Review Article

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TANAFFOS

Role of Procalcitonin in the Prognosis of Mortality in Patients Admitted to the Intensive Care Unit: A Review Study

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Background: This review study aimed to investigate the role of PCT in the prognosis of mortality among patients admitted to the intensive care units (ICU). Procalcitonin (PCT) is a polypeptide and prohormone of calcitonin. This prohormone is secreted by thyroid gland C cells in response to hypercalcemia, and Its elevated level indicates infection, especially bacterial infections, in which there is a systematic response to infection.

Materials and Methods: This narrative review study was performed based on Cochrane collaboration recommendations for reviews. We reviewed all the titles and abstracts of published research articles with the following inclusion criteria studies aimed to confirm the function of a prognostic model in predicting mortality or survival, (b) mortality or survival of a specific endpoint (for example, 30 days), (c) patients admitted to intensive care units, and d) the articles written in English. The exclusion criteria of the current review included: (a) articles whose data were not specifically focused on prognosis of patients in ICU, (b) articles that did not provide sufficient information on the cause of death of patients in ICU, and (c) articles focusing on the treatment of comorbid patients with infections in ICU. The search was conducted on Google Scholar, PubMed, Magiran, ScienceDirect, and SID. Also, to search Iranian databases, including SID and Magiran, the same terms and expressions were searched.

Results: Based on the findings of this review, serum levels of PCT were reported within the range of at least 5 to more than 16 ng/ml in patients admitted to ICU. The mortality rate was estimated at 5.7% to 79% in these patients. Moreover, the incidence of sepsis was reported from 13% to 77.6%.

Conclusion: Serum levels of PCT as a prognostic factor may help early detection, and better classification of the poor prognoses sepsis patients and more invasive treatment of patients admitted to ICU and are at risk for mortality.

Key words: Prophylaxis; Procalcitonin; Prognosis; Sepsis

INTRODUCTION

Procalcitonin (PCT), a 116 amino acid polypeptide with a molecular weight of about 14.5 kDa, is a prohormone belonging to the calcitonin family. This prohormone is secreted by thyroid gland C cells in response to hypercalcemia (1). PCT structure is composed of three parts: end-part amino acids, immature calcitonin, and terminal-carboxyl calcitonin peptide. This prohormone is converted to active intracellular hormone by proteolytic enzymes (2).

In normal physiological conditions, in a healthy person, the PCT level in the systemic circulation is very low (<0.05 ng/mL) (3). During systemic inflammation, especially bacterial infections, PCT is produced by macrophages and monocytes of various organs and is released into blood circulation, which increases the PCT concentration. Studies have shown that PCT is an essential marker for the diagnosis of bacterial infections and also has a direct relationship with the severity of the infection (4-6). Therefore, PCT is an appropriate biomarker for diagnosing bacterial or fungal infections and sepsis (7).

Prognostic estimation methods in the intensive care unit (ICU) have different goals. Initially, prognostic models might be used to detect the poor prognosis cases by comparing the results of cases of other care units. Also, the next step is to identify high-risk subgroups and classification of patients based on their paraclinical findings (8). As a result, prognostic models can be implemented to support decision-making (including estimating the prognosis and informing the patients and their families). Also, these models can be used to predict the mortality rate in the ICU (9).

The prevalence of severe sepsis and septic shock has been increasing in recent years, especially in the ICUs (10). Sepsis and septic shock are also the most common mortality causes in the ICU (11). Subsequently, early diagnosis of infection in ICU patients and the rapid onset of proper treatment are the most critical factors affecting the clinical decision-making and reducing mortality in these patients. Therefore, accurate diagnosis and proper antibiotic treatment can increase these patients' survival rates (5). However, blood cultures detect only about 30% of bacterial infections, and positive blood cultures may not be detected within 48-48 hours (12). Various studies have indicated a direct relationship between serum levels of PCT and mortality rates (3, 13-15); therefore, PCT levels can be helpful for early classification, and better treatment of the patients admitted to the ICT and are at risk of death.

There are several published systematic reviews about the role of PCT in appropriate management of critically ill patients, but neither of them has considered the role of PCT in ICU patients. Hence, this review study was performed with the aim of investigating the role of PCT in the prognosis of death in patients admitted to the ICU.

MATERIALS AND METHODS

This narrative review study was performed based on Cochrane collaboration recommendations for reviews. For this purpose, the seven steps, including the designing question, selection of eligibility criteria, literature review, selection and deletion of articles, evaluation of the quality of papers, extraction of the necessary information, and presenting were followed.

Eligibility criteria

We reviewed all the titles and abstracts of published research articles with the following inclusion criteria: (a) studies aimed to confirm the function of a prognostic model in predicting mortality or survival, (b) mortality or survival of a specific endpoint (for example, 30 days), (c) patients admitted to intensive care units, and d) the articles written in English.

The exclusion criteria of the current review included: (a) articles whose data were not specifically focused on prognosis of patients in ICU, (b) articles that did not provide sufficient information on the cause of death of patients in ICU, and (c) articles focusing on the treatment of comorbid patients with infections in ICU. Also, all papers published in non-English or Persian languages, the study of animal models, the lack of presented data or poor description of applied methods, non-clinical studies, experimental studies, experts' opinion, letter to editor, review articles, systematic reviews, meta-analyses, case reports, case reports, comparative studies, and the studies on children were excluded from this study. The study type was limited to clinical trials, cohort, and prospective cross-sectional studies.

The literature review

In this study, the literature review was carried out by two specialized researchers who consistently communicated with each other to calibrate their search

strategies. The search was conducted on Google Scholar, PubMed, Magiran, ScienceDirect, and SID. The initial search was performed in December 2018 and updated in March 2019. The following keywords were searched: ICU and Procalcitonin, in combination with Prognostic Value, Mortality, Sepsis, and Bacterial Infection, and the articles published until 2019 were retrieved. Also, to search Iranian databases, including SID and Magiran, the same terms and expressions were searched. Search on these databases was done without any limitation or filtering. The appropriate BOOLEANs and wild cards were applied to reach the best results.

Study selection and data extraction

At first, titles and summaries of all articles were reviewed, and the articles related to study objectives were selected. Then, the full text of selected articles was obtained, and the articles which were consistent with inclusion criteria were evaluated. The data of included studies were recorded in data extraction forms by both authors to determine whether the articles met the inclusion criteria. Articles related to our goals were entered, and other articles were removed. Data were reviewed separately by two authors. In the next step, the two authors consulted, removed the unrelated articles, carefully evaluated the remaining studies, and extracted the necessary information. The process and counts of selected articles are shown in the PRISMA diagram (Figure 1).

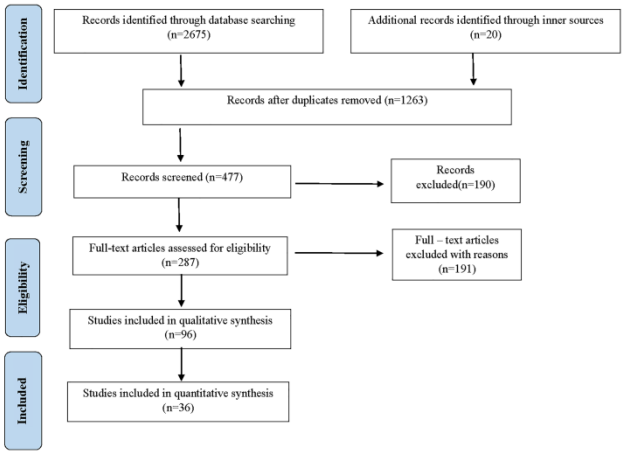

Figure 1. PRISMA chart of the systematic review of the articles searched using Google scholar, PubMed, ScienceDirect, SID, and Magiran databases

Study designs

At first, the summary of related articles was explored. The articles which met the inclusion criteria entered the study for further review and evaluation. After removing the unrelated articles, the full text of all articles was extracted and carefully studied. A standard form was used for collecting data. The first author did the assessment, and in case of doubt, the co-author was consulted. From each selected study, we extracted the following data: size and nature of the sample, geographical location of the plan, rate of admission, duration of follow-up in the ICU, time of data collection, and mortality rate in the ICU.

RESULTS

After searching Google Scholar, PubMed, and ScienceDirect databases, 2675 articles were obtained. We found 1836 articles in primary search in Google Scholar, 918 articles in PubMed, and 921 in ScienceDirect. Also, 20 articles were found in Magiran and 15 in SID databases. After screening the titles and abstracts of these articles, 2197 articles were excluded from the study due to not providing the same purpose as the current study, and the unrelated studies were also excluded, and 478 articles remained. Also, 1417 articles were excluded due to the repetition of the project. The full text of 96 articles was evaluated in terms of inclusion criteria.

Among the included studies, 60 articles were excluded due to insufficient data, and 36 articles entered the study for data extraction (Figure 1). The reasons for removing these articles in detail were as follows: no access to the full text of the article (n=10), articles published in non-English or Persian languages (n=12), no data or poor description of applied methods (n=12), study types of letters to the editor (n=5) and review, systematic review, and meta-analysis articles (n=47).

In total, 36 articles were included in the data extraction phase after evaluation of the full text of retrieved articles. In these studies, PCT levels of about 17080 ICU-admitted patients had been evaluated. Due to varied study types of included studies and high potential heterogeneity. Thus, just a simple report of data was performed in this study.

Regarding study locations, most of these studies had been conducted in different areas across the Europe and

Asia, and some in the United States. About 6 studies (8.3%) had been conducted in Spain and India, six studies (5.5%) in France, Australia, Germany, Greece, Malaysia, and Italy, and one article (2.7%) in other countries. Totally, 16 studies (44.4%) had been done in Europe, 17 studies (47.2%) in Asia, and three studies (8.3%) in the US and Australia. In total, one study (2.7%) had been conducted in Iran.

The duration of the study was 1 to 10 years. In various studies, the duration of follow-up of PCT levels in patients admitted to ICU was reported from one day to 30 days after admission. The mortality rate in these patients was reported between 5.7% and 79%. The highest mortality rate was reported in the studies conducted in India and Pakistan. In different studies, serum levels of PCT had been reported from at least 5ng/dL to more than 16ng/dL in patients admitted to ICU, which was >10ng/dL in most studies. The prevalence of sepsis had been reported between 13% and 77.6%. Table 1 shows some of the relevant variables, including size and nature of the sample, the geographical location of the study, the acceptance rate, follow-up time in the ICU, mortality rate, mean serum level of PCT, and serum concentration of C-reactive protein (CRP). These studies had been conducted in 21 countries around the world. The articles were evaluated by quality assessment, which is presented in Table 2.

Table 1. Frequency and serum level of PCT in patients admitted to ICU

Authors	Year	Country	Study design	Number of sample	ICU	Follow-up (day)	Mortality rate (%)	PCT test	Mean serum level of PCT ng/mL	concentration of CRP mg/dL	Rate of sepsis (%)	Other bacterial infections (%)
Adamik et al (16)	2000	Poland	prospective	41	heart	5	61	Lumitest PCT	≤10	Not reported	61	32
Clec'h et al (17)	2004	France	prospective	75	heart	10	66.7	Not reported	≤14	≤12	65	77
Clec'h et al (18)	2006	France	prospective	36	Multi-sections	1	69.4	KRYPTOR-PCT	≤10	≤10	36	Not reported
Dahaba et al (19)	2006	Australia	prospective	69	surgery	28	26.1	Lumitest PCT	≤9	≤10	100	25
Meng et al (20)	2009	China	prospective	86	Multi-sections	28	37	PCT-Q	≤10	≤10	76	Not reported
Karlsson et al (21)	2010	فنلاند	prospective	242	Multi-sections	2	24.2	Cobas PCT	≤12	Not reported	50	28.5
Jensen et al (22)	2011	Denmark	Randomized controlled	1200	Multi-sections	28	31	PCT-Q	≤10	≤10	40.9	Not reported
Tschaikowsky et al (23)	2011	Germany	prospective	51	Multi-sections	28	31.3	KRYPTOR-PCT	≤5	≤2.5	35	Not reported
Savva et al (24)	2011	Greece	prospective	206	emergency	28	9.7	PCT-Q	≤12.9	Not reported	77.6	Not reported
Giamarellos-Bourboulis et al (25)	2011	Greece	prospective	922	Multi-sections	1	17	KRYPTOR-PCT	≤12	Not reported	25.6	Not reported
Guan et al (26)	2011	China	prospective	37	Multi-sections	28	32.4	Lumitest PCT	≤10	≤10	100	Not reported
Mobaien et al (27)	2011	Iran	descriptive	35	Multi-sections	3	51.4	PCT-Q	≤10	Not reported	100	Not reported
Feng et al (28)	2012	China	prospective	102	Multi-sections	28	43	VIDAS	≤10	≤11	100	Not reported
Kenzaka et al (29)	2012	Japan	prospective	206	emergency	28	9.7	PCT-Q	≤10	≤10	13	Not reported
Ruiz-Rodriguez et al (30)	2012	Spain	prospective	27	Multi-sections	2	66.7	Lumitest PCT	≤10	Not reported	100	Not reported
Yin et al (31)	2013	China	prospective	680	emergency	30	33.1	VIDAS	≤11	Not reported	56	44
Suberviola et al (32)	2013	Spain	prospective	137	Multi-sections	1	29.9	KRYPTOR-PCT	≤13	≤21	29	Not reported
Yaroustovsky et al (33)	2013	Russia	prospective	81	heart	28	45.7	VIDAS	≤16	Not reported	59	Not reported
Schuetz et al (34)	2013	America	prospective	154	Multi-sections	3	29.2	VIDAS	≤10	Not reported	18	Not reported
Mat-Nor et al (35)	2014	Malaysia	prospective	67	Multi-sections	2	40.3	KRYPTOR-PCT	≤8	Not reported	71	Not reported
Lin et al (5)	2014	China	prospective	102	Multi-sections	28	42.2	VIDAS	≤11	≤8	54.8	19
Masson et al (36)	2014	Italy	prospective	100	Multi-sections	28	50	Cobas PCT	≤11	Not reported	38	10
Jain et al (37)	2014	India	prospective	54	Multi-sections	28	50.9	Not reported	≤13	≤21	71	25
Mat-Nor et al (38)	2015	Malaysia	prospective	239	Multi-sections	3	28.5	KRYPTOR-PCT	≤10	Not reported	68.6	Not reported
Zhou et al (39)	2015	Australia	prospective	71	Multi-sections	28	17	BRAHMS PCT ECLIA	≤10	≤10	Not reported	Not reported
Bloos et al (40)	2016	Germany	Clinical trial	8174	Multi-sections	28	28.3	PCT-Q	≤10	≤12	13.3	Not reported
Huang et al (41)	2016	Taiwane	prospective	48	Multi-sections	5	16.7	PCT-Q	≤11	Not reported	41.1	14.3
Schuetz et al (42)	2017	Sweden	prospective	646	Multi-sections	28	22	KRYPTOR-PCT	≤10	Not reported	54	Not reported
Surti et al (43)	2018	India	prospective	300	heart	3	8	Not reported	≤11	Not reported	14	47
Aygun et al (44)	2018	Turkey	prospective	417	Multi-sections	28	3.1	KRYPTOR-PCT	≤10	≤10	36.8	Not reported
Demirdal et al (45)	2018	India	prospective	156	Multi-sections	1	60.3	PCT-Q	≤10	≤14	44.2	41
Ahmed at al (46)	2018	Pakistan	prospective	103	Multi-sections	5	79	Not reported	≤10	Not reported	Not reported	41.7
Mazo et al (47)	2018	Spain	prospective	100	Multi-sections	3	22.2	PCT-Q	≤10	Not reported	Not reported	Not reported
Hu et al (48)	2018	China	prospective	141	Multi-sections	28	28.8	VIDAS	≤10	≤10	100	-
Clementi et al (49)	2019	Italy	prospective	122	Heart surgery	30	5.7	KRYPTOR-PCT	≤10	Not reported	37.7	Not reported
Ryoo et al (50)	2019	South Korea	prospective	1772	Multi-sections	28	20.7	Not reported	≤14	≤12	100	Not reported

Table 2. Quality assessment of the studies

Reference	Measuring interventional variables	How to properly measure the sample	Precise explanation of intervention method	Departing from main purpose of intervention	Lost data	Bias in reporting the final results	Without bias
16	Yes	No	Yes	No	Yes	Yes	No
17	yes	No	No	No	yes	yes	No
18	yes	yes	yes	No	unknown	yes	No
19	yes	No	yes	No	yes	yes	No
21	yes	yes	yes	No	yes	yes	No
21	No	yes	yes	No	yes	yes	No
22	No	yes	yes	No	yes	yes	No
23	No	yes	yes	No	yes	yes	No
24	No	No	yes	yes	unknown	yes	No
25	No	yes	yes	No	yes	yes	No
26	No	yes	yes	No	yes	yes	yes
27	yes	yes	yes	No	yes	No	No
28	yes	yes	yes	No	yes	yes	No
29	yes	No	yes	No	yes	yes	yes
30	No	yes	yes	No	yes	No	No
31	yes	No	yes	No	yes	No	No
32	yes	yes	yes	No	yes	No	No
33	yes	No	yes	No	unclear	No	No
34	yes	yes	yes	No	yes	No	No
35	yes	yes	yes	No	yes	No	No
5	yes	yes	yes	No	yes	yes	No
36	yes	yes	yes	No	yes	yes	No
37	yes	yes	No	unknown	yes	yes	No
38	yes	yes	yes	No	unknown	yes	No
39	yes	yes	yes	No	yes	No	yes
40	yes	yes	yes	No	yes	yes	No
41	No	yes	yes	No	yes	yes	No
42	yes	yes	yes	No	yes	yes	yes
43	yes	No	No	No	yes	yes	No
44	yes	yes	yes	No	yes	yes	yes
45	yes	yes	yes	No	unknown	yes	No
46	yes	yes	No	unknown	yes	yes	No
47	No	yes	yes	No	yes	yes	yes
48	yes	yes	yes	unknown	yes	unknown	No
49	yes	No	yes	No	yes	yes	yes
50	yes	yes	No	No	yes	yes	yes

DISCUSSION

According to the findings of this study, the serum level of PCT is one of the most important prognostic factors in ICUs, which is more rapid and easier than other tests indicating infection. Also, sepsis is one of the most important mortality causes among these patients, which can lead to death in the absence of timely ICU admission and lack of proper treatment.

Serum level of procalcitonin

Plasma PCT as a precursor of calcitonin has a half-life of about 25 to 30 hours. Its value increases over 3 to 6 hours from the time of the initial stimulation, and the higher value is accompanied by a poorer prognosis (45). Increased rate suggests the presence of more severe infection, especially bacterial infections, due to the systemic response to it (46). A review of the studies shows a significant

relationship between mortality rate in patients admitted to ICU and different types of infections caused by hospital admission (6, 51, 52). Therefore, owning appropriate diagnostic methods is necessary to provide a proper estimation of prognosis for identification of these infections in hospitalized patients for the treatment team in order to reduce mortality rates. The highest amount of PCT is found in severe infections, such as septic shock; thus, early diagnosis can provide appropriate therapeutic interventions (37).

The serum level of PCT is very low (less than 0.05 ng/ml) in the absence of infection in the blood (3). However, serum level of PCT increases with infection, and in most studies, it has been reported that PCT level in dead patients was > 10 ng/ml (11, 53). PCT significantly decreases in the serum of patients in response to appropriate treatment (3, 11). Following the reduced level of serum PCT, the survival rate of patients increases (54). Therefore, monitoring of serum level of PCT might be an indicator of survival due to appropriate response to treatment during the disease.

Charles et al. studied the reduction of PCT in patients admitted to ICU and compared the clinical outcomes of the patients, and reported that increased survival rate has a close relationship with decreased serum PCT levels (55). It was also reported that serum PCT levels was much less than 10 ng/ml in patients who had no infection during ICU hospitalization and also in patients who survived (9, 41).

Generally, serum PCT level seems a sensitive criterion for differentiation between non-microbial and microbial infections and determining its activity and prediction of response to treatment. However, one of the limitations of PCT in the diagnosis of infectious diseases is that in some cases, serum PCT levels have also been reported to increase in noninfectious conditions (56, 57). In this regard, some studies also have shown no significant relationship between serum PCT levels and prediction of bacterial infection (7, 51). It has also been reported in some studies that no increment was observed in serum PCT levels despite infection in ICU patients (30, 34, 35). Similarly, according to various studies carried out in this field, more studies are needed to evaluate the diagnostic value of PCT in the prediction of bacterial infection in patients admitted to the ICU.

Procalcitonin serum level and prognosis

PCT is useful for predicting the risk of short-term mortality. Demirdal et al. performed 3642 PCT tests on 156 patients admitted to the ICU and concluded that the maximum increase in PCT levels is within the first day to a 90-day period, which is an independent predictor of mortality in these patients (7). However, another study reported that PCT has poor diagnostic value in predicting mortality at early admission in ICU (44). The findings of studies reported in Table 1 show that PCT can differentiate noninfectious from infectious patients, and its effect on mortality prediction can be attributed to the patient's characteristics, clinical symptoms, number and time of PCT measurements, and sensitivity of the method used for PCT measurement (58). However, PCT in different clinical conditions can be useful for the prognosis of patient's status, and it is suggested that in malignancies, in addition to routine laboratory tests, serum PCT levels be evaluated because this method might predict the risk of different infections in these patients; thus, treatment procedures can be done as soon as possible, and mortality rates will be reduced in patients admitted to the ICU.

Procalcitonin serum level and sepsis

Sepsis is a critical clinical condition caused by bacterial infection and leads to acute disorder in the functioning of vital organs (54). This condition is one of the main life-threatening causes in patients admitted to the ICU, and better results can be expected by timely and appropriate treatment with antibiotics (36). Laboratory methods, including blood cell count and immunological tests, have lower sensitivity and specificity in the diagnosis of sepsis in comparison with blood culture (15). Therefore, researchers and physicians have tested other blood biochemical markers to seek the possibility of accurate diagnosis of sepsis in a shorter time (41).

Nowadays, PCT is widely accepted in the clinical diagnosis of sepsis before blood culture (37). Several studies have reported that the severity of sepsis has a direct relationship with PCT levels (30, 41, 47, 50). In this regard, PCT is considered as one of the markers of bacteremia and sepsis, like as cytokines, interleukins, and CRP (7, 48, 50). In addition, it has been reported that PCT can differentiate bacterial infections from inflammatory sepsis in 77% of cases according to other clinical parameters (59).

PCT concentration in blood is related to the mortality rate of patients with sepsis (27, 30, 48, 50). Generally, PCT can diagnose a significant proportion of patients with sepsis, and, given that sepsis is one of the acute conditions among patients admitted to ICU, it has a direct effect on the mortality rate of these patients. Therefore, the diagnostic tests of this health condition should have high sensitivity. PCT cannot be used as the only diagnostic indicator of sepsis, but given the ease and speed of the test, it can be used as part of the sepsis screening tool. PCT has a relative value for the protective diagnosis of sepsis; further studies are recommended in order to reach more definitive results in this field.

Serum C Reactive Protein vs. procalcitonin

CRP is one of the acute phase reactants, which is made during inflammatory processes. The systemic activation of the inflammatory process is the body's proper response to the disease process (50). The emergence, increase, or decrease in the amount of each acute-phase protein during an infection is different and independent of others. For example, CRP appears 6 to 8 hours after infection in the serum and reaches its maximum level after 48 to 72 hours.

On the other hand, CRP levels remain high during infection, and studies have shown that during treatment with antibiotics, the amount of this protein decreases in less than 24 hours (60). Comparison of PCT and CRP markers in the diagnosis of bacterial infections in systemic inflammatory patients indicates that PCT measurement has higher sensitivity and specificity than CRP measurement in detecting bacterial infections (61). Accordingly, it is suggested that both PCT and CRP markers be used simultaneously to detect bacterial infections for suitable prognosis of patients in ICU and to reduce the mortality rate in these patients.

CONCLUSION

Increased PCT can indicate a risk of infection in patients admitted to the ICU and also has a relationship with mortality due to infection in these patients. However, this sensitivity is not observed for CRP. PCT is recommended as a daily test for these patients, which can improve the ability of ICU physicians for timely diagnosis and appropriate treatment at an early stage of infectious disease. According to the studies conducted in this regard, serum PCT levels can provide a good prognosis of mortality rate in the ICU.

REFERENCES

1. Schneider HG, Lam QT. Procalcitonin for the clinical laboratory: a review. ***Pathology*** 2007;39(4):383-90.
2. Eschborn S, Weitkamp JH. Procalcitonin versus C-reactive protein: review of kinetics and performance for diagnosis of neonatal sepsis. ***J Perinatol*** 2019;39(7):893-903.
3. Pepper DJ, Sun J, Rhee C, Welsh J, Powers JH 3rd, Danner RL, et al. Procalcitonin-Guided Antibiotic Discontinuation and Mortality in Critically Ill Adults: A Systematic Review and Meta-analysis. ***Chest*** 2019;155(6):1109-18.
4. Luyt CE, Combes A, Reynaud C, Hekimian G, Nieszkowska A, Tonnellier M, et al. Usefulness of procalcitonin for the diagnosis of ventilator-associated pneumonia. ***Intensive Care Med*** 2008;34(8):1434-40.
5. Lin KH, Wang FL, Wu MS, Jiang BY, Kao WL, Chao HY, et al. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection in patients with liver cirrhosis: a systematic review and meta-analysis. ***Diagn Microbiol Infect Dis*** 2014;80(1):72-8.
6. 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(10):CD007498.

7. Demirdal T, Sen P, Nemli SA. Diagnostic Value of Procalcitonin in Predicting Bacteremia in Intensive Care Unit. ***Indian J Crit Care Med*** 2018;22(2):78-84.
8. Riley RD, Moons KG, Altman DG. Prognostic factor research. ***Prognosis Research in Health Care: Concepts, Methods, and Impact*** 2019;24:107.
9. Carvalho GMC, Leite TT, Libório AB. Prediction of 60-Day Case Fatality in Critically Ill Patients Receiving Renal Replacement Therapy: External Validation of a Prediction Model. ***Shock*** 2018;50(2):156-61.
10. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. ***Intensive Care Med*** 2013;39(2):165-228.
11. Vazquez-Grande G, Kumar A. Optimizing antimicrobial therapy of sepsis and septic shock: focus on antibiotic combination therapy. ***Semin Respir Crit Care Med*** 2015;36(1):154-66.
12. 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.
13. Khanna AK, Meher S, Prakash S, Tiwary SK, Singh U, Srivastava A, et al. Comparison of Ranson, Glasgow, MOSS, SIRS, BISAP, APACHE-II, CTSI Scores, IL-6, CRP, and Procalcitonin in Predicting Severity, Organ Failure, Pancreatic Necrosis, and Mortality in Acute Pancreatitis. ***HPB Surg*** 2013;2013:367581.
14. Bloos F, Trips E, Nierhaus A, Briegel J, Heyland DK, Jaschinski U, et al. Effect of Sodium Selenite Administration and Procalcitonin-Guided Therapy on Mortality in Patients With Severe Sepsis or Septic Shock: A Randomized Clinical Trial. ***JAMA Intern Med*** 2016;176(9):1266-76.
15. Nelson J, Hansen C, Scupp T, Brainard J. Implications of Procalcitonin Testing in Critically Ill Patients with Sepsis. ***Am J Respir Crit Care Med*** 2019;199(2):232-4.
16. Adamik B, Kübler-Kielb J, Golebiowska B, Gamian A, Kübler A. Effect of sepsis and cardiac surgery with cardiopulmonary bypass on plasma level of nitric oxide metabolites, neopterin, and procalcitonin: correlation with mortality and postoperative complications. ***Intensive Care Med*** 2000;26(9):1259-67.
17. 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.
18. Clec'h C, Fosse JP, Karoubi P, Vincent F, Chouahi I, Hamza L, et al. Differential diagnostic value of procalcitonin in surgical and medical patients with septic shock. ***Crit Care Med*** 2006;34(1):102-7.
19. Dahaba AA, Hagara B, Fall A, Rehak PH, List WF, Metzler H. Procalcitonin for early prediction of survival outcome in postoperative critically ill patients with severe sepsis. ***Br J Anaesth*** 2006;97(4):503-8.
20. Meng FS, Su L, Tang YQ, Wen Q, Liu YS, Liu ZF. Serum procalcitonin at the time of admission to the ICU as a predictor of short-term mortality. ***Clin Biochem*** 2009;42(10-11):1025-31.
21. Karlsson S, Heikkinen M, Pettilä V, Alila S, Väisänen 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.
22. Jensen JU, Hein L, Lundgren B, Bestle MH, Mohr TT, Andersen MH, et al. 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(9):2048-58.
23. Tschaikowsky K, Hedwig-Geissing M, Braun GG, Radespiel-Troeger M. Predictive value of procalcitonin, interleukin-6, and C-reactive protein for survival in postoperative patients with severe sepsis. ***J Crit Care*** 2011;26(1):54-64.
24. Savva A, Raftogiannis M, Baziaka F, Routsi C, Antonopoulou A, Koutoukas P, et al. Soluble urokinase plasminogen activator receptor (suPAR) for assessment of disease severity in ventilator-associated pneumonia and sepsis. ***J Infect*** 2011;63(5):344-50.
25. Giamarellos-Bourboulis EJ, Tsangaris I, Kanni T, Mouktaroudi M, Pantelidou I, Adamis G, et al. Procalcitonin as an early indicator of outcome in sepsis: a prospective observational study. ***J Hosp Infect*** 2011;77(1):58-63.

26. Guan J, Lin Z, Lue H. Dynamic change of procalcitonin, rather than concentration itself, is predictive of survival in septic shock patients when beyond 10 ng/mL. ***Shock*** 2011;36(6):570-4.
27. Mobaien AR, Shams S. The Role of Procalcitonin in Severity and Outcome of Patients with Sepsis in ICU during Treatment. ***Qom University of Medical Sciences Journal*** 2011;5(2):82-6.
28. Feng L, Zhou X, Su LX, Feng D, Jia YH, Xie LX. Clinical significance of soluble hemoglobin scavenger receptor CD163 (sCD163) in sepsis, a prospective study. ***PLoS One*** 2012;7(7):e38400.
29. Kenzaka T, Okayama M, Kuroki S, Fukui M, Yahata S, Hayashi H, et al. Use of a semiquantitative procalcitonin kit for evaluating severity and predicting mortality in patients with sepsis. ***Int J Gen Med*** 2012;5:483-8.
30. Ruiz-Rodríguez JC, Caballero J, Ruiz-Sanmartin A, Ribas VJ, Pérez M, Bóveda JL, et al. Usefulness of procalcitonin clearance as a prognostic biomarker in septic shock. A prospective pilot study. ***Med Intensiva*** 2012;36(7):475-80.
31. Yin Q, Liu B, Chen Y, Zhao Y, Li C. The role of soluble thrombomodulin in the risk stratification and prognosis evaluation of septic patients in the emergency department. ***Thromb Res*** 2013;132(4):471-6.
32. Suberviola B, Castellanos-Ortega A, Ruiz Ruiz A, Lopez-Hoyos M, Santibañez M. Hospital mortality prognostication in sepsis using the new biomarkers suPAR and proADM in a single determination on ICU admission. ***Intensive Care Med*** 2013;39(11):1945-52.
33. Yaroustovsky M, Plyushch M, Popov D, Samsonova N, Abramyan M, Popok Z, et al. Prognostic value of endotoxin activity assay in patients with severe sepsis after cardiac surgery. ***J Inflamm (Lond)*** 2013;10(1):8.
34. Schuetz P, Maurer P, Punjabi V, Desai A, Amin DN, Gluck E. Procalcitonin decrease over 72 hours in US critical care units predicts fatal outcome in sepsis patients. ***Crit Care*** 2013;17(3):R115.
35. Mat Nor MB, Md Ralib A. Procalcitonin clearance for early prediction of survival in critically ill patients with severe sepsis. ***Crit Care Res Pract*** 2014;2014:819034.
36. Masson S, Caironi P, Spanuth E, Thomae R, Panigada M, Sangiorgi G, et al. Presepsin (soluble CD14 subtype) and procalcitonin levels for mortality prediction in sepsis: data from the Albumin Italian Outcome Sepsis trial. ***Crit Care*** 2014;18(1):R6.
37. Jain S, Sinha S, Sharma SK, Samantaray JC, Aggrawal P, Vikram NK, et al. Procalcitonin as a prognostic marker for sepsis: a prospective observational study. ***BMC Res Notes*** 2014;7:458.
38. Mat-Nor MB, Md Ralib A, Abdulah NZ, Pickering JW. The diagnostic ability of procalcitonin and interleukin-6 to differentiate infectious from noninfectious systemic inflammatory response syndrome and to predict mortality. ***J Crit Care*** 2016;33:245-51.
39. Zhou G, Ho KM. Procalcitonin concentrations as a predictor of unexpected readmission and mortality after intensive care unit discharge: A retrospective cohort study. ***J Crit Care*** 2016;33:240-4.
40. Bloos F, Trips E, Nierhaus A, Briegel J, Heyland DK, Jaschinski U, et al. Effect of Sodium Selenite Administration and Procalcitonin-Guided Therapy on Mortality in Patients With Severe Sepsis or Septic Shock: A Randomized Clinical Trial. ***JAMA Intern Med*** 2016;176(9):1266-76.
41. Huang MY, Chen CY, Chien JH, Wu KH, Chang YJ, Wu KH, et al. Serum Procalcitonin and Procalcitonin Clearance as a Prognostic Biomarker in Patients with Severe Sepsis and Septic Shock. ***Biomed Res Int*** 2016;2016:1758501.
42. Schuetz P, Birkhahn R, Sherwin R, Jones AE, Singer A, Kline JA, et al. Serial Procalcitonin Predicts Mortality in Severe Sepsis Patients: Results From the Multicenter Procalcitonin MOnitoring SEpsis (MOSES) Study. ***Crit Care Med*** 2017;45(5):781-9.
43. Surti J, Jain I, Shah K, Mishra A, Kandre Y, Garg P, et al. Predictive efficacy of procalcitonin, platelets, and white blood cells for sepsis in pediatric patients undergoing cardiac surgeries who are admitted to intensive care units: Single-center experience. ***Ann Pediatr Cardiol*** 2018;11(2):137-42.
44. Aygun F. Procalcitonin Value Is an Early Prognostic Factor Related to Mortality in Admission to Pediatric Intensive Care Unit. ***Crit Care Res Pract*** 2018;2018:9238947.

45. Demirdal T, Sen P, Nemli SA. Diagnostic Value of Procalcitonin in Predicting Bacteremia in Intensive Care Unit. ***Indian J Crit Care Med*** 2018;22(2):78-84.
46. Ahmed S, Siddiqui I, Jafri L, Hashmi M, Khan AH, Ghani F. Prospective evaluation of serum procalcitonin in critically ill patients with suspected sepsis- experience from a tertiary care hospital in Pakistan. ***Ann Med Surg (Lond)*** 2018;35:180-4.
47. Mazo C, Borgatta B, Pont T, Sandiumenge A, Moyano S, Roman A, et al. Procalcitonin accurately predicts lung transplant adults with low risk of pulmonary graft dysfunction and intensive care mortality. ***J Crit Care*** 2018;44:142-7.
48. Hu C, Zhou Y, Liu C, Kang Y. Pentraxin-3, procalcitonin and lactate as prognostic markers in patients with sepsis and septic shock. ***Oncotarget*** 2017;9(4):5125-36.
49. Clementi A, Virzì GM, Muciño-Bermejo MJ, Nalesso F, Giavarina D, Carta M, Brocca A, et al. Presepsin and Procalcitonin Levels as Markers of Adverse Postoperative Complications and Mortality in Cardiac Surgery Patients. ***Blood Purif*** 2019;47(1-3):140-8.
50. Ryoo SM, Han KS, Ahn S, Shin TG, Hwang SY, Chung SP, et al. The usefulness of C-reactive protein and procalcitonin to predict prognosis in septic shock patients: A multicenter prospective registry-based observational study. ***Sci Rep*** 2019;9(1):6579.
51. Anderson DJ, Moehring RW, Sloane R, Schmader KE, Weber DJ, Fowler VG Jr, et al. Bloodstream infections in community hospitals in the 21st century: a multicenter cohort study. ***PLoS One*** 2014;9(3):e91713.
52. Jhan JY, Huang YT, Shih CH, Da Yang J, Lin YT, Lin SJ, et al. Procalcitonin levels to predict bacterial infection in surgical intensive care unit patients. ***Formosan Journal of Surgery*** 2017;50(4):135.
53. Patnaik R, Azim A. Diagnostic Value of Procalcitonin in Predicting Bacteremia in Intensive Care Unit. ***Indian J Crit Care Med*** 2018;22(5):389.
54. Mobaien A, Shams S. Plasma procalcitonin level as a predictor of treatment response in ICU patients with bacterial sepsis. ***Tehran University Medical Journal*** 2010;68(2):110-5.
55. Charles PE, Tinel C, Barbar S, Aho S, Prin S, Doise JM, et al. Procalcitonin kinetics within the first days of sepsis: relationship with the appropriateness of antibiotic therapy and the outcome. ***Crit Care*** 2009;13(2):R38.
56. Weidner W, Wagenlehner FM. Re: Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. ***Eur Urol*** 2014;66(1):178.
57. 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.
58. Li Z, Wang H, Liu J, Chen B, Li G. Serum soluble triggering receptor expressed on myeloid cells-1 and procalcitonin can reflect sepsis severity and predict prognosis: a prospective cohort study. ***Mediators Inflamm*** 2014;2014:641039.
59. Yap CY, Aw TC. The use of procalcitonin in clinical practice. ***Proceedings of Singapore Healthcare*** 2014;23(1):33-7.
60. Oliveira CF, Botoni FA, Oliveira CR, Silva CB, Pereira HA, Serufo JC, et al. Procalcitonin versus C-reactive protein for guiding antibiotic therapy in sepsis: a randomized trial. ***Crit Care Med*** 2013;41(10):2336-43.
61. Simon L, Saint-Louis P, Amre DK, Lacroix J, Gauvin F. Procalcitonin and C-reactive protein as markers of bacterial infection in critically ill children at onset of systemic inflammatory response syndrome. ***Pediatr Crit Care Med*** 2008;9(4):407-13.