation

The sample size was calculated for chi-square test of independence with difference '1' (2-1*2-1) at 95% significance level by assuming a power of 90%, with the medium effect size of 0.4.

Clinical assessment

Patients meeting the inclusion criteria were classified into three categories- sepsis, severe sepsis, or septic shock using systemic inflammatory response syndrome (SIRS) criteria obtained from The American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (ACCP/SCCM) held in 1991.[9] A detailed history was obtained from all the patients, and general physical and systemic examination was done. The APACHE II (Acute Physiology and Chronic Health Evaluation) severity scoring system has been used for predicting disease severity and mortality in intensive care units, which was calculated on the day of admission.[10] There are updated versions of APACHE scoring system, however, due to their increased complexity APACHE II is preferred in the clinical settings.

Clinical Investigations:

All patients underwent hematological investigations, including hemoglobin, total leukocytes, platelets measured using an automated 3-part cell analyzer (Nihon Kohden). The prothrombin time was measured using a Stago analyzer. Biochemistry analysis was performed to measure blood urea, serum creatinine, serum sodium, serum potassium, random blood sugar, and liver function test. All biochemistry tests were performed using standard methods using EM-360 analyzer (Transasia). Blood and urine samples were cultured for microbiological analyses.

Serum procalcitonin levels were measured using Finecare^{TM} procalcitonin rapid quantitative test, a sandwich fluorescence immunoassay, and measured on a Finecare^{TM} FIA system. The test uses fluorescently labeled detector procalcitonin antibodies that form immune complexes with the procalcitonin in the sample. These immune complexes are then recognized by procalcitonin antibodies on the test strip where fluorescence intensity is measured.

Statistical analyses

All data were analyzed using statistical software R v 3.6.0 and a p value <0.05 was considered as statistically significant. Descriptive statistics of variables were analyzed and presented as percentages. Chi-square test was used to compare the categorical variables like number of survivors. For serum procalcitonin levels, which is a continuous variable, either Kruskal-Wallis or Mann-Whitney test was used depending on the number of groups to be compared. For a pair-wise comparison of various sepsis severity categories, Dunn test was used. Independent sample t-test was used to compare procalcitonin levels among patients infected with methicillin resistant or methicillin sensitive *Staphylococcus aureus*.

The specificity and false positivity rate of serum procalcitonin levels for predicting infection and type of bacteria were calculated and receiver operating characteristic (ROC) curve was plotted. The area under the receiver operating characteristic curve (AUROC) was calculated and the AUROC closer to 1.0 was considered significant. Correlation of serum procalcitonin and other demographic and clinical parameters was plotted, and Pearson's correlation values are denoted.

Results

We categorized the total 75 study participants based on either their serum procalcitonin levels or their APACHE II scores. Majority of the patients (76%) in both APACHE II < 30 and ≥ 30 categories had serum procalcitonin ≥2 (*p* value 1.00) (Table 1).

In patients with an APACHE II score < 30 and serum procalcitonin < 2, the survival rate was 89%. While in patients with APACHE II score < 30 and serum procalcitonin ≥ 2 the survival rate was 72% (Table 1). However, this correlation was statistically non-significant (*p* value 0.412). Almost all patients (99.89%) with APACHE II score ≥ 30 and procalcitonin < 2 succumbed to death due to sepsis, while there were more survivors (61%) among patients with APACHE II score ≥ 30 and procalcitonin ≥ 2 (*p* value 0.027). The dependence of serum procalcitonin on patient survival is therefore significant only when APACHE II score is ≥ 30.

Table 1: Distribution of sepsis patients based on APACHE II score and serum procalcitonin levels and their relationship with the outcome.

APACHE II score	**Procalcitonin (ng/mL)**	**Total Subjects N (%)**	***p* Value**	**Survivors N (%)**	**Non-Survivors N (%)**	***p* Value**
< 30	<2	9 (23.68)	1.00	8 (88.89)	1 (11.11)	0.412
	≥2	29 (76.32)		21 (72.41)	8 (27.59)	
	Total	38		29	9	
≥ 30	<2	9 (24.32)		1 (0.11)	8 (99.89)	0.027
	≥2	28 (75.68)		17 (60.71)	11 (39.29)	
	Total	37		18	19	

In our population of 75 sepsis patients, there were 26 patients each of sepsis and severe sepsis, while 23 patients suffering from septic shock (Table 2). When the treatment outcome was correlated with disease severity, we found that sepsis has a low mortality (15%) while there were comparable chances of survival if the patients had severe sepsis or septic shock. Therefore, a significant association exists between disease severity and treatment outcome (*p*= 0.0184). There is also an increasing trend of serum procalcitonin levels, according to increasing disease severity (*p*= 1.80E-09 as calculated by a Kruskal-Wallis test). For each pair of disease severity category, there is a significant difference ($p < 0.001$) as calculated by pair-wise comparison using Dunn test.

Table 2: Disease outcome and serum procalcitonin levels in each severity group.

Severity of Disease	**Survivors N (%)**	**Non survivors N (%)**	**Total N (%)**	***p* Value**	**procalcitonin (ng/mL) Mean ± SD**	***p* Value**
Sepsis	22 (84.62)	4 (15.38)	26 (34.67)	0.0184	2.88 ± 1.56	1.80E-09
Severe Sepsis	13 (50)	13 (50)	26 (34.67)		5.42 ± 2.72	
Septic Shock	12 (52.17)	11 (47.83)	23 (30.66)		9.01 ± 3.94	
Total	47	28	75			
Pair-wise comparison of procalcitonin levels						
Severity of Disease				***p* Value**		
Sepsis		Severe sepsis		2.80E-05		
Sepsis		Septic shock		8.10E-08		
Septic shock		Sepsis		0.00051		

Of the 75 patients, 53 (71%) of total patients showed signs of bacterial or fungal growth in cultures; majority of these contained gram negative bacteria (49%) (Table 3). Gram-positive bacteria were present in 15% patients and fungal pathogens were present in 7% patients. Among

the 53 culture positive patients, a total of 57% patients survived. The survival rate was higher with Gram-positive bacteria (73%) while lower with fugus (40%). Gram-negative bacteria only slightly favored survival (54%). There was a higher survival rate among culture negative patients (77%). The correlation of presence of growth and disease mortality was not statistically significant (p= 0.1929).

Serum procalcitonin levels in culture positive population (6.23±4.04, mean ± S.D.) was significantly different than levels in culture negative populations (4.22 ± 2.56, mean ± S.D.) (p =0.03996), and majority of the patients in all categories had procalcitonin ≥2.0 ng/mL (p = 1) (Table 3). The levels were higher in patients infected with bacteria (6.49 ± 5.31 and 6.35 ± 3.83), while they were lower in fungal positive (4.80 ± 2.46) as well as culture negative patients (4.22 ± 2.56) (p= 0.0853) (Table 3).

Table 3**:** Presence of microorganisms in the patients and their relation to procalcitonin and survival.

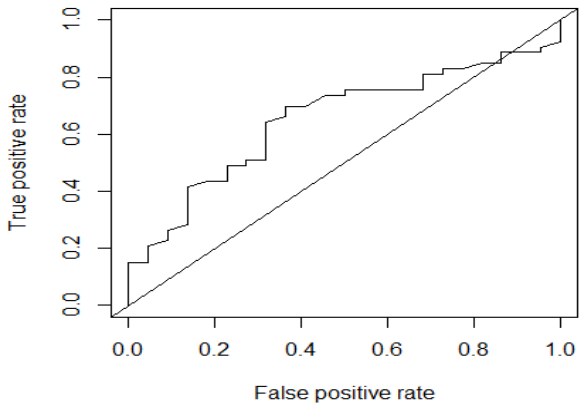
Outcome		**Gram-positive N (%)**	**Gram-negative N (%)**	**Fungus N (%)**	**None N (%)**	**Total N (%)**	***p* value**
Survival[a]	Survivors	8(72.73)	20(54.05)	2(40)	17 (77.27)	47 (62.67)	0.1929
	Non-survivors	3(27.27)	17(45.95)	3(60)	5 (22.73)	28 (37.33)	
	Total	11 (14.67)	37 (49.33)	5 (6.67)	22 (29.33)	75 (100)	
Procalcitonin (ng/mL)	Mean ± SD	6.49 ± 5.31	6.35 ± 3.83	4.80 ± 2.46	4.22 ± 2.56		0.0853
	≥2.0	46(86.79)			19(86.36)	65	1.00
	<2.0	7(13.21)			3(13.64)	10	
	Total	53 (70.67)			22 (29.33)	75	

We plotted Receiver Operating Characteristic (ROC) curve for serum procalcitonin levels in culture positive and culture negative samples (Figure 1). The area under the ROC curve (AUROC) for serum procalcitonin for predicting sample culture was 65.18%. The cutoff point for probability of individual belong to "Positive sample culture" is 0.6494(ng/mL). The sensitivity of the model is 69.81% and the specificity is 63.63%. The calculated model is:

$$\log\left(\frac{Positive\ sample\ culture}{Sterile\ sample\ culture}\right) = -0.04767 + 0.1878 * (\text{Serum procalcitonin})$$

For every one-unit change in procalcitonin, the log odds of individual having positive sample culture (versus individual is in sterile sample culture) is increased by 0.1878. Serum procalcitonin is therefore, significant in predicting the infection in the current model. (p value for Wald test: 0.0431). Here the intercept value was not significant in the prediction of sample culture in the model. (*p value* for Wald test: 0.9922).

Figure 1: ROC curve of serum procalcitonin level in study population for predicting infection.



Serum procalcitonin levels differed to a great extent among different infectious agents (p= 0.3496) (Table 4). Higher procalcitonin was found with pathogens such as *Leptospira*, *Pseudomonas*, and *Escherichia coli*. Interestingly, the serum procalcitonin level of Methicillin resistant Staphylococcus aureus (MRSA) containing patients was significantly higher than patients containing a Methicillin sensitive variety (8.48 ± 5.60 ng/mL vs 1.8 ± 0.33; p= 0.0098).

Table 4: Procalcitonin levels in patients infected with various pathogens.

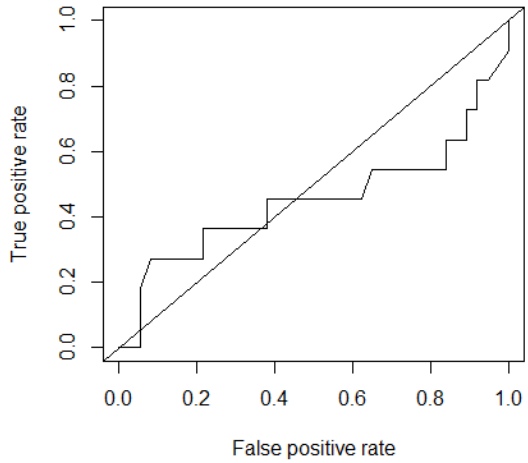
Causative agent	**Procalcitonin (ng/mL) Mean ±SD**	***p* Value**
Escherichia coli	6.7 ± 4.48	0.3496
Klebsiella pneumoniae	4.1 ± 2.13	
Pseudomonas aeruginosa	6.94 ± 3.75	
Acinetobacter baumanni	5.57 ± 1.23	
Leptospira	8.6 ± 0	
Methicillin resistant *Staphylococcus aureus*	8.48 ± 5.60	
Methicillin sensitive *Staphylococcus aureus*	1.8 ± 0.33	
Corynebacterium diphtheriae	6.7 ± 0	
Candida albicans	4.32 ± 2.04	
Mucor	5.54 ± 3.76	

Next, we plotted ROC curve for serum procalcitonin levels in the Gram Positive/Negative culture isolates (Figure 2). The AUROC for serum procalcitonin for predicting culture isolate was 45.20%. The cutoff point for probability of individual having Gram-positive bacteria is 0.2295. The sensitivity of the model is 45.45% and the specificity is 62.16%. For every one-unit change in procalcitonin, the log odds of individual having Gram-positive culture isolate is increased by 0.0085. Serum procalcitonin is not significant in the prediction of culture isolate in the model (p-value for Wald test: 0.9180). The descriptive model is:

$\log(\frac{Gram\ positive}{Gram\ negative})$= -1.2678 + 0.0085 *(Serum procalcitonin)

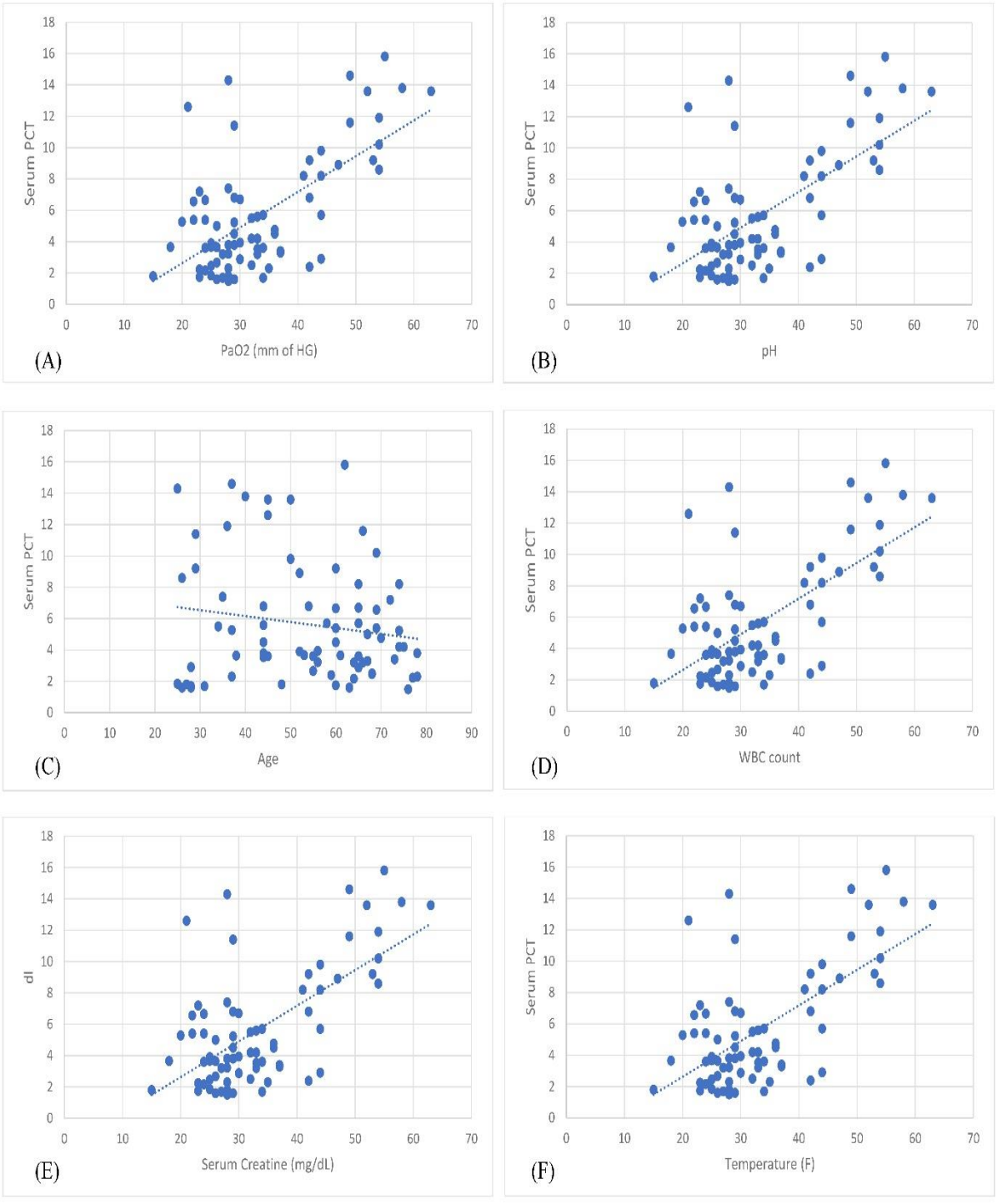
Here, intercept value was significant in predicting culture isolate (p-value for Wald test: 0.0463).

Figure 2: ROC curve showing distribution of Serum procalcitonin in patients with Gram-positive and Gram-negative bacteria.



Further, correlation of serum procalcitonin level was measured with different demographic and clinical parameters. We found a negative correlation of procalcitonin with partial pressure of oxygen (PaO_2) (r = -0.3874524, *p* value 0.0005942) and pH (r = -0.8052, *p* value 2.2E-16), while no correlation was found with patient age (r = -0.1596769, *p* value 0.1712), white blood cell (WBC) count (r = 0.1435, *p* value 0.2193), serum creatinine (r = 0.190599, *p* value 0.1014), or body temperature (r = 0.0154, *p* value 0.8956) (Figure 3).

Figure 3: Correlation between serum procalcitonin and different demographic and clinical parameters. Correlation between procalcitonin and PaO_2 (A), pH (B), age (C), WBC count (D), serum creatinine (E), and body temperature (F).



Discussion

Sepsis is characterized by a dysregulated response to infection by the host. The infectious agents responsible for sepsis may vary from Gram-positive or Gram-negative bacteria to fungi, although incidences of fungal sepsis are lower.[11] We analyzed a group of 75 sepsis patients for their disease severity and infection condition and distributed them according to their procalcitonin levels. We then used the measured procalcitonin levels to predict disease severity, presence of infection, and the type of infectious agent.

We found that procalcitonin is able to predict sepsis outcome when combined with an APACHE II score. Procalcitonin was found to be a significant predictor of sepsis severity and hence is crucial for the ICUs as the mortality due to sepsis is dependent on disease severity. A few other

biochemical markers have been proposed to predict severity and outcome of a sepsis, including C-reactive protein, cytokine interleukin-6, and macrophage migration inhibitory factor.[12] It was found previously that procalcitonin levels are higher in patients with septic shock than without.[13-15]

Our analysis shows that procalcitonin levels are significantly different in culture positive patients than in culture negative patients (*p* value 0.03996). This is consistent with a few published studies in the literature.[14, 16, 17] The area under the ROC curve was found to be 65.18% with sensitivity and specificity of 69.81% and 63.63%, respectively. A previous report has shown that procalcitonin can be a predictor of blood positive culture with an AUROC of 0.94, sensitivity of 73%, and specificity of 97%.[16] Procalcitonin has been used in predicting infection and bacteremia in patients who suffered sepsis due to neutropenia.[18] It has been reported to discriminate between infectious and non-infectious sepsis.[19]

Our results show that patients with bacterial infections have significantly higher procalcitonin than those with fungal infections, as also reported by others.[20] We found that majority of infectious sepsis occurs due to Gram-negative bacteria and procalcitonin levels are similarly elevated in both cases, consistent with earlier reports.[13, 20, 21] However, there are a few reports suggesting that procalcitonin can be elevated in Gram-negative sepsis than in Gram-positive.[15, 18] Procalcitonin has a moderate predictive value for the presence of Gram-positive or Gram-negative bacteria in our ROC analysis. The AUROC for predicting culture isolate was 45.20% with a sensitivity of 45.45% and a specificity of 62.16%. Leli et al. had shown similar findings with an AUROC of 0.765, a sensitivity of 62%, and a specificity of 82%.[20] Similarly, Gupta et al. showed that AUROC of procalcitonin in predicting Gram-positive or Gram-negative sepsis is 0.612 with a sensitivity of 75% and a specificity of 46%.[22] Li et al. have found that AUROC for such analysis is 0.793 with a sensitivity of 77% and a specificity of 68%.[21] Previous studies have also found that procalcitonin is a better choice than C-reactive protein to discriminate the infectious agent of sepsis.[23, 24] Antibiotic resistance obtained by the Gram-positive bacteria *S. aureus* poses a serious threat to all sepsis patients. Among the culture positive patients, we found that procalcitonin levels differed significantly between MRSA and MSSA. Therefore, using procalcitonin as a marker for differentiating MRSA and MSSA could be important for better disease outcome.

The present study is limited by the fact that all sepsis patients admitted to the ICU were included in the study and were not differentiated based on the underlying cause of sepsis. Still, it proves usability of procalcitonin as a significant marker of infection. Procalcitonin as a biochemical marker has a promising role; however, its levels may also be elevated in conditions unrelated to sepsis such as cardiac arrest, heat shock and some autoimmune disorders.[25, 26] Therefore, it is advisable for the physician to assess the situation in the clinical context and patient's history. In summary, endogenous markers such as procalcitonin can be a better predictor of disease outcome and severity of sepsis. Procalcitonin measurements in the intensive care units should be essential to decide the antibiotic treatment for severe sepsis patients.

Conclusion

In the current study, we deciphered the role of procalcitonin in predicting sepsis severity and presence of infection. We showed that procalcitonin concentrations have a significant discriminatory power to for Gram-positive and Gram-negative infections. We conclude that procalcitonin should be used in conjunction with existing scoring methods to better predict the outcome of sepsis.

References

1. 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(7):1792-9.

2. Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database Syst Rev. 2017;10:CD007498.
3. Becker KL, Nylen ES, White JC, Muller B, Snider RH, Jr. Clinical review 167: Procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis: a journey from calcitonin back to its precursors. J Clin Endocrinol Metab. 2004;89(4):1512-25.
4. Muller B, Becker KL, Schachinger H, Rickenbacher PR, Huber PR, Zimmerli W, et al. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. Crit Care Med. 2000;28(4):977-83.
5. Ruiz-Alvarez MJ, Garcia-Valdecasas S, De Pablo R, Sanchez Garcia M, Coca C, Groeneveld TW, et al. Diagnostic efficacy and prognostic value of serum procalcitonin concentration in patients with suspected sepsis. J Intensive Care Med. 2009;24(1):63-71.
6. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet. 2020;395(10219):200-11.
7. Klein Klouwenberg PM, Ong DS, Bonten MJ, Cremer OL. Classification of sepsis, severe sepsis and septic shock: the impact of minor variations in data capture and definition of SIRS criteria. Intensive Care Med. 2012;38(5):811-9.
8. Gupta S, Sakhuja A, Kumar G, McGrath E, Nanchal RS, Kashani KB. Culture-Negative Severe Sepsis: Nationwide Trends and Outcomes. Chest. 2016;150(6):1251-9.
9. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest. 1992;101(6):1644-55.
10. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818-29.
11. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med. 2003;348(16):1546-54.
12. Dambrauskas Z, Gulbinas A, Pundzius J, Barauskas G. Value of the different prognostic systems and biological markers for predicting severity and progression of acute pancreatitis. Scand J Gastroenterol. 2010;45(7-8):959-70.
13. Clec'h C, Ferriere F, Karoubi P, Fosse JP, Cupa M, Hoang P, et al. Diagnostic and prognostic value of procalcitonin in patients with septic shock. Crit Care Med. 2004;32(5):1166-9.
14. Karlsson S, Heikkinen M, Pettila V, Alila S, Vaisanen S, Pulkki K, et al. Predictive value of procalcitonin decrease in patients with severe sepsis: a prospective observational study. Crit Care. 2010;14(6):R205.
15. Yunus I, Fasih A, Wang Y. The use of procalcitonin in the determination of severity of sepsis, patient outcomes and infection characteristics. PLoS One. 2018;13(11):e0206527.
16. Mustafic S, Brkic S, Prnjavorac B, Sinanovic A, Porobic Jahic H, Salkic S. Diagnostic and prognostic value of procalcitonin in patients with sepsis. Medicinski Glasnik. 2018;15(2):93-100.
17. Sharma R, Vijayakumar M. Procalcitonin for improved assessment and an answer to sepsis dilemma in critically ill-a myth, a hype, or a reality? Nitte Univ J Health Sci. 2014;4(1):57-65.
18. Koivula I, Hamalainen S, Jantunen E, Pulkki K, Kuittinen T, Nousiainen T, et al. Elevated procalcitonin predicts Gram-negative sepsis in haematological patients with febrile neutropenia. Scand J Infect Dis. 2011;43(6-7):471-8.
19. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis. 2013;13(5):426-35.

20. Leli C, Ferranti M, Moretti A, Al Dhahab ZS, Cenci E, Mencacci A. Procalcitonin levels in gram-positive, gram-negative, and fungal bloodstream infections. Dis Markers. 2015;2015:701480.
21. Li S, Rong H, Guo Q, Chen Y, Zhang G, Yang J. Serum procalcitonin levels distinguish Gram-negative bacterial sepsis from Gram-positive bacterial and fungal sepsis. J Res Med Sci. 2016;21:39.
22. Gupta S, Jaswani P, Sharma RK, Agrawal S, Prasad N, Sahu C, et al. Procalcitonin as a diagnostic biomarker of sepsis: A tertiary care centre experience. J Infect Public Health. 2019;12(3):323-9.
23. Wang D, Tao X, Guo W, Liu H, Cheng S, Wang J. The diagnostic ability of procalcitonin to differentiate Gram-negative bacteria from Gram-positive bacteria and fungal bloodstream infections in critically ill patients. Eur J Inflamm. 2020; 17:2058739219841469.
24. Brodska H, Malickova K, Adamkova V, Benakova H, Stastna MM, Zima T. Significantly higher procalcitonin levels could differentiate Gram-negative sepsis from Gram-positive and fungal sepsis. Clin Exp Med. 2013;13(3):165-70.
25. Reinhart K, Meisner M. Biomarkers in the critically ill patient: procalcitonin. Crit Care Clin. 2011;27(2):253-63.
26. Schuetz P, Affolter B, Hunziker S, Winterhalder C, Fischer M, Balestra GM, et al. Serum procalcitonin, C-reactive protein and white blood cell levels following hypothermia after cardiac arrest: a retrospective cohort study. Eur J Clin Invest. 2010;40(4):376-81.