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Review Article

THE ROLE OF SERUM PROCALCITONIN AS A DIAGNOSTIC MARKER IN PATIENTS WITH DENGUE: A REVIEW

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ABSTRACT

Dengue is the most rapidly spreading vector-borne disease in the world. An estimated 2.5 billion people live in dengue-endemic countries. Most cases of dengue are asymptomatic; however, the disease can progress to a severe cases with plasma leakage, hemorrhage, and shock. The treatment options are limited and are focused mostly on supportive care. Procalcitonin is regarded as a biomarker specific for bacterial infections. The current literature contains only five papers addressing the topic of the clinical relevance of serum procalcitonin in patients with dengue. Serum procalcitonin levels tend to be elevated in patients who experience organ failure, shock, or dengue hemorrhagic fever; however, this difference was not statistically significant in all studies. Serum procalcitonin demonstrated strong diagnostic utility for detecting bacterial coinfection or bacteremia, and can be used to exclude bacteremia in dengue patients. The majority of the reviewed studies involved small sample sizes, which often precluded reaching statistical significance. The utility of serum procalcitonin as a diagnostic marker in patients with dengue remains insufficiently explored, and further research is necessary to fully understand its clinical role.

KEYWORDS: dengue, procalcitonin, tropical diseases, hemorrhagic fever, diagnostic marker.

1. Introduction

Dengue is the most rapidly spreading vector-borne disease in the world and it is estimated that 2.5 billion people live in dengue endemic countries [1,2]. Dengue is caused by an infection with a single-stranded positive-sense ribonucleic acid virus: the dengue virus (DENV), which belongs to the *Flaviviridae* family and has four antigenically distinct serotypes: DENV-1, DENV-2, DENV-3, and DENV-4 [3]. The anthropoid vectors for transmission of the DENV viruses are infected mosquitoes from the *Aedes* genus, principally *A. aegypti* [1].

Between November 2022 and November 2023, dengue cases were reported in all six World Health Organization (WHO) regions. Close to 80% of cases in 2023 were reported in the Americas. With endemicity established in tropical and subtropical regions worldwide, the European WHO Region, which had no reports of dengue outbreaks since 1928, remains nonendemic. However, since 2010, autochthonous cases have been reported in countries like Croatia, France, Israel, Italy, Portugal, and Spain [4–6]. Furthermore, the number of imported cases in the region is on the rise, primarily originating from Asia [7]. The significant increase in dengue transmission is heavily influenced by globalization and climate change, as temperature and humidity variations modulate several physical and behavioral traits of mosquitoes [8]. For example, higher temperatures lengthen the lifespan of *Aedes* mosquitoes, increasing their potential as transmitting vectors. A recent study revealed that climate suitability for transmission has expanded in regions of North America, East Asia, and the Mediterranean basin, where endemicity has not yet been established [9].

The clinical presentation of dengue can vary, with most cases (approximately 54%) being asymptomatic [10]. Symptomatic dengue typically manifests as a mild to moderate, nonspecific, acute febrile illness, which can, however, progress to a severe cases with plasma leakage, hemorrhage, and shock [1,6]. Identifying which patients are at risk of developing severe dengue remains challenging. In 2009, the WHO created an updated dengue case classification criteria for the disease's diagnosis and assessment of its severity [1]. These guidelines distinguish the following categories: (1) probable dengue/dengue (a certainty of diagnosis can only be reached after laboratory confirmation), (2) dengue with warning signs, and (3) severe dengue [11]. Dengue is deemed "probable" if the patient lives or has recently traveled to an endemic

area, has pyrexia, and meets 2 of the following criteria: nausea or vomiting, rash, aches and pains, a positive tourniquet test, leukopenia or any warning sign. Warning signs include abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy, restlessness, liver enlargement >2 cm, and laboratory results: increase in hematocrit (HCT) concurrent with rapid decrease in platelet count. Warning signs should alert physicians as they can serve as a predictors of the disease's upcoming progression. However, even patients without warning signs can develop severe dengue [1].

Prior to the publication of the abovementioned criteria, dengue was classified according to the 1997 WHO classification by severity of plasma leakage as "classic" dengue fever (DF), dengue hemorrhagic fever (DHF) – DF with plasma leakage, or dengue shock syndrome (DSS) – DHF with shock [12]. While the 2009 criteria are considered the most up-to-date, the 1997 criteria are still being referred to in research.

According to the WHO, approximately 500,000 people per year suffer from severe DF, with mortality rates reaching 10% in hospitalized patients. However, this relatively high percentage can be reduced by early diagnosis and treatment [13]. The treatment for DF is relatively limited and focused mostly on supportive care, as there are no specific antiviral drugs available [14]. In nonsevere cases, patients can be treated at home with the recommendation of rest, antipyretic drugs, and oral rehydration solutions. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided due to the risk of hemorrhagic complications [15].

Procalcitonin (PCT) is a protein that consists of 116 amino acids and is a precursor of the hormone calcitonin, which is regarded as a biomarker specific for bacterial infections [16,17]. In clinical settings, PCT aids in the diagnosis of bacterial infection or sepsis and can be useful in guiding antibiotic therapy. Under normal conditions, serum PCT levels remain low (≤ 0.1 ng/mL), but in the presence of bacterial infection, serum PCT levels increase proportionally to the severity of the infection. PCT levels above 2 ng/mL suggest a systemic infection, whereas PCT levels ≥10 ng/mL indicate a high likelihood of severe bacterial sepsis or septic shock [16].

The production of PCT is mediated by cytokines: interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) activate its production, whereas interferon-γ (IFN-γ), which is secreted in viral infections, counterregulates it [18]. PCT can be detected in serum 3 to 4 hours following the infection and peaks at 6 to 12 hours [16]. In addition to infection, several other factors are known to contribute to the elevation of serum PCT levels, including trauma, mechanical injury, burns, surgical procedures, and neoplasms [19].

Furthermore, in some severe viral infections, for example in patients with severe coronavirus disease 2019 (COVID-19) infection, serum PCT can also be increased. A meta-analysis by Heidari-Beni et al. showed, that the odds of more severe course of COVID-19 was higher in subjects with elevated serum PCT [20]. Additionally, a study by Gautam et al. suggests that PCT is a better indicator of severity than of bacterial coinfection [21].

The clinical relevance of serum PCT in patients with dengue remains a poorly researched subject. The existing literature contains only a limited number of studies specifically addressing this topic, mostly in the context of the severity of the disease or bacterial coinfection. In this review, we assess the current body of knowledge and provide an overview of the role of serum PCT as a diagnostic marker in dengue.

2. Materials and Methods

We searched the Google Scholar database for articles published before September 2024 using the following search string: *intitle:"dengue" AND intitle:"procalcitonin"*, yielding 6 results. Additionally, we searched the PubMed database using similar criteria and the following search string: *(dengue[Title/Abstract]) AND (procalcitonin[Title/Abstract])*, yielding 22 results. From the list of total of 28 results, in our analysis we included only original research articles written in English or with translations available. Then, we excluded: (1) duplicates, (2) articles that we did not have access to, (3) preprints, (4) nonpeer-reviewed articles, and (5) retracted articles. After initial elimination, the selected articles were fully analyzed. Only five of the analyzed research papers were considered sufficiently relevant for inclusion in this review.

3. Results

Only five studies were focused primarily on the use of PCT, either independently or in combination with other factors, as a diagnostic marker in patients with dengue. All of the analyzed studies included only adult patients. The key findings from the reviewed literature are summarized in Table 1.

3.1. Serum procalcitonin evaluation methods

The study by Sani et al. used Procalcitonin Rapid Test Kit (EasyDiagnosis Biomedicine Co., Ltd, Wuhan, China) to determine PCT levels. Blood samples of 0.5 µL were used for the analysis. The detection limit was 0.1 ng/mL and its coefficients of variation for low and high concentrations were 5.9% and 6.9%, respectively [22].

Thanachartwet et al. measured PCT levels by an electrochemiluminescence method (Elecsys BRAHMS PCT, Roche Diagnostic, Mannheim, Germany) using a Cobas e 411 immunoassay analyzer (Roche Diagnostic, Mannheim, Germany). The detection limit was 0.02 ng/mL. The coefficients of variation for low and high concentrations were 1.7% and 1.4%, respectively [23].

Shyamali et al. determined PCT levels using an enzyme-linked immunosorbent assay (ELISA) for PCT (Abcam, Cambridge, UK). Unfortunately, no additional details about the assay's characteristics were provided by the authors [24].

Azmi et al. tested whole blood samples of 75 µL mixed with the buffer for analysis. PCT was measured using Finecare™ PCT Rapid Test along with Finecare™ FIA Meter (CIGA Healthcare Ltd., Ballymena, UK). The system uses the fluorescence immunoassay technique and has a measuring range of 0-100 ng/mL. The intra- and inter-assay coefficients of variation are <15%. Additionally, the correlation between Finecare™ PCT and Elecsys BRAHMS PCT, which was used by Thanachartwet et al., is good, with a correlation coefficient of 0.9552 [23,25].

Chen et al. did not provide any information about methods of PCT levels assessment used in their study [26].

3.2. Disease severity

Sani et al. focused their research on clinical factors, including PCT, indicating severe dengue infection [22]. This cross-sectional study included 133 adult patients with serologically-confirmed DF, hospitalized at Hospital Selayang, Malaysia. 88% of the analyzed subjects suffered from uncomplicated DF, whereas 12% presented with severe DF, with shock (44%) or organ failure (56%). Serum PCT levels were examined within 24 hours of admission. Sani et al. reported that the median level of serum PCT in patients with severe DF was greater than that in patients with nonsevere DF: 0.35 ng/mL (0.15–4.4) vs. 0.28 ng/mL (0.17–0.54), however the difference between the analyzed groups was not statistically significant (p = 0.518). Furthermore, a multivariate analysis demonstrated that lethargy and serum albumin <35g/L combined with PCT >0.3 ng/mL can predict severe DF with a 73% sensitivity and 85% specificity. Additionally, PCT, when raised to a median of 3.6 ng/mL (3.2–4.0), was found to be significantly associated with death (p = 0.021).

Similarly to the abovementioned authors, Thanachartwet et al. also researched the role of PCT independently, and in combination with peripheral venous lactate (PVL), in predicting shock or organ failure in patients with dengue [23]. This prospective observational study was conducted at the Hospital for Tropical Diseases in Bangkok, Thailand and included 160 patients with confirmed dengue, among whom 20% developed shock and/or organ failure. Serum PCT and PVL levels were assessed on admission. The authors also observed that the levels of serum PCT were greater in patients with shock and/or organ failure; however, in contrast to the results obtained by Sani et al. [22], the difference was statistically significant (p = 0.001). Using a stepwise multivariate logistic regression analysis, the authors concluded that PCT ≥0.7 ng/mL (odds ratio (OR): 4.80; 95% confidence interval (CI): 1.60–14.45; p = 0.005) and PVL ≥2.5 mmol/L (OR: 27.99, 95% CI: 8.47–92.53; p <0.001) were independently associated with progression to dengue shock and/or organ failure. In addition to this, PCT ≥0.7 ng/mL and PVL ≥2.5 mmol/L were assessed as a combined bioscore using a logistic regression model. Higher bioscores were associated with increased occurrence of dengue shock and/or organ failure, with ORs of 22.23 (95% CI 7.85–63.00) for PCT ≥0.7 ng/mL and 30.00 (95% CI 5.76–156.31) for PVL ≥2.5 mmol/L (p <0.001). Furthermore, PCT ≥0.7 ng/mL and PVL ≥2.5 mmol/L combined provided good prognostic value for predicting dengue shock and/or organ failure, with an area under the receiver operating characteristic curve (AUROC) of 0.83 (95% CI: 0.74–0.92), with 81.2% sensitivity (95% CI: 63.6–92.8%), and 84.4% specificity (95% CI: 76.9–90.2%).

A study by Shyamali et al. [24] included 193 adult patients with dengue infection admitted to the National Institute of Infectious Diseases Sri Lanka, 64 (33%) of whom were diagnosed with DHF and 7 (3.6%) developed shock. Serum PCT levels were higher in patients with DHF (median: 0.13 ng/mL, interquartile range (IQR): 0.07–0.20 ng/mL) compared to those who did not develop DHF (median: 0.08 ng/mL, IQR: 0.04–0.13 ng/mL) and the difference was statistically significant (p = 0.009). Furthermore, elevated PCT (>0.1 ng/mL) was associated with the presence of DHF (OR: 1.9, 95% CI: 1.0–3.6), but it was not significant (p = 0.05). Moreover, the researchers reported no significant difference in PCT levels between patients who developed DSS and those who did not (p = 0.64). Neither of the analyzed patients with DSS had PCT above 0.7 ng/mL, which was the cutoff value suggested by Thanachartwet et al. for predicting dengue shock [23]. Additionally, patients with detectable serum PCT were more likely to also have detectable serum lipopolysaccharide (LPS); however, this difference was also statistically insignificant (p = 0.09).

3.3. Bacterial coinfection or bacteremia

Azmi et al. conducted a cross-sectional study evaluating the performance of point-of-care (POC) PCT for the early detection of bacterial coinfection in patients with severe dengue admitted to the intensive care unit (ICU) in two centers in Malaysia [25]. The study included 50 adult patients with dengue, 14 (28%) of whom had bacterial coinfection on admission to the ICU. The bacterial coinfection status was determined on the basis of the microbiological culture status of samples taken from blood or other body fluids. Patients with severe dengue and bacterial coinfection had significantly higher serum PCT levels on admission to the ICU than did those without coinfection (82.4 ± 68.9 vs. 41.1 ± 52.4 mg/L, p = 0.027). Analysis of the receiver operating characteristic (ROC) curve indicated that serum PCT can be useful in discriminating patients with severe dengue with and without bacterial coinfection, with an AUROC of 0.768 (95% CI: 0.627–0.875, p = 0.001). When the PCT cutoff point was set at 0.5 ng/mL, the sensitivity of PCT was 100% (95% CI: 76.8–100), the specificity was 27.8% (95% CI: 14.2–45.2), the positive likelihood ratio (LR) was 1.38 (1.1–1.7), and the negative LR was < 0.1. For the cutoff point of 4.6 ng/mL, which was ideal for the analyzed cohort, the sensitivity was 64.3% (95% CI: 35.1–87.2), and the specificity was 83.3% (95% CI: 67.2–93.6), the positive LR was 3.9 (1.7–8.8), and the negative LR was 0.4 (95% CI: 0.2–0.9). Additionally, the researchers compared the AUCs for PCT and for C-reactive protein (CRP) and obtained higher values for PCT; however, the difference was not statistically significant (p = 0.484).

Chen et al. conducted a retrospective study investigating the diagnostic performance of PCT for detecting bacteremia among ICU patients with severe dengue [26]. The study was conducted at Chi Mei Medical Center and included 102 patients, 27 (26.5%) of whom had concomitant bacteremia. The mean serum PCT value was 12.3 ng/mL, and serum PCT levels were significantly higher in patients with bacteremia than in those without bacteremia (p = 0.046). The AUROC for PCT as a diagnostic marker of bacteremia was 0.749. For this purpose, the best cutoff value for PCT was 1.14 ng/mL, which resulted in the sensitivity of 81.5% (95% CI: 61.9–93.6) and the specificity of 59.5% (95% CI: 47.4–70.7), with the positive predictive value (PPV) of 42.3% (95% CI: 28.7–56.8) and the negative predictive value (NPV) of 89.8% (95% CI: 77.8–96.6).

Table 1. Analyzed literature and key findings. Abbreviations: PCT – procalcitonin, DF – dengue fever, PVL – peripheral venous lactate, ICU – intensive care unit, ELISA – enzyme-linked immunosorbent assay.

Reference	Year	Sample size	PCT evaluation method	Key findings
Sani et al. [22]	2019	133	Immunofluorescence	Median PCT level was higher in patients with severe DF, but the difference was not significant. Lethargy, hypoalbuminemia and elevated PCT combined can predict severe DF. Elevated PCT was associated with death.
Thanachartwet et al. [23]	2016	160	Electrochemiluminescence	Serum PCT levels were higher in patients with dengue shock and/or organ failure. PCT combined with PVL can predict occurrence of dengue shock and/or organ failure with high sensitivity and specificity.
Shyamali et al. [24]	2020	193	ELISA	Serum PCT levels were higher in patients with DHF compared to those who did not develop DHF.
Azmi et al. [25]	2022	50	Immunofluorescence	Serum PCT is a good marker of detecting bacterial coinfection in patients with dengue.
Chen et al. [26]	2016	102	-	Serum PCT has good diagnostic performance for detecting bacteremia in patients with dengue. Due to high negative predictive value, serum PCT can PCT can be used for excluding concomitant bacteremia among patients with severe dengue in the ICU.

4. Discussion

The current literature review has investigated serum PCT levels in patients with dengue, primarily in relation to two key aspects: disease severity and bacterial coinfection. Overall, serum PCT levels tend to be elevated in patients who experience organ failure, shock, or DHF; however, this difference was not statistically significant in all studies. Furthermore, serum PCT demonstrated strong diagnostic utility for detecting bacterial coinfection or bacteremia, and due to its high NPV, can be used to exclude bacteremia in patients with dengue. Nevertheless, the majority of the reviewed studies involved small sample sizes, ranging from 50 to 193 patients, which often precluded reaching statistical significance. Consequently, the utility of serum PCT as a diagnostic marker in patients with dengue remains insufficiently explored, and further research is necessary to fully understand its clinical relevance.

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