

Procalcitonin and sepsis in the Emergency Department: an update

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Abstract. – OBJECTIVE: Due to significant mortality and morbidity which may be reduced by prompts treatment, there is great interest in determining an ideal biomarker for the diagnosis of sepsis upon presentation to the Emergency Department. The most specific test is a positive blood culture, but its sensitivity is very low, and the results are usually available 2 days after sampling. For this reason, research is conducted into serum biomarkers with greater sensitivity for which results can be available within hours of presentation. High initial procalcitonin levels are a sensitive marker of bacterial infection, and the degree of procalcitonin elevation may determine which patients are at greater risk for adverse outcomes (mortality or ICU admission). The purpose of this narrative review is to evaluate the utility of procalcitonin as a diagnostic marker of sepsis in the emergency department and the use of procalcitonin-guided management algorithms.

MATERIALS AND METHODS: A PubMed search was conducted in June 2020 for procalcitonin, resulting in the retrieval of 371 articles which were screened for relevance. 48 articles were included in the review.

CONCLUSIONS: Procalcitonin elevation may be used as an indication for initiation of antibiotic treatment, and antibiotics may be discontinued once procalcitonin normalizes. This approach leads to reduced antibiotic consumption, but it is not yet clear whether it ensures better outcomes for patients. Procalcitonin in centers where it is available could be a useful diagnostic and prognostic biomarker for patients presenting to the Emergency Department with symptoms suggestive of sepsis. Further research is however required to determine whether the use of procalcitonin measurements in management algorithms leads to improved patient outcomes.

Key Words:

Sepsis Syndrome, Biomarker, Procalcitonin, Presepsin, Emergency department.

Introduction

Sepsis syndrome has a complex underlying pathophysiology and despite extensive research, the ideal biomarker for the clinical decision-making, diagnosis and prognosis of the syndrome has yet to be identified. Several biomarkers have been used to facilitate improved monitoring, management and risk stratification of the sepsis syndrome, but none of them is sufficiently sensitive and specific to be regarded as a gold standard. Especially in the Emergency Department setting where patients may present in critical condition with symptomatology suggestive of sepsis, a biomarker which can aid in the differential diagnosis between disseminated bacterial infection and non-infectious causes of severe systemic inflammatory response syndrome (SIRS) would be particularly useful¹. Procalcitonin has been used as a possible marker of the systemic inflammatory response to infection and numerous studies have proved its efficacy as a marker of critical illness and sepsis. This study aimed to summarize the existed literature regarding the role of procalcitonin in the assessment of patients with sepsis in the emergency department setting, and its predictive value as a prognostic factor of the sepsis syndrome and its various stages².

Procalcitonin is a protein produced by the parafollicular cells of the thyroid gland, which is

cleaved to produce calcitonin, a hormone which regulates calcium homeostasis. Calcitonin increases calcium deposition in bones and reduces serum calcium levels. It can be used therapeutically in the management of severe hypercalcemia. Aside from its physiological function, procalcitonin gene expression is induced by lipopolysaccharide and systemic inflammatory mediators, such as interleukin 6 and tumor necrosis factor, so the serum concentration of procalcitonin increases dramatically during systemic bacterial infections and levels appear to normalize just as rapidly once the infection is cleared. It is considered an acute phase reactant and for this reason serum procalcitonin may be a useful biomarker for sepsis. The test is not routinely available at all hospitals, but it is not particularly expensive and its widespread use may lead to improved patient outcomes³. Most promising clinical applications for the measurement of serum procalcitonin in the Emergency Department are to determine which patients have a disseminated bacterial infection and when antibiotics should be initiated. The degree of procalcitonin elevation may mirror disease severity and it could be used to identify those at higher risk of mortality, and those most likely to require admission to the intensive care unit (ICU)⁴. The purpose of this article is to review the diagnostic and prognostic significance of procalcitonin measurement upon presentation in the emergency department and to review the literature on procalcitonin guided management algorithms based on these results, which have the potential of reducing healthcare related costs and leading to improved patient outcomes.

Materials and Methods

We conducted a PubMed search on June 2020 using the terms ‘procalcitonin’ as “Title/Abstract” or as “MeSH Terms”. The structure of the search in the “Search details” window of the PubMed website was emergency service; hospital; procalcitonin; sepsis. We also reviewed the references of all identified manuscripts to identify additional relevant publications. All observational studies and randomized trials on the sensitivity, specificity negative and positive predictive value on the use of procalcitonin for the diagnosis of sepsis in the emergency department were included, as were observational studies on the association of procalcitonin levels on ED presentation with patient outcomes. Case reports, case series, studies not

in adults, and studies not requiring procalcitonin measurement upon initial presentation were excluded. Only publications in English were included. Though this is a narrative review, we opted to include a PRISMA flowchart and use a search methodology consistent with systematic reviews.

Results

The initial search gave 371 results, which were screened for relevance based on the title and abstract. The full text of articles which were deemed relevant was accessed and the most important information is presented in the tables of this review. The search process and results are presented in detail in the PRISMA flow chart, although this is not a systematic review (Figure 1). Research conducted on the role of procalcitonin measurements in the Emergency Department can be grouped in to 3 categories with minimal overlap: studies on the use of procalcitonin as a diagnostic marker to rule out (or in some cases rule in) sepsis (26 articles), those on its use as a predictive factor of severe outcomes (18 articles) and those on the utility of procalcitonin measurements to guide management decisions (4 articles). The findings of the review are presented and discussed in the following sections.

Procalcitonin May Aid in the Prompt Identification of Sepsis Due to Bacterial Infection in the Emergency Department

Sepsis is usually diagnosed clinically when systemic signs of inflammation are present along with an identifiable focus of infection. The gold standard for the diagnosis is the isolation of the causative pathogen in blood cultures. Blood cultures are however highly likely to be negative even in the presence of sepsis, and while a positive culture provides a definitive diagnosis, negative results have no predictive value. Depending on the focus of the infection, the causative organism can also be isolated from other clinical samples, such as urine in the case of urinary tract infections, sputum in the case of pneumonia, pleural fluid in the case of pleural empyema and ascitic fluid in the case of bacterial peritonitis. In elderly patients who are typically disoriented and unable to provide an accurate history or to comply with a physical exam, identification of the focus of infection is even more challenging. For this reason, biomarkers may be used to either rule in or rule out sepsis or to estimate its severity.

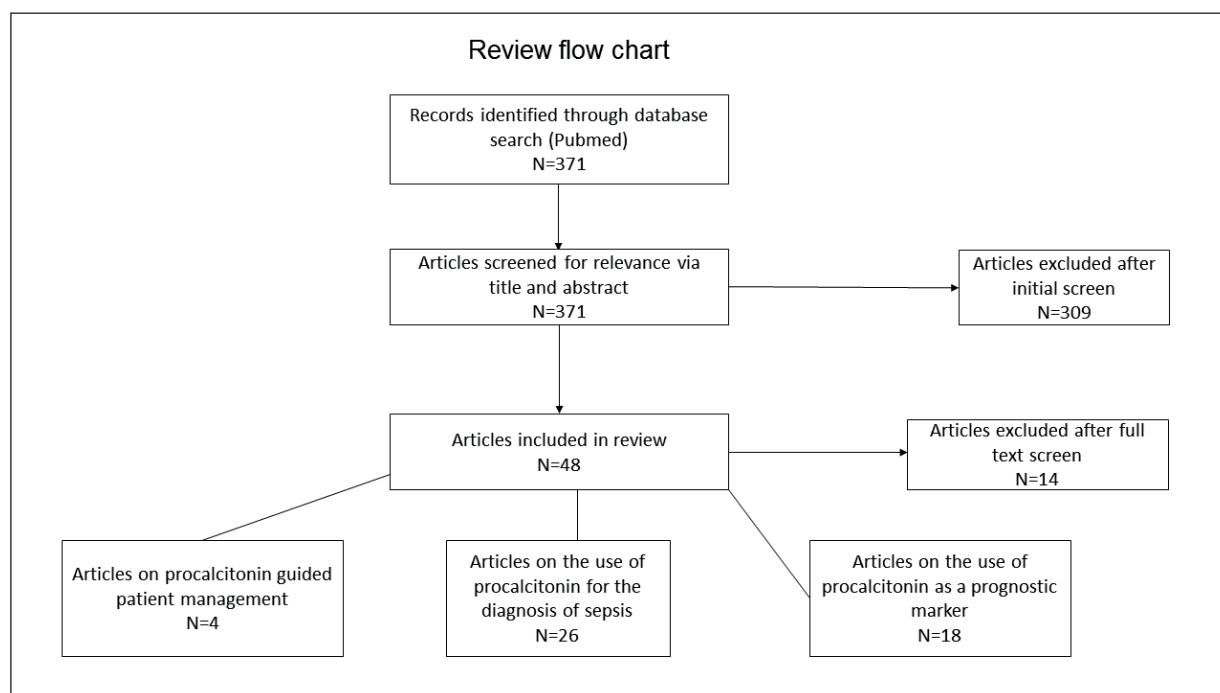


Figure 1. PRISMA flow chart detailing the article selection process for this review.

Some studies^{5,6} have been published regarding the value of procalcitonin as a diagnostic marker for sepsis and as an indicator of its severity, both alone and in comparison with other putative biomarkers of sepsis. Compared to lactate, procalcitonin may be more sensitive for mild cases of sepsis (suggesting it is more useful to rule out sepsis), whereas lactate has a stronger correlation with severe sepsis and septic shock. The association of lactate with more severe disease was also noted in other studies⁷, but it is less specific, especially in patients with advanced cancer⁸. It also appears to be more sensitive for bacteremia due to gram – organisms compared to gram + bacteremia^{6,9}. C-reactive protein (the term refers to the fact that it interacts with protein C produced by *Streptococcus pneumoniae*) is another ubiquitous acute phase reactant which is greatly elevated in bacterial infections. It is unclear which biomarker is preferable, as certain studies¹⁰⁻¹³ suggest that procalcitonin is more accurate than CRP for the diagnosis of sepsis, whereas other studies^{14,15}, though comparatively fewer and of lower quality would suggest the opposite. According to a Spanish cohort study of 653 patients, procalcitonin with a cutoff of 2.54 ng/ml had an AUC of 0.705 with a 95% confidence interval of [0.653-0.758] compared to 0.654 [0.604-0.705] for 4.1 mmol/L for lac-

tate and 0.579 [0.527-0.631] for 156 mg/L for CRP. Procalcitonin at a cutoff value of 2.54 ng/mL was clearly superior to CRP and lactate at their respective cutoffs in this cohort, with a specificity and sensitivity of 60.3% [52.3-67.7] and specificity of 70.5% [65.2-75.2]. It should however be noted that sensitivity and specificity vary greatly depending on the cutoff value, with lower cutoff values being characterized by higher sensitivity and greater cutoff values having better specificity⁹. The available data does indeed suggest that procalcitonin is a superior biomarker of sepsis compared to CRP, but this has not been conclusively proven and it may in fact not be relevant, as composite biomarkers may be more relevant to clinical practice. Composite scores utilizing more than one biomarker may be superior than any single test used in isolation¹⁶, and one such promising composite marker is the combination of procalcitonin with soluble phospholipase A2 group IIA¹⁷. Procalcitonin may also be comparable in accuracy or even superior compared to another promising biomarker, presepsin, especially in patients with acute renal failure¹⁸. The accuracy of procalcitonin as a biomarker may differ based on chronic comorbidities, especially renal failure. Procalcitonin is cleared by the kidneys and is also removed by dialysis, rendering its use unreliable in pa-

tients presenting with severe renal impairment¹⁹. Apart from culture, Polymerase Chain Reaction assays for the detection of common pathogens may also be used for the diagnosis of sepsis, and procalcitonin elevation may have a stronger correlation with positive PCR as compared to blood cultures²⁰. Other studies^{21,22} also favored the assumption that it is more strongly correlated with clinical sepsis as opposed to blood culture positivity. Procalcitonin appears to be more useful for ruling out sepsis compared to ruling it in, a fact which underlies its usefulness to aid in the decision whether to initiate or withhold antibiotics²³⁻²⁷. In the case of urinary tract infections, procalcitonin may aid in the identification of acute pyelonephritis and may also suggest the need for drainage procedures in pyelonephritis due to urinary calculi^{28,29}. In the case of acute prostatitis, procalcitonin may be less accurate as a biomarker compared to the prostate specific antigen³⁰. The studies examining the use of procalcitonin as a diagnostic marker for sepsis are presented in Table I.

Procalcitonin in the Emergency Department as a Predictor of Adverse Outcomes Including Mortality

While the evidence regarding the utility of procalcitonin as a diagnostic marker for sepsis remains inconclusive, it may be more valuable as a predictive factor for adverse outcomes in patients presenting to the ED with clinical features typical of sepsis. Different procalcitonin cut-off value may be used to differentiate between sepsis, severe sepsis and septic shock, with more severe conditions being associated with higher quantitative procalcitonin levels³¹. Extremely high procalcitonin levels (>32.5 ng/mL) on admission may be a sensitive and independent predictor of mortality³². Lee et al³³ with a smaller sample found an association between procalcitonin elevation and risk of ICU admission but no association with mortality, which could be an error due to the small sample size. Low procalcitonin levels on admission may be associated with better outcomes³⁴. The association with mortality may be corroborated by other biomarkers typically associated with negative outcomes, such as brain natriuretic peptide³⁵, MR-proADM^{36,37}, pentraxin 3, interleukin 6³⁸ and lactate^{39,40}. Procalcitonin levels fall rapidly once infection is cleared, and sustained elevation 4 days after admission appears to be an accurate predictor of mortality^{41,42}.

MR-proADM may in fact be a more accurate predictor than procalcitonin and clinical scores, such as CRB-65, MEDS and SOFA according to Saeed et al⁴³.

Procalcitonin elevation as a predictive factor for mortality may be comparable in accuracy to clinical scores, such as the MEDS score, with a composite biomarker integrating procalcitonin into the MEDS score may be more accurate than either index alone⁴⁴. Combination of the MEDS score with procalcitonin measurement may enable better evaluation and prognostic stratification of patients presenting to the ED with clinical features typical of sepsis⁴⁵, and this composite marker may also retain its accuracy in patients admitted for severe influenza (in which bacterial superinfection is common)⁴⁶. Though procalcitonin and the MEDS score appear to be preferable to the SOFA and aSOFA score as predictive factors of mortality, one group suggested a modification of the qSOFA score to include an ordinal scale of procalcitonin with a score of 0-2 (<0.25 ng/mL, 0.25-2 ng/mL, >2 ng/mL) in order to increase its sensitivity and specificity for predicting 30 day mortality⁴⁷. The studies relevant to the prognostic value of procalcitonin in patients presenting to the ED with suspected sepsis are presented in Table II.

Treatment Decisions Guided by Procalcitonin Elevation in the Emergency Department

A Cochrane review conducted in 2017 summarized the empirical evidence regarding the use of procalcitonin algorithms for the initiation and discontinuation of antibiotic treatment, as well as the effect of the use of such algorithms on patient outcomes. The review included 6708 patients from 26 different trials. The use of algorithms guided by serum procalcitonin measurements (with an initial measurement during the evaluation of the patient in the emergency department) were associated with reduced mortality and reduced total antibiotic exposure. The algorithms used were not identical between the trials, but in most cases antibiotics would be initiated after an initial measurement above a preset cutoff value (above 0.25 or 0.5 ug/L), and serial procalcitonin measurements would be obtained daily, with discontinuation of antibiotics after a 90% reduction from the peak measurement, or with normalization of serum procalcitonin (< 0.1 ug/L). The data presented in the review suggests that the use of procalcitonin algorithms may lead

Table 1. Studies of the use of procalcitonin as a diagnostic marker of sepsis.

Author, year	Study design	Setting	Participants, N	Summary of findings
Caterino et al ³⁶ , 2004	Prospective cohort study	Emergency department	108 > 65 years old	Procalcitonin with a cutoff of 0.2 ng/mL was sensitive for bacteremia in elderly patients, suggesting it may be useful to rule out infection. Abnormal white blood cell count was inferior to procalcitonin as a marker of sepsis.
Lai et al ²⁷ , 2010	Prospective cohort study	Emergency department	264 patients, age > 65	Procalcitonin levels correlated with the diagnosis of sepsis but in patients > age 75 the utility of procalcitonin was limited to the exclusion of bacteremia.
Riedel et al ²¹ , 2011	Case-Control	Emergency department	367 patients admitted to the ED, 295 controls, 662 total	Procalcitonin with a cutoff of 0.1 ng/mL had a negative predictive value of 98% and a positive predictive value of 17% for infection with positive blood cultures.
Uuisitalo-Seppala et al ¹² , 2011	Prospective cohort study	Emergency department	539	Procalcitonin levels were associated with severe sepsis, as was the concentration of interleukin 6. Procalcitonin and IL-6 had a significantly stronger association with severe sepsis compared to CRP.
Hettwer et al ²⁰ , 2012	Cross-sectional	Emergency department	200	Patients admitted to the emergency department with positive PCR for bacterial pathogens had higher procalcitonin levels, but such a correlation was not observed regarding positive blood cultures.
Jaimes et al ¹³ , 2013	Cross-sectional	Emergency department	765	Procalcitonin, d-dimers and CRP were not sufficiently accurate as markers of infection, but procalcitonin with a cutoff of 2 ng/mL was useful as a predictive factor of severe sepsis.
Hicks et al ²⁴ , 2014	Prospective cohort study	Emergency department	66	Procalcitonin elevation in the presence of SIRS criteria is useful for the timely detection of sepsis in the ED.
Magrini et al ¹¹ , 2014	Cohort study	Emergency department with inpatient follow up	513	Procalcitonin was more accurate as a diagnostic marker of sepsis, whereas CRP and complete white blood cell count were more accurate predictive factors of negative outcomes.
Talebi-Taher et al ¹⁴ , 2014	Case control	Emergency department	150 patients, > 65 years old	CRP was superior to procalcitonin for the differentiation between sepsis and SIRS, whereas IL-6 was superior to the other biomarkers for the differentiation between SIRS and the age-matched controls that presented to the ED without SIRS or infection.
Kim et al ²³ , 2015	Prospective cohort study	Emergency department	3305	Procalcitonin with a cutoff of 0.1 ng/mL had an acceptable negative predictive value (95.1) for ruling out bacteremia. Elevated values however had limited positive predictive value. Accuracy for ruling in sepsis was increased when neutrophil count and body temperature were accounted for along with procalcitonin. Positive predictive value of procalcitonin for sepsis using 0.1, 1, 2, and 5 ng/mL as the cut-off values were 21.2, 32.2, 34.2, and 37.0% respectively.
Nakamura et al ¹⁹ , 2015	Prospective cohort study	Emergency department with inpatient follow up	393	The patients were divided into acute kidney injury (AKI) and non-AKI group, and further each group in sepsis and non-sepsis category. The results showed that the levels of PCT were significantly higher in the sepsis group than in the non-sepsis group among the non-AKI and each AKI patients ($p < 0.0001$). In Failure AKI patients, the diagnostic accuracy of PCT was significantly lower than non-AKI patients. It was suggested that clinicians should be careful in using PCT value to diagnose sepsis in patients with AKI failure under RIFLE criteria.

Continued

Table 1 (Continued). Studies of the use of procalcitonin as a diagnostic marker of sepsis.

Author, year	Study design	Setting	Participants, N	Summary of findings
Yilmaz et al ¹⁵ , 2015	Retrospective cohort	Emergency department, inpatient follow up	129 patients, 65 geriatric (> 65 years old), 64 younger adults	Procalcitonin levels had no correlation with the severity of infection in either adult or geriatric patients. CRP elevation was greater in younger adults with infection and sepsis compared to the geriatric group.
Kece et al ⁸ , 2016	Case-control	Emergency department	86	Procalcitonin elevation was more specific than lactate for the diagnosis of sepsis in cancer patients but less sensitive. Both markers were associated with poor outcomes.
Ko et al ²⁹ , 2016	Retrospective cohort	Emergency department (initial presentation), inpatient urology unit	49	In patients with pyelonephritis secondary to hydronephrosis due to obstruction of a ureter by a calculus, procalcitonin elevation > 0.52 ng/mL was an accurate predictor of septic shock, (sensitivity and specificity 86.7% and 85.3% respectively).
Wiwatcharagoses et al ²² , 2016	Prospective cohort study	Emergency department with inpatient follow up	110	Procalcitonin with a cutoff value of 2 ng/mL was an accurate diagnostic marker for severe sepsis, but specificity for bacteremia (positive blood cultures) and septic shock was lower.
Lin et al ⁶ , 2017	Retrospective cohort	Emergency department	866	PCT alone with a cutoff value of 0.5 ng/mL was an accurate predictor of gram- bacteremia, and superior to lactate (cutoff of 19.8 mg/dL) and CRP (cutoff of 0.8 ng/dL). Same sample as Kim 2018.
Ljungstrom et al ⁶ , 2017	Retrospective cohort	Emergency department	1572	A composite biomarker consisting of procalcitonin, lactate, CRP and neutrophil to lymphocyte ratio was superior to any single biomarker for the diagnosis of severe sepsis or septic shock, but procalcitonin alone was comparable to the composite biomarker for the diagnosis of sepsis according to the sepsis-3 criteria.
Ahn et al ³⁰ , 2018	Retrospective cohort	Emergency department, study	132 follow up in urology inpatient department	The delta neutrophil index and prostate specific antigen levels were predictive of sepsis due to acute prostatitis, whereas procalcitonin was not.
Karon et al ⁷ , 2018	Cross-sectional	Emergency department	504	Procalcitonin as a diagnostic marker for sepsis was not superior compared to lactate, neutrophil count and absolute wight blood cell count. Initial lactate was the most sensitive and specific biomarker for severe sepsis and septic shock.
Kim et al ⁵ , 2019	Retrospective cohort	Emergency department	866	Procalcitonin is an accurate biomarker for sepsis according to the sepsis 3 definition, while the degree of elevation correlates with disease severity. The authors consider optimal cutoff values for serum procalcitonin 0.41 ng/mL for sepsis and 4.7 ng/mL for septic shock.

Continued

Table 1 (Continued). Studies of the use of procalcitonin as a diagnostic marker of sepsis.

Author, year	Study design	Setting	Participants, N	Summary of findings
Levine et al ²⁵ , 2018	Retrospective cohort	Emergency department	293	<p>In a cohort of patients presenting to the ED with symptoms of a urinary tract infection, the absence of procalcitonin elevation (cutoff of 0.25 ng/mL) had an acceptable negative predictive value to rule out a UTI. Negative procalcitonin along with urinalysis not suggestive of infection could be used as a criterion to withhold antibiotics in patients presenting with typical urinary tract infection symptoms.</p> <p>An algorithm utilizing procalcitonin and soluble phospholipase A2 group IIA had a negative predictive value of 93% in the original cohort.</p>
Mearrelli et al ¹⁷ , 2018	Prospective cohort study	Emergency department	836 patients, 716 with sepsis and 120 with non-infectious SIRS	359
Contenti et al ¹⁰ , 2019	Prospective cohort study	Emergency department	806 patients 366 with acute renal failure and 440 without	653
Nakamura et al ¹⁸ , 2019	Retrospective cohort study	Emergency department, follow up in ICU	Emergency department	<p>Procalcitonin and presepsin were superior to lactate and CRP for predicting sepsis and septic shock, whereas procalcitonin was marginally superior to presepsin (cutoff of 0.25 ng/mL for procalcitonin, 500 pg/mL for presepsin)</p> <p>Procalcitonin was more accurate than presepsin as a predictor of sepsis in patients with severe acute renal failure. Optimal procalcitonin cutoff for diagnosing sepsis 4.07 ng/ml.</p>
Varela-Patino et al ⁹ , 2020	Retrospective cross-sectional	Emergency department	Emergency department, follow up in urology wards	<p>Procalcitonin had the highest sensitivity and specificity for gram- sepsis compared to CRP and lactate. Sensitivity of procalcitonin was higher for gram – compared to gram + bacteremia.</p> <p>Procalcitonin and presepsin had a strong association with sepsis in patients presenting to the ED with acute obstructive pyelonephritis, and may indicate the need for emergency drainage procedures.</p>
Tambo et al ²⁸ , 2020	Retrospective cohort study	Emergency department, follow up in urology wards	61	

Table II. Studies on the use of procalcitonin as a prognostic factor for adverse outcomes.

Author, year	Study design	Setting	Participants, N	Summary of findings
Lee et al ⁴⁴ , 2008	Prospective cohort	Emergency department, inpatient follow up	525	The MEDS score was the most specific marker for predicting early (up to 5 days after admission) and late mortality (5-30 days after admission), whereas procalcitonin was the most sensitive. A combination of procalcitonin and the MEDS score may be superior to either index alone.
Freund et al ³⁹ , 2012	Prospective cohort	Emergency department, inpatient follow up	462	Lactate elevation was more sensitive for severe sepsis, whereas procalcitonin was more sensitive for any case of sepsis. A combination of lactate and procalcitonin elevation was associated with an increased risk of death or ICU admission.
Travalgino et al ³⁷ , 2012	Case-control	Emergency department	128 patients presenting to the ED with fever	Procalcitonin levels had a significant quantitative association with APACHE II quartiles. PCT levels were also significantly correlated with admission from the ED, and the association was stronger for procalcitonin alone compared to MR-proADM alone.
Magrini et al ⁴² , 2013	Prospective cohort	Emergency department with inpatient follow up	261	PCT levels increased at 5 days after initiation of antibiotic therapy was an independent predictor of mortality (OR = 1.29, p < 0.02) in septic patients. It was concluded that PCT is a useful marker for diagnosis of infections, and for prognostic stratification in patients with acute infectious diseases at their arrival in ED. The PCT variations after antibiotic treatment were highly predictive for in-hospital mortality.
Park et al ³¹ , 2013	Prospective cohort	Emergency department with 28 day follow up,	240	Procalcitonin levels were higher in patients with septic shock, and a cutoff of 0.42 ng/mL had a sensitivity of 80% and specificity value of 50% for septic shock. Procalcitonin elevation may be useful to identify patients at risk of adverse outcomes.
Zhao et al ⁴⁵ , 2013	Prospective cohort	Emergency department, 28 day follow up	504	Only procalcitonin and the MEDS score were independent predictors of 28 day mortality, whereas CRP and IL-6 were not. Combination of the MEDS score with procalcitonin measurement may enable better evaluation and prognostic stratification of patients presenting to the ED with clinical features typical of sepsis.
Hur et al ³⁵ , 2014	Prospective cohort	Emergency department	340	Procalcitonin and BNP concentrations were significantly higher in non-survivors compared to survivors. In survivors, follow-up procalcitonin measurements were lower than the initial value. Diagnosis of sepsis based on a procalcitonin cutoff appears to be more sensitive but less specific than a clinical diagnosis of sepsis.
Choe et al ³⁴ , 2016	Retrospective registry based study	Emergency department, 28 day follow up	1212	Amongpatients diagnosed with severe sepsis or septic shock, low procalcitonin levels were associated with reduced mortality and correlated with lower CRP and lactate, negative blood cultures and no organ failure.
Lee et al ³³ , 2016	Prospective cohort	Emergency department	36	Procalcitonin elevation was predictive of ICU admission for elderly patients presenting to the ED with symptoms of sepsis, as were interleukins 5, 6 and 10. None of the biomarkers were however predictive of mortality.

Continued

Table II (Continued). Studies on the use of procalcitonin as a prognostic factor for adverse outcomes.

Author, year	Study design	Setting	Participants, N	Summary of findings
Peschanski et al ³² , 2016	Retrospective cohort	Emergency department enrollment with inpatient follow up	188	Elevated procalcitonin at admission had moderate predictive value for in hospital mortality in septic patients. A very high threshold of 32.5 ng/mL had a positive predictive value of 73% and negative predictive value of 89% for in hospital death.
Schuetz et al ⁴¹ , 2017	Prospective multicenter cohort study	Emergency department with inpatient follow up	858 initially enrolled, 646 alive after day 4 (included in analysis)	In patients admitted from the ED due to severe sepsis or septic shock, sustained procalcitonin elevation on day 4 after admission (inability to decrease procalcitonin by at least 80% of baseline) was associated with a twofold increase in 28 day mortality.
Julian-Jimenez et al ³⁶ , 2019	Prospective cohort study	Emergency department with 130 day follow up	136	Procalcitonin with a cutoff of 1ng/mL was correlated with mortality 6,27 (1.88-20.83), but the strongest correlation among the biomarkers studied was for MR-pro-ADM.
Saeed et al ⁴³ , 2019	Prospective multicenter cohort study	Emergency department with 28 day follow up	1175 (derivation cohort), 896 (validation cohort)	Quantitative procalcitonin elevation was associated with an increased risk for 28 day mortality. MR-proADM was significantly more accurate as a predictor of mortality compared to procalcitonin, CRP, lactate and clinical score such as CURB-65, SOFA and NEWS. MR-proADM was also more strongly associated with the decision to admit patients to the hospital compared with the other biomarkers and clinical scores.
Shim et al ⁴⁰ , 2019	Prospective cohort	Emergency department, 28 day follow up	199	Lactate was more sensitive than procalcitonin for predicting 28 day mortality and positive blood cultures. Whole blood procalcitonin was comparable to serum procalcitonin as a biomarker of sepsis and a predictor of 28 day mortality
Song et al ³⁸ , 2019	Prospective cohort	Emergency department	142	The diagnostic and prognostic value of interleukin 6 was superior to both procalcitonin and pentraxin 3 in patients presenting to the emergency department with features of sepsis.
Teng et al ⁴⁶ , 2019	Retrospective cohort	Emergency department, inpatient follow up	364 patients with severe influenza admitted from the ED	Procalcitonin and the MEDS score were independent predictors of 28 day mortality. The combination of these 2 measures was superior to the SOFA score for predicting mortality. It is unclear whether procalcitonin elevation in influenza is indicative of bacterial superinfection and sepsis, as opposed to severe viral pneumonia.
Yu et al ⁴⁷ , 2019	Retrospective cohort	Emergency department, inpatient follow up	1318	An ordinal scale of procalcitonin with a score of 0-2 (<0.25 ng/mL, 0.25-2 ng/mL, > 2 ng/mL) when added to the qSOFA score appeared to increase its sensitivity and specificity for predicting 30 day mortality.

to improved outcomes, but does not enable the comparison between different algorithms, and it is still unclear what the ideal cutoff value for the initiation of antibiotics is, and what criterion should be used to discontinue treatment. It should be noted that antibiotic treatment duration should be the shortest possible, to reduce adverse events from drug toxicity and to prevent the selection of resistant strains⁴⁸. Gille-Johnson⁴⁹, however, suggested that procalcitonin could in fact be inferior to other commonly used markers of severe sepsis, thus undermining its value to aid the decision whether to initiate antibiotic treatment (Figure 2).

In the case of acute cholangitis, procalcitonin elevation may correlate with positive blood cultures and serum procalcitonin may be increased prior to the emergence of severe disease, functioning as a predictive factor of a complicated disease course. Thus, it was suggested that procalcitonin elevation in cholangitis could suggest the need for urgent biliary decompression before it was clinically evident^{50,51}. The studies relevant to the use of procalcitonin measurements in the emergency department to reach management decisions are summarized in Table III.

Conclusions

Serum procalcitonin (PCT) has emerged as a highly accurate biomarker for differentiating sepsis from other non-infectious triggers, as PCT increases earlier, better differentiates infective from non-infective causes of inflammation, more closely correlates with sepsis severity in terms of shock and organ dysfunction and better predicts outcome when followed in time. However, PCT measurement is more costly, time-consuming, and not ubiquitously available, especially when compared with biomarkers, such as lactate and CRP.

It has been shown that PCT is a valuable tool to guide antibiotic treatment in patients with bacterial infections. However, PCT is also less than a universal and perfect biomarker, and its physiologic role remains unknown. An increase in PCT is associated not only with disseminated bacterial infection, but also with non-infectious disease or other microbial infections. In the emergency department, an initial elevated PCT level could be used as a cue for the initiation of antibiotics, whereas the absence of PCT elevation could

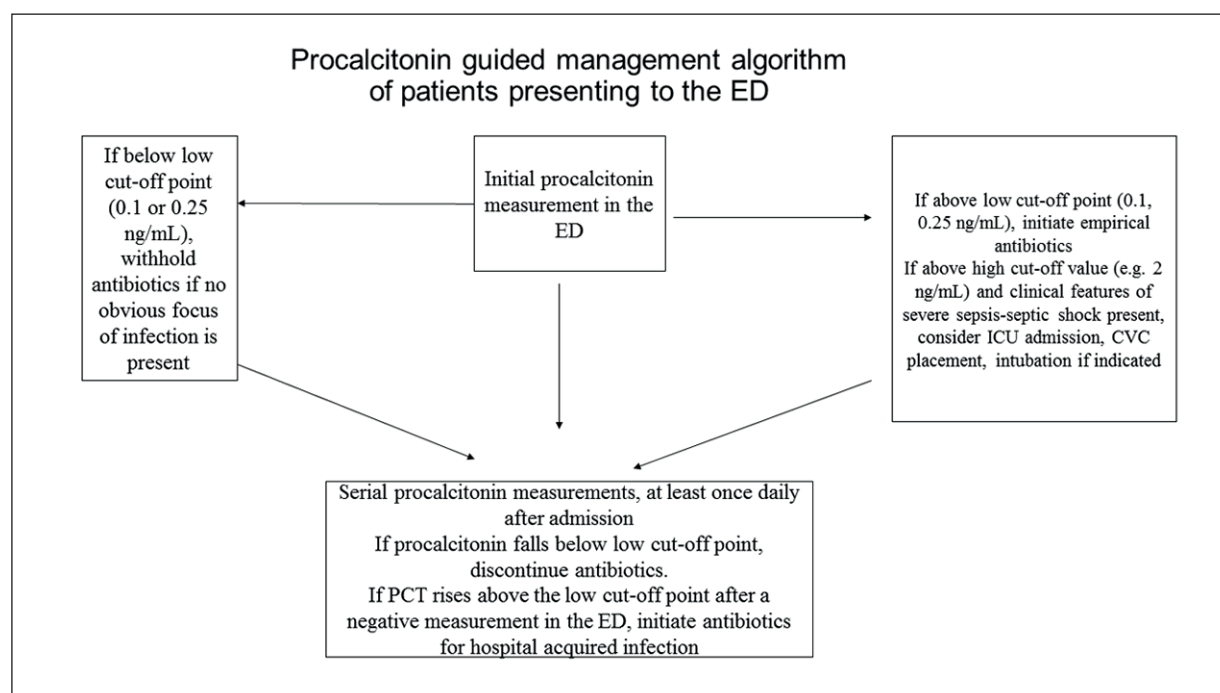


Figure 2. Procalcitonin cut-off values used to rule out sepsis are typically < 0.5 ng/mL, with 0.25 and 0.1 ng/mL used in certain studies. An initial measurement under this value can be used as a criterion to withhold empirical antibiotic treatment. Levels above this value suggest that antibiotics may be required. During follow-up, antibiotics may be discontinued if levels fall below these values during the course of the hospitalization. Lower cut-off values lead to increased sensitivity but decreased specificity. Procalcitonin values associated with severe disease and adverse outcomes are > 2 ng/mL, with increasing procalcitonin levels reflecting more severe disease. A common procalcitonin guided algorithm is presented in this figure.

Table III. Studies on the use of procalcitonin measurements in the emergency department to guide management decisions.

Author, year	Study design	Setting	Participants, N	Summary of findings	Notes
Gille-Johnson et al ⁴⁹ , 2012	Prospective cohort	Emergency department	404	Procalcitonin elevation had increased sensitivity for severe sepsis but for the guidance of the decision to initiated antibiotics it was inferior to clinical judgement and CRP.	
Shinya et al ⁵⁰ , 2014	Cross-sectional	Emergency department	110	Procalcitonin elevation in acute cholangitis was correlated with blood culture positivity and high levels indicated more severe disease requiring biliary decompression.	Procalcitonin elevation could indicate the need for urgent biliary decompression in cases of cholangitis where that would not be clinically evident based on the Tokyo 2013 guidelines
Schuetz et al ⁴⁸ , 2017	Systematic review and meta-analysis of randomized trials	Emergency Department, follow up in wards and ICU	6708 patients from 26 trials	Use of procalcitonin guided algorithms for initiation and discontinuation of antibiotic treatment resulted in reduced exposure to antibiotics and lower mortality.	Adjusted OR 0.83, 95% CI 0.70 to 0.99, $p = 0.037$ for mortality and adjusted OR 0.68, 95% C 0.57 to 0.82, $p < 0.001$ for antibiotic related side effects.
Lee et al ⁵¹ , 2018	Prospective cohort	Emergency department with inpatient follow up	204	Procalcitonin was the biomarker with the strongest association with blood culture positivity and adverse outcomes in patients with cholangitis. Procalcitonin could be used as an indicator for the need of urgent biliary decompression.	

prompt clinicians to withhold antibiotics in patients in whom an infection was initially suspected and pursue further diagnostic investigations. Future studies should focus on PCT kinetics, and the possible role of serial PCT measurements to assess the need for continued antibiotic treatment.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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References

- 1) Long B, Koefman A. Ready for prime time? Biomarkers in sepsis. *Emerg Med Clin North Am* 2017; 35: 109-122.
- 2) Liu HH, Guo JB, Geng Y, Su L. Procalcitonin: present and future. *Ir J Med Sci* 2015; 184: 597-605.
- 3) Mewes JC, Pulia MS, Mansour MK, Broyles MR, Nguyen HB, Steuten LM. The cost impact of PCT-guided antibiotic stewardship versus usual care for hospitalised patients with suspected sepsis or lower respiratory tract infections in the US: A health economic model analysis. *PLoS One* 2019; 14: e0214222.
- 4) Schuetz P, Bolliger R, Merker M, Christ-Crain M, Stolz D, Tamm M, Luyt CE, Wolff M, Schroeder S, Nobre V, Reinhart K, Branche A, Damas P, Nijsten M, Deliberato RO, Verduri A, Begh e B, Cao B, Shehabi Y, Jensen JS, Beishuizen A, de Jong E, Briel M, Welte T, Mueller B. Procalcitonin-guided antibiotic therapy algorithms for different types of acute respiratory infections based on previous trials. *Expert Rev Anti Infect Ther* 2018; 16: 555-564.
- 5) Kim SJ, Hwang SO, Kim YW, Lee JH, Cha K-C. Procalcitonin as a diagnostic marker for sepsis/septic shock in the emergency department; a

- study based on Sepsis-3 definition. *Am J Emerg Med* 2019; 37: 272-276.
- 6) Lin CT, Lu JJ, Chen YC, Kok VC, Horng JT. Diagnostic value of serum procalcitonin, lactate, and high-sensitivity C-reactive protein for predicting bacteremia in adult patients in the emergency department. *Peer J* 2017; 5: e4094.
 - 7) Karon BS, Tolan N V, Wockenfus AM, Block DR, Baumann NA, Bryant SC, Clements CM. Evaluation of lactate, white blood cell count, neutrophil count, procalcitonin and immature granulocyte count as biomarkers for sepsis in emergency department patients. *Clin Biochem* 2017; 50: 956-958.
 - 8) Keçe E, Yaka E, Yılmaz S, Doğan NÖ, Alyeşil C, Pekdemir M. Comparison of diagnostic and prognostic utility of lactate and procalcitonin for sepsis in adult cancer patients presenting to emergency department with systemic inflammatory response syndrome. *Turkish J Emerg Med* 2016; 16: 1-7.
 - 9) Varela-Patiño M, Lopez-Izquierdo R, Velayos-Garcia P, Alvarez-Manzanares J, Ramos-Sanchez C, Carbajosa-Rodriguez V, Martin-Rodriguez F, Eiros JM. Usefulness of infection biomarkers for diagnosing bacteremia in patients with a sepsis code in the emergency department. *Le Infez Med* 2020; 28: 29-36.
 - 10) Contenti J, Ocelli C, Lemoel F, Ferrari P, Levrant J. Presepsin versus other biomarkers to predict sepsis and septic shock in patients with infection defined by Sepsis-3 criteria: the PREDI study of diagnostic accuracy. *Emergencias* 2019; 31: 311-317.
 - 11) Magrini L, Gagliano G, Travaglino F, Vetrone F, Marino R, Cardelli P, Salerno G, Di Somma S. Comparison between white blood cell count, procalcitonin and C reactive protein as diagnostic and prognostic biomarkers of infection or sepsis in patients presenting to emergency department. *Clin Chem Lab Med* 2014; 52: 1465-1472.
 - 12) Uusitalo-Seppälä R, Koskinen P, Leino A, Peuruuori H, Vahlberg T, Rintala EM. Early detection of severe sepsis in the emergency room: diagnostic value of plasma C-reactive protein, procalcitonin, and interleukin-6. *Scand J Infect Dis* 2011; 43: 883-890.
 - 13) Jaimes FA, De La Rosa GD, Valencia ML, Arango CM, Gomez CI, Garcia A, Ospina S, Osorno SC, Henao AI. A latent class approach for sepsis diagnosis supports use of procalcitonin in the emergency room for diagnosis of severe sepsis. *BMC Anesthesiol* 2013; 13: 23.
 - 14) Talebi-Taher M, Babazadeh S, Barati M, Latifnia M. Serum inflammatory markers in the elderly: are they useful in differentiating sepsis from SIRS? *Acta Med Iran* 2014; 52: 438-442.
 - 15) Yılmaz H, Duran L, Yanik K, Altuntaş M, Sünbül M. Differences in the effectiveness of serum biomarkers for the diagnosis of bacterial infections in adult and elderly patients admitted to the emergency department. *Turkish J Med Sci* 2015; 45: 553-557.
 - 16) Ljungström L, Pernestig A-K, Jacobsson G, Andersson R, Usener B, Tilevik D. Diagnostic accuracy of procalcitonin, neutrophil-lymphocyte count ratio, C-reactive protein, and lactate in patients with suspected bacterial sepsis. *PLoS One* 2017; 12: e0181704.
 - 17) Mearelli F, Fiotti N, Giansante C, Casarsa C, Orso D, De Helmersen M, Altamura N, Ruscio M, Castello LM, Colonetti E, Marino R, Barbati G, Bregnocchi A, Ronco C, Lupia E, Montrucchio G, Mui-san ML, Di Somma S, Avanzi GC, Biolo G. Derivation and validation of a biomarker-based clinical algorithm to rule out sepsis from noninfectious systemic inflammatory response syndrome at emergency department admission: a multicenter prospective study. *Crit Care Med* 2018; 46: 1421-1429.
 - 18) Nakamura Y, Hoshino K, Kiyomi F, Kawano Y, Mizunuma M, Tanaka J, Nishida T, Ishikura H. Comparison of accuracy of presepsin and procalcitonin concentrations in diagnosing sepsis in patients with and without acute kidney injury. *Clin Chim Acta* 2019; 490: 200-206.
 - 19) Nakamura Y, Murai A, Mizunuma M, Ohta D, Kawano Y, Matsumoto N, Nishida T, Ishikura H. Potential use of procalcitonin as biomarker for bacterial sepsis in patients with or without acute kidney injury. *J Infect Chemother Off J Japan Soc Chemother* 2015; 21: 257-263.
 - 20) Hettwer S, Wilhelm J, Schürmann M, Ebelt H, Hammer D, Amoury M, Hofmann F, Oehme A, Wilhelms D, Kekulé AS, Klöss T, Werdan K. Microbial diagnostics in patients with presumed severe infection in the emergency department. *Med Klin Intensivmed Notfmed* 2012; 107: 53-62.
 - 21) Riedel S, Melendez JH, An AT, Rosenbaum JE, Zenilman JM. Procalcitonin as a marker for the detection of bacteremia and sepsis in the emergency department. *Am J Clin Pathol* 2011; 135: 182-189.
 - 22) Wiwatcharagoses K, Kingnakom A. Procalcitonin under Investigation as a means of detecting severe sepsis, septic shock and bacteremia at Emergency Department, Rajavithi Hospital. *J Med Assoc Thai* 2016; 99 Suppl 2: S63-8.
 - 23) Kim SY, Jeong TD, Lee W, Chun S, Min WK. Procalcitonin in the assessment of bacteraemia in emergency department patients: results of a large retrospective study. *Ann Clin Biochem* 2015; 52: 654-659.
 - 24) Hicks CW, Engineer RS, Benoit JL, Dasarathy S, Christenson RH, Peacock WF. Procalcitonin as a biomarker for early sepsis in the emergency department. *Eur J Emerg Med* 2014; 21: 112-117.
 - 25) Levine AR, Tran M, Shepherd J, Naut E. Utility of initial procalcitonin values to predict urinary tract infection. *Am J Emerg Med* 2018; 36: 1993-1997.
 - 26) Caterino JM, Scheatzle MD, Forbes ML, D'Antonio JA. Bacteremic elder emergency department patients: procalcitonin and white count. *Acad Emerg Med* 2004; 11: 393-396.
 - 27) Lai CC, Chen SY, Wang CY, Wang JY, Su CP, Liao CH, Tan CK, Huang YT, Lin HI, Hsueh PR. Di-

- agnostic value of procalcitonin for bacterial infection in elderly patients in the emergency department. *J Am Geriatr Soc* 2010; 58: 518-522.
- 28) Tambo M, Taguchi S, Nakamura Y, Okegawa T, Fukuhara H. Presepsin and procalcitonin as predictors of sepsis based on the new Sepsis-3 definitions in obstructive acute pyelonephritis. *BMC Urol* 2020; 20: 23.
 - 29) Ko YH, Ji YS, Park S-Y, Kim SJ, Song PH. Procalcitonin determined at emergency department as an early indicator of progression to septic shock in patient with sepsis associated with ureteral calculi. *Int Braz J Urol* 2016; 42: 270-276.
 - 30) Ahn HK, Koo KC, Chung BH, Lee KS. Comparison of the delta neutrophil index with procalcitonin, erythrocyte sedimentation rate, and C-reactive protein as predictors of sepsis in patients with acute prostatitis. *Prostate Int* 2018; 6: 157-161.
 - 31) Park JH, Wee JH, Choi SP, Park KN. Serum procalcitonin level for the prediction of severity in women with acute pyelonephritis in the ED: value of procalcitonin in acute pyelonephritis. *Am J Emerg Med* 2013; 31: 1092-1097.
 - 32) Peschanski N, Chenevier-Gobeaux C, Mzabi L, Lucas R, Ouahabi S, Aquilina V, Brunel V, Lefevre G, Ray P. Prognostic value of PCT in septic emergency patients. *Ann Intensive Care* 2016; 6: 47.
 - 33) Lee WJ, Woo SH, Kim DH, Seol SH, Park SK, Choi SP, Jekarl DW, Lee SO. Are prognostic scores and biomarkers such as procalcitonin the appropriate prognostic precursors for elderly patients with sepsis in the emergency department? *Aging Clin Exp Res* 2016; 28: 917-924.
 - 34) Choe EA, Shin TG, Jo IJ, Hwang SY, Lee TR, Cha WC, Sim MS. The Prevalence and clinical significance of low procalcitonin levels among patients with severe sepsis or septic shock in the Emergency Department. *Shock* 2016; 46: 37-43.
 - 35) Hur M, Kim H, Lee S, Cristofano F, Magrini L, Marino R, Gori CS, Bongiovanni C, Zancla B, Cardelli P, Di Somma S. Diagnostic and prognostic utilities of multimarkers approach using procalcitonin, B-type natriuretic peptide, and neutrophil gelatinase-associated lipocalin in critically ill patients with suspected sepsis. *BMC Infect Dis* 2014; 14: 224.
 - 36) Julián-Jiménez A, Yañez MC, González-Del Castillo J, Salido-Mota M, Mora-Ordoñez B, Aranz-Nieto MJ, Chanovas-Borras MR, Llopis-Roca F, Mòdol-Deltell JM, Muñoz G. Prognostic power of biomarkers for short-term mortality in the elderly patients seen in Emergency Departments due to infections. *Enferm Infecc Microbiol Clin* 2019; 37: 11-18.
 - 37) Travaglino F, De Berardinis B, Magrini L, Bongiovanni C, Candelli M, Silveri NG, Legramante J, Galante A, Salerno G, Cardelli P, Di Somma S. Utility of Procalcitonin (PCT) and Mid regional pro-Adrenomedullin (MR-proADM) in risk stratification of critically ill febrile patients in Emergency Department (ED). A comparison with APACHE II score. *BMC Infect Dis* 2012; 12: 184.
 - 38) Song J, Park DW, Moon S, Cho HJ, Park JH, Seok H, Choi WS. Diagnostic and prognostic value of interleukin-6, pentraxin 3, and procalcitonin levels among sepsis and septic shock patients: a prospective controlled study according to the Sepsis-3 definitions. *BMC Infect Dis* 2019; 19: 968.
 - 39) Freund Y, Delerme S, Goulet H, Bernard M, Riou B, Hausfater P. Serum lactate and procalcitonin measurements in emergency room for the diagnosis and risk-stratification of patients with suspected infection. *Biomarkers Biochem Indic Exp response, susceptibility to Chem* 2012; 17: 590-596.
 - 40) Shim BS, Yoon YH, Kim JY, Cho YD, Park SJ, Lee ES, Choi SH. Clinical Value of whole blood procalcitonin using point of care testing, quick sequential organ failure assessment score, C-Reactive protein and lactate in Emergency Department patients with suspected infection. *J Clin Med* 2019; 8.
 - 41) Schuetz P, Birkhahn R, Sherwin R, Jones AE, Singer A, Kline JA, Runyon MS, Self WH, Courtney DM, Nowak RM, Gaieski DF, Ebmeyer S, Johannes S, Wiemer JC, Schwabe A, Shapiro NI. Serial procalcitonin predicts mortality in severe sepsis patients: results from the multicenter procalcitonin monitoring sepsis (MOSES) Study. *Crit Care Med* 2017; 45: 781-789.
 - 42) Magrini L, Travaglino F, Marino R, Ferri E, De Berardinis B, Cardelli P, Salerno G, Di Somma S. Procalcitonin variations after Emergency Department admission are highly predictive of hospital mortality in patients with acute infectious diseases. *Eur Rev Med Pharmacol Sci* 2013; 17 Suppl 1: 133-142.
 - 43) Saeed K, Wilson DC, Bloos F, Schuetz P, van der Does Y, Melander O, Hausfater P, Legramante JM, Claessens YE, Amin D, Rosenqvist M, White G, Mueller B, Limper M, Callejo CC, Brandi A, Macchi MA, Cortes N, Kutz A, Patka P, Yañez MC, Bernardini S, Beau N, Dryden M, van Gorp ECM, Minieri M, Chan L, Rood PPM, Del Castillo JG. The early identification of disease progression in patients with suspected infection presenting to the emergency department: a multi-centre derivation and validation study. *Crit Care* 2019; 23: 40.
 - 44) Lee CC, Chen SY, Tsai CL, Wu SC, Chiang WC, Wang JL, Sun HY, Chen SC, Chen WJ, Hsueh PR. Prognostic value of mortality in emergency department sepsis score, procalcitonin, and C-reactive protein in patients with sepsis at the emergency department. *Shock* 2008; 29: 322-327.
 - 45) Zhao Y, Li C, Jia Y. Evaluation of the Mortality in Emergency Department Sepsis score combined with procalcitonin in septic patients. *Am J Emerg Med* 2013; 31: 1086-1091.
 - 46) Teng F, Wan TT, Guo SB, Liu X, Cai JF, Qi X, Liu WX. Outcome prediction using the Mortality in Emergency Department Sepsis score combined

- with procalcitonin for influenza patients. *Med Clin (Barc)* 2019; 153: 411-417.
- 47) Yu H, Nie L, Liu A, Wu K, Hsein YC, Yen DW, Lee MTG, Lee CC. Combining procalcitonin with the qSOFA and sepsis mortality prediction. *Medicine (Baltimore)* 2019; 98: e15981.
- 48) Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, Bouadma L, Luyt CE, Wolff M, Chastre J, Tubach F, Kristoffersen KB, Burkhardt O, Welte T, Schroeder S, Nobre V, Wei L, Bucher HC, Bhatnagar N, Annane D, Reinhart K, Branche A, Damas P, Nijsten M, de Lange DW, Deliberato RO, Lima SS, Maravić-Stojković V, Verduri A, Cao B, Shehabi Y, Beishuizen A, Jensen JS, Corti C, Van Oers JA, Falsey AR, de Jong E, Oliveira CF, Beghe B, Briel M, Mueller B. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev* 2017; 10: CD007498.
- 49) Gille-Johnson P, Hansson KE, Gardlund B. Clinical and laboratory variables identifying bacterial infection and bacteraemia in the emergency department. *Scand J Infect Dis* 2012; 44: 745-752.
- 50) Shinya S, Sasaki T, Yamashita Y, Kato D, Yamashita K, Nakashima R, Yamauchi Y, Noritomi T. Procalcitonin as a useful biomarker for determining the need to perform emergency biliary drainage in cases of acute cholangitis. *J Hepatobiliary Pancreat Sci* 2014; 21: 777-785.
- 51) Lee YS, Cho KB, Park KS, Lee JY, Lee YJ. Procalcitonin as a decision-supporting marker of urgent biliary decompression in acute cholangitis. *Dig Dis Sci* 2018; 63: 2474-2479.