Validity of procalcitonin as diagnostic biomarker for infective endocarditis

Momen M. Thabet[a*], Marwan S. Mahmoud[b], Ayman Khairy Mohamed Hassan[b], Ehsan A. Hassan[c], Khaled Mohamed Hassanein[c], Mona Hussein Abdel-Rahim[c]

[a]Department of Microbiology and Immunology, Faculty of Pharmacy, South Valley University, Qena, Egypt.

[b]Department of Cardiology, Assiut University Heart Hospital, Assiut University, Assiut, Egypt.

[c]Department of Medical Microbiology and Immunology, Faculty of Medicine, Assiut University, Assiut, Egypt.

Abstract

Background: Infective endocarditis (IE) is still a fatal infection with high morbidity and mortality. Successful patient outcomes depend on prompt diagnosis and effective therapy. Blood cultures are usually time consuming and sometimes echocardiography is falsely negative. Thus, a straightforward blood test may assist early diagnosis of IE. Multiple studies have revealed that procalcitonin (PCT) was highly associated with bacteremia - the main diagnostic criteria for endocarditis - in patients with fever.

Objectives: We aimed to assess the diagnostic significance of procalcitonin concentration in suspected patients of IE.

Patients and methods: Twenty-two patients admitted to Assiut University Heart Hospital with a suspicion of IE were enrolled in a prospective study. Based on clinical, microbiological, and echocardiographic findings, Modified duke criteria were applied to the cases to confirm their diagnosis as definite, possible, or rejected IE cases before testing for procalcitonin was done. The study also included fifteen healthy volunteers for comparison with IE patients.

Results: Procalcitonin was significantly higher (P-value <0.05) in patients diagnosed as definite and possible IE than with healthy volunteers. The area under the ROC curve was 0.705. At cutoff value of 0.425 ng/ml, the procalcitonin test's sensitivity, specificity, negative predictive value, and positive predictive values were 47.6%, 93.3%, 56%, and 90.9%, respectively.

Conclusion: This study implies that procalcitonin may be a valuable supplementary diagnostic marker in IE diagnosis. A threshold value of 0.425 ng/ml should be used for ruling out endocarditis in routine clinical practice and the diagnosis of IE can be strongly excluded below this value.

Keywords: Procalcitonin; Infective endocarditis; Duke criteria.

DOI: 10.21608/svuijm.2023.212553.1589

***Correspondence:** pharmacistmomen@gmail.com

Received: 22 April, 2023.

Revised: 1 May, 2023.

Accepted: 23 May, 2023.

Published: 5 June, 2023

Cite this article as: Momen M. Thabet, Marwan S. Mahmoud, Ayman Khairy Mohamed Hassan, Ehsan A. Hassan, Khaled Mohamed Hassanein, Mona Hussein Abdel-Rahim. (2023). Validity of procalcitonin as diagnostic biomarker for infective endocarditis. *SVU-International Journal of Medical Sciences*. Vol.6, Issue 2, pp: 347-352.

Introduction

Infective endocarditis (IE) is still a fatal infection with high morbidity and mortality **(Burton and Geraci, 2008; Habib et al., 2009)**. This fatality is due to intracardiac and extracardiac complications developing during the interval between the onset of symptoms and diagnosis. Frequently, this delay lasts several weeks **(Knudsen et al., 2009)**.

Successful patient outcomes depend on prompt diagnosis and effective therapy **(Mueller et al., 2004)**. Although blood culture and echocardiography are the gold standard for diagnosis, blood cultures are usually time consuming and sometimes echocardiography is falsely negative. **(Knudsen et al., 2010)**. Thus, a simple straightforward blood test, which may assist in determining whether IE is present or absent in suspected cases, would be highly desired **(Knudsen et al., 2010; Mueller et al., 2004)**.

Procalcitonin (PCT) is universally released in response to endotoxin and other bacterial infection-related mediators, such as interleukin-1 (IL-1), tumor necrosis factor (TNF), and IL-6 **(Muller et al., 2001)**. As a result, its levels substantially connect to the severity and extent of bacterial infections **(Gogos et al., 2000)**. Multiple studies have revealed that PCT was highly associated with bacteremia - the main diagnostic criteria for endocarditis - in patients with fever **(Schuetz et al., 2016)**. Thus, PCT seems to be helpful in distinguishing patients with IE.

In various studies, PCT-guided antibiotic therapy has been shown to decrease the duration of antibiotic treatment for sepsis, decrease antibiotic costs and decrease the annual ICU re-infection rate by 35.1% **(Jeon et al., 2019)**.

Here, we assessed the significance of procalcitonin concentration in serum of suspected cases as a diagnostic biomarker for IE.

Patients and methods

Patients: From August 2020 to August 2021, 22 patients who were admitted to the Assiut University Heart Hospital with a suspicion of IE were enrolled in a prospective study. Every patient underwent a thorough history taking and clinical examination which included demographic data, clinical symptoms, and complications, underlying cardiac disease, and co-morbid illnesses. The study was approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Assiut University according to the principles of the Declaration of Helsinki.

Based on clinical, echocardiographic findings and microbiological, Modified duke criteria were applied to the cases to confirm their diagnosis as definite, possible, or rejected IE cases before testing for procalcitonin was done. The study also included 15 healthy volunteers for comparison with IE patients.

Sample collection: Blood samples were collected from all IE patients before any empirical antibiotic treatment as well as from healthy volunteers. Five ml blood samples in plain vacutainer tubes were used to separate serum samples to be stored at - 20°C for serological testing of procalcitonin.

Methods: Human Procalcitonin (PCT) ELISA kit (SinoGeneClon, Hangzhou, China) was used to quantitatively detect the procalcitonin level in serum samples from the examined cases. The quantitative test method has a quantitative detection range of 0.04 to 0.8 ng/ml and an

analytical sensitivity of 0.008 ng/ml. The procalcitonin concentrations of IE patients (both definite and possible cases) were compared to those of healthy volunteers.

Statistical analysis

Statistical analyses were carried out using IBM SPSS (version 22, SPSS Inc). The Mann-Whitney *U* test was used for the non-parametric continuous data, which were expressed as median and interquartile range. P-value was considered significant when ≤ 0.05.

Procalcitonin's sensitivity and specificity for detecting IE across a range of concentrations were evaluated using a receiver operator characteristic (ROC) curve. The ROC analysis was also used to determine the appropriate procalcitonin concentration for calculating positive and negative predictive accuracy.

Results

The median age of enrolled patients was 33.5 years with a range between 19 and 54 years. Upon application of the modified Duke criteria to the study cases, 17 (77.3%) were determined to have definite IE, 4 (18.2%) to have possible IE, and only one did not meet the criteria and was excluded.

Procalcitonin was significantly higher (P-value = 0.038) in patients diagnosed as definite and possible IE (median: 0.41 ng/ml, range: 0.18 - 3.3 ng/ml) than with healthy volunteers (median: 0.3 ng/ml, range: 0.22 – 0.44 ng/ml) (**Fig.1**).

The area under the ROC curve (AUC) was 0.705 (95% CI 0.534 to 0.875). The ROC curve revealed that 0.425 ng/ml of procalcitonin was the optimal concentration for calculating both positive and negative predictive accuracy. At this cutoff, the procalcitonin test's sensitivity, specificity, negative predictive value, and positive predictive values were 47.6%, 93.3%, 56%, and 90.9%, respectively (**Fig.2**).

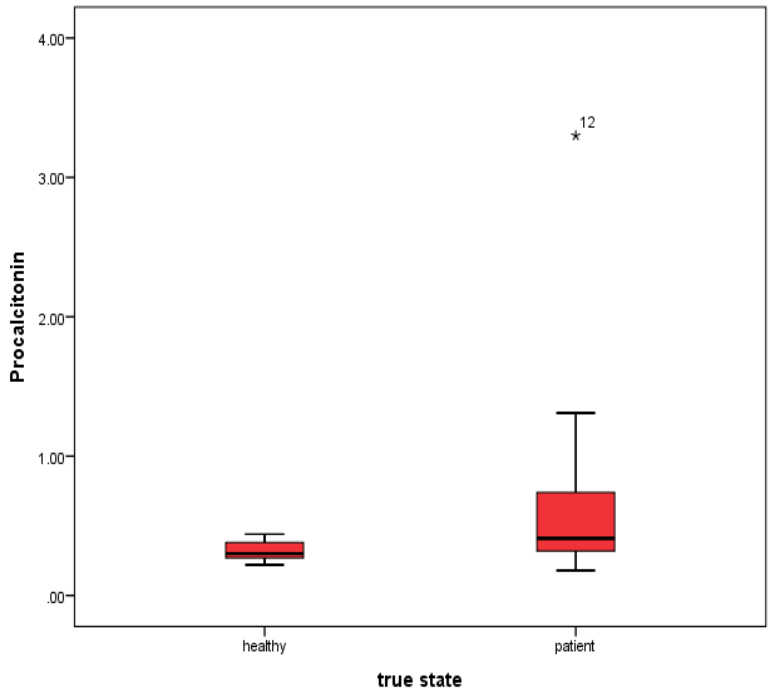

Fig.1. Serum procalcitonin concentrations in patients with IE and healthy volunteers.

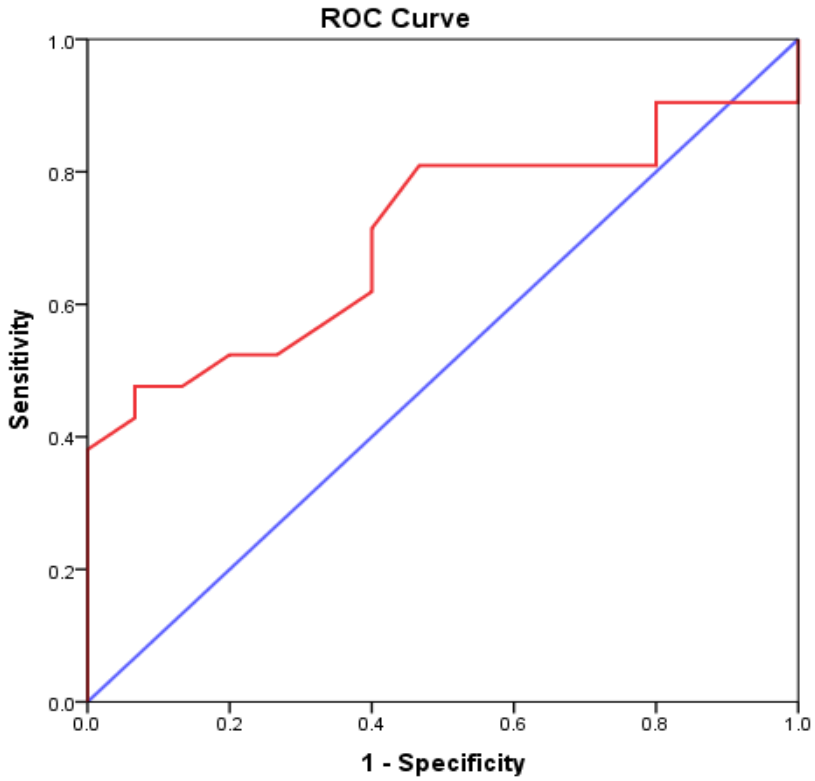

Fig.2.ROC curve of procalcitonin to predict IE with AUC = 0.705

Discussion

Diagnosis of infective endocarditis remains difficult for clinicians because of varied clinical manifestations **(Pierce et al., 2012)**. Procalcitonin diagnostic performance was assessed in this study in a cohort of patients who had previously been diagnosed with IE. Using Mann-Whitney U test, procalcitonin was significantly higher (P-value <0.05) in patients diagnosed as definite and possible IE than with healthy volunteers. This significant difference conforms to that in another study involving a group of 50 patients with IE compared to a control group of healthy volunteers **(Kocazeybek et al., 2003)**.

In a study conducted in 2004, an assay based on time-resolved amplified cryptate emission (TRACE) technology (Kryptor-PCT) was used to quantify the procalcitonin level with analytical sensitivity of the quantitative test method of 0.02 ng/ml. They showed AUC of 0.856 **(Mueller et al., 2004)** that was higher than that revealed in our study (0.705).

It is unclear from Mueller's publication whether the PCT samples were taken prior to antibiotic medication in patients with IE or infected individuals in the control group. In our trial, antimicrobial therapy was not started until after blood was collected.

The area under the ROC curve value of 0.705 in our study complied with that revealed in a meta-analysis study that reviewed six studies including more than 1000 episodes of suspected infection and showed AUC value of 0.71 **(Yu et al., 2013)**. Both values indicated that procalcitonin has a fair but not good diagnostic accuracy.

Using a cut-off value of 2.3 ng/mL, PCT had an 81% sensitivity and 85%

specificity in predicting IE (**Mueller et al., 2004**). Our study revealed a significantly lower cut-off value of 0.425 ng/ml than that was shown by Mueller et al and subsequently lower sensitivity of 47.6%. This is probably because the comparison involved a group of IE patients to a control group of healthy volunteers not a control group of patients with other final diagnoses like sepsis, pneumonia, arthritis, viral infection, septic deep venous thrombosis, perimyocarditis, and others as mentioned by Mueller et al.

Interestingly, the cut-off value of 0.425 ng/ml in our study showed an excellent specificity (93.3%) result reflecting the usefulness of procalcitonin as an exclusion biomarker for diagnosis of IE.

Conclusion

This study implies that procalcitonin may be a valuable supplementary diagnostic marker in the IE diagnosis. A threshold value of 0.425 ng/ml should be used for ruling out endocarditis in routine clinical practice and the diagnosis of IE can be strongly excluded. Whereas above this threshold, further examination and testing will be essential to confirm the diagnosis.

Limitation of the study

Because of small sample size and being a single centered study, our findings must be further verified by additional studies before specific recommendations can be made about the use of procalcitonin for ruling out the diagnosis of IE especially the ideal cut-off value of it.

References

- **Burton MJ, and Geraci SA. (2008)**. Infective endocarditis prevention: update on 2007 guidelines. American Journal of Medicine, 121(6): 484-486.
- **Gogos CA, Drosou E, Bassaris HP, and Skoutelis A. (2000)**. Pro- versus anti-inflammatory cytokine profile in patients with severe sepsis: a marker for prognosis and future therapeutic options. Journal of Infectious Diseases, 181(1): 176-180.
- **Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, et al. (2009)**. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. European Heart Journal, 30(19):2369-2413.
- **Jeon K, Suh JK, Jang EJ, Cho S, Ryu HG, Na S, et al. (2019)**. Procalcitonin-Guided Treatment on Duration of Antibiotic Therapy and Cost in Septic Patients (PRODA): a Multi-Center Randomized Controlled Trial. Journal of Korean Medical Science, 34(14): e110.
- **Knudsen JB, Fuursted K, Petersen E, Wierup P, Molgaard H, Poulsen SH, et al. (2010)**. Procalcitonin in 759 patients clinically suspected of infective endocarditis. American Journal of Medicine, 123(12): 1121-1127.
- **Knudsen JB, Fuursted K, Petersen E, Wierup P, Mølgaard H, Poulsen SH, et al. (2009)**. Infective endocarditis: a continuous challenge. The recent experience of a European tertiary center. Journal of Heart Valve Disease, 18(4): 386-394.

- **Kocazeybek B, Kucukoglu S, and Oner YA. (2003)**. Procalcitonin and C-reactive protein in infective endocarditis: correlation with etiology and prognosis. Chemotherapy, 49(1-2): 76-84.
- **Mueller C, Huber P, Laifer G, Mueller B, and Perruchoud AP. (2004)**. Procalcitonin and the early diagnosis of infective endocarditis. Circulation, 109(14): 1707-1710.
- **Muller B, White JC, Nylen ES, Snider RH, Becker KL, and Habener JF. (2001)**. Ubiquitous expression of the calcitonin-i gene in multiple tissues in response to sepsis. Journal of Clinical Endocrinology and Metabolism, 86(1): 396-404.
- **Pierce D, Calkins BC, and Thornton K. (2012)**. Infectious endocarditis: diagnosis and treatment. American Family Physician, 85(10): 981-986.
- **Schuetz P, Daniels LB, Kulkarni P, Anker SD, and Mueller B. (2016)**. Procalcitonin: A new biomarker for the cardiologist. International Journal of Cardiology, 223: 390-397.
- **Yu CW, Juan LI, Hsu SC, Chen CK, Wu CW, Lee CC, et al. (2013)**. Role of procalcitonin in the diagnosis of infective endocarditis: a meta-analysis. American Journal of Emergency Medicine, 31(6): 935-941.