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ORIGINAL RESEARCH INTENSIVE CARE

Point-of-care procalcitonin for early detection of bacterial coinfection in patients with severe dengue admitted to the intensive care units

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Abstract

Background: Early detection of bacterial coinfection in severe dengue remains challenging. Point-of-care (POC) procalcitonin (PCT) may be used for this role, but it needs to be investigated. We evaluated the performance of POC PCT for early detection of bacterial coinfection in patients with severe dengue admitted to the intensive care units (ICU).

Methodology: In this cross-sectional study, we analyzed PCT level in severe dengue patients with and without bacterial coinfection upon their ICU admission. The diagnostic efficacy of PCT for the coinfection was determined through analysis of the receiver operating characteristics (ROC) curve.

Results: Fifty patients with severe dengue were enrolled over a one-year period. Fourteen (28.0%) of these patients had bacterial coinfection on ICU admission. PCT was significantly higher in patients with the coinfection than those without (36.2 ± 41.8 vs 3.6 ± 5.6 ng/mL, P = 0.012). The Area Under the Curve (AUC) of 0.768, ideal cut-off of more than 4.6 ng/mL, sensitivity of 64.3% and specificity of 83.3% revealed that PCT was a good marker for detecting bacterial coinfection in our severe dengue cohort.

Conclusion: Point-of-care procalcitonin provides early detection of bacterial coinfection with a good performance in patients with severe dengue; however, larger studies are warranted to validate these findings with quantification.

Abbreviations: APACHE - Acute Physiological and Chronic Health Evaluation; AUC - Area Under the Curve; CRP - C-reactive protein; ICU - intensive care unit; POC - Point-of-care; PCT – procalcitonin; ROC - receiver operating characteristics curve

Key words: Procalcitonin; Coinfection; Severe Dengue; Intensive Care Units

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1. Introduction

Dengue infection has been seen in Malaysia for over a century and has been considered as endemic for the last 20 years.[1] Although most of the clinical manifestations of dengue may be mild or even asymptomatic, it can also rapidly progress to severe infection requiring intensive care unit (ICU) admission. In Malaysia, severe dengue is one of the most common diagnoses leading to ICU admission in Ministry of Health hospitals, with associated in-hospital mortality rate of 8.9%.[2]

At the same time, the cases of bacterial coinfection in dengue have been increasingly reported.[3] The clinical course of dual infections may result in reciprocal interactions, which may carry significant mortality. In a study by Amancio et al., 45 (46.4%) of 97 severe dengue patients admitted to ICU received antibiotics, and presumably 7 (36.8%) deaths were attributed to bacterial coinfection.[4] This finding reminds us the importance of early detection and prompt antibiotic therapy for the dengue patients with bacterial coinfection in the ICU. This may be challenging with the use of routine markers such as total white blood cell (WBC) count or C-reactive protein (CRP), which can be altered by virtually any inflammatory conditions.

Procalcitonin (PCT) is an immunologically active protein, induced through different steps of activation during bacterial infections. It has been shown as a good marker for the diagnosis, severity assessment and outcome prediction, particularly in patients with bacterial infection.[5] Because PCT has also been suggested as a good marker for excluding bacterial coinfection among ICU patients with influenza,[6] we hypothesized that PCT could provide early detection of bacterial coinfection among patients with severe dengue in the ICU. Review of the current literature revealed that only one study has evaluated the role of PCT to exclude bacterial coinfection in ICU patients with severe dengue.[7] However, this study was retrospective in nature, and was conducted outside our local ICU setting. More importantly, PCT was measured using the standard laboratory method which may take up to several days, and thus may not be suitable for early detection of the bacterial coinfection. Early detection will also prevent overuse of antibiotics, which may have side-effects and lead to antimicrobial resistance.[8]

We investigated the diagnostic efficacy of PCT, measured with a point-of-care (POC) device, for the early detection of bacterial coinfection among patients with severe dengue admitted to our ICU. Other than to qualifying the diagnostic performance of POC PCT for bacterial coinfection in patients with severe dengue, this study also hopes to help facilitate appropriate antibiotic stewardship in the ICU.

2. Methodology

This cross-sectional study was conducted over a one-year period, from 30th September 2020 to 30th September 2021, in the ICU of two university-affiliated hospitals in Malaysia. The protocol of this study was approved by both institutional research ethics committees. All participants or their legally acceptable representatives gave written informed consents to participate in this study.

The inclusion criteria for the study were adult patients (aged 18 years or older) who fulfilled the operational definitions of severe dengue, were tested positive for dengue NS1 antigen, and required admission to the ICU. Patients who received systemic antibiotic before admission blood culture were excluded from the study.

Severe dengue was defined as the presence of any one of the following: 1) decompensated shock due to severe plasma leakage, 2) compensated shock due to severe plasma leakage, 3) respiratory compromise due to severe plasma leakage, 4) severe hepatitis, 5) severe bleeding that required intervention, or 6) severe organ involvement such as acute kidney injury defined by elevated serum creatinine (according to gender-specific levels), myocarditis or encephalopathy.[8] The decompensated shock was defined as presence of systolic blood pressure (SBP) of less than 90 mmHg, or mean arterial pressure of less than 65 mmHg, or a drop in SBP of more than 40 mmHg from the patient's usual baseline readings. The compensated shock required signs of impaired peripheral perfusion, occurring in combination rather than singly, in presence of SBP of more than 90 mmHg. Severe hepatitis was defined as aspartate transaminase level of more than 1000 IU/L, or alanine transaminase level above 1000 IU/L.

The presence or absence of bacterial coinfection on ICU admission was according to the baseline microbiological culture status taken either from the blood or other body fluids. Participants were classified into the bacterial coinfection group if this baseline culture was positive or into the no bacterial coinfection group if this baseline culture was negative.

Upon admission to ICU, 1 mL of arterial blood was obtained from the participants for measurement of PCT. The specimens were tested immediately in the ICU. The test procedure required 75 µL of the whole blood sample to be mixed with the buffer for analysis. PCT was measured using POC analyzers (Finecare™ PCT Rapid Test along with Finecare™ FIA Meter by CIGA Healthcare Ltd., Ballymena, UK), which were available in each of the two participating ICUs. The system uses the fluorescence immunoassay technique and measures the PCT quantitatively. The turnaround time of the system is 15 min. The assay has a measuring range of 0.1 - 100 ng/mL. As per the manufacturer, the intra- and

Table 1. Baseline characteristics and clinical outcome in severe dengue patients

Parameter	All patients (n = 50)	Patients with bacterial coinfection (n = 18)	Patients without bacterial co-infection (n = 32)	P
Demographic				
Age (years)	44.2 (20.0)	38.9 (21.6)	46.6 (19.2)	0.230
Sex (male)	18 (36.0)	4 (28.6)	14 (38.9)	0.495
Body mass index (kg/m^2)	25.3 (5.60)	25.3 (8.0)	25.3 (4.4)	1.000
Clinical				
Comorbidities				
Diabetes mellitus	15 (30.0)	4 (28.6)	11 (30.6)	0.891
Hypertension	11 (22.0)	1 (7.1)	10 (27.8)	0.114
Ischaemic heart disease	6 (40.0)	0 (0)	6 (16.7)	0.103
Chronic kidney disease	6 (40.0)	2 (14.3)	4 (11.1)	0.756
Severity of illness				
APACHE II	9.2 (7.1)	10.3 (7.2)	8.8 (7.1)	0.498
SOFA score	5.4 (4.1)	6.8 (4.2)	4.8 (3.9)	0.129
Signs of severe dengue				
Compensated shock	21 (42.0)	8 (57.1)	13 (36.1)	0.176
Decompensated shock	9 (18.0)	3 (21.4)	6 (17.6)	0.694
Respiratory compromise	23 (46.0)	10 (71.4)	13 (36.1)	0.024
Severe hepatitis	1 (2.0)	1 (7.1)	0 (0)	0.225
Severe bleeding	15 (30.0)	7 (50.0)	8 (22.2)	0.054
Phase of dengue				
Febrile	50 (100)	18 (100)	32 (100)	1.000
Interventions within 24 hours in ICU				
Antibiotic	45 (90.0)	14 (100)	31 (86.1)	0.142
Blood or blood products	22 (44.0)	10 (71.4)	12 (33.3)	0.015
Mechanical ventilation	23 (46.0)	10 (71.4)	13 (36.1)	0.024
Inotropic or vasopressor	18 (36.0)	8 (57.1)	10 (27.8)	0.052
Renal replacement therapy	10 (20.0)	3 (21.4)	7 (19.4)	0.875
Laboratory				
Platelets (/μL)	94.4 (64.6)	78.3 (61.4)	100.7 (65.5)	0.274
Total white cell count (/μL)	7.5 (5.3)	9.1 (5.5)	6.9 (5.1)	0.197
Lactate (mmol/L)	2.1 (2.2)	2.8 (2.4)	1.8 (2.0)	0.127
C-reactive protein (mg/L)	52.7 (59.8)	82.4 (68.9)	41.1 (52.4)	0.027
Clinical outcome				
ICU length of stay (days)	7.7 (13.7)	14.8 (24.5)	4.9 (3.4)	0.158
Hospital length of stay (days)	11.5 (16.0)	19.9 (28.4)	8.3 (4.3)	0.149
ICU-mortality		4 (28.6)	4 (11.1)	0.131

inter-assay coefficients of variation are less than 15%. A correlation study done in our local laboratory showed that the correlation between Finecare™ PCT and Elecys BRAHMS PCT is good, with a correlation coefficient of 0.9552.

Baseline data included demographic variables, e.g., age, sex, and body mass index, clinical variables including comorbidities, severity of illness as represented by the Acute Physiological and Chronic Health Evaluation [APACHE] II score and Sequential Organ Failure Assessment [SOFA] score, and interventions received in the first 24 h of ICU admission in terms of antibiotics, blood or blood products administration, mechanical ventilation, inotropic or vasopressor support, and renal replacement therapy; and laboratory variables, e.g.,

platelets, WBC count, lactate and CRP levels). The participants were followed up until the results of their admission blood and/or other microbiological culture were available. The management of severe dengue was left up to the discretion of the attending ICU physicians. For descriptive purposes, we also recorded the clinical outcome of our participants in terms of their ICU length of stay, hospital length of stay and ICU-mortality.

Statistical analysis

Continuous variables are presented as mean ± standard deviation, while categorical variables are presented as frequency (percentage). Comparison of the continuous variables was performed with independent t-test while that of the categorical variables was achieved with Chi-squared test. Analysis of receiver operating characteristics (ROC) curve was done to assess the diagnostic performance of PCT; area under the curve (AUC) of 0.7 – 0.8 was considered as good, 0.8 – 0.9 as very good and more than 0.9 as excellent. Clinical validity was assumed at an AUC of more than 0.7.[10] The optimal cut-off point was defined using the Youden's Index. The sensitivity, specificity, and likelihood ratio (LR) were calculated; these were reported with their 95% confidence interval (CI). Comparison of two ROC curves was analyzed using the DeLong test. Statistical analysis was performed using SPSS version 24.0 (IBM, Armonk, NY, USA) and MedCalc® for Windows, version 17.5.5 (MedCalc Software, Ostend, Belgium). P-value ≤ 0.05 was considered statistically significant.

In this study, we wanted to show that the AUC of 0.8 for PCT was significantly different from the null hypothesis value of 0.5. Using the ratio of the sample in negative to positive groups of 4:1,[11] significance at 0.05 and power of 0.8, we needed to study 9 patients with bacterial coinfection and 36 patients without coinfection, adding up to a total of at least 45 patients with severe dengue.

3. Results

A total of 50 severe dengue participants were included in this study. Of note, 14 (28.0%) of these 50 participants had bacterial coinfection on ICU admission. The coinfection was detected from blood culture in 5 (35.7%), other culture in 8 (57.1%) and combination of both in 1 (7.2%) of these 14 participants. Seven (50.0 %) of these 14 participants had Gram-positive bacteria: the most common type being *Staphylococcus aureus* (Figure 1). Another 5 (35.7%) had Gram-negative organism while the remaining 2 (14.3%) of these 14 participants had mixed growth of bacteria.

The baseline demographic, clinical and laboratory characteristics as well as the clinical outcome of the included participants are presented in Table 1. At baseline, there was no significant difference in the demographic characteristics between those with and

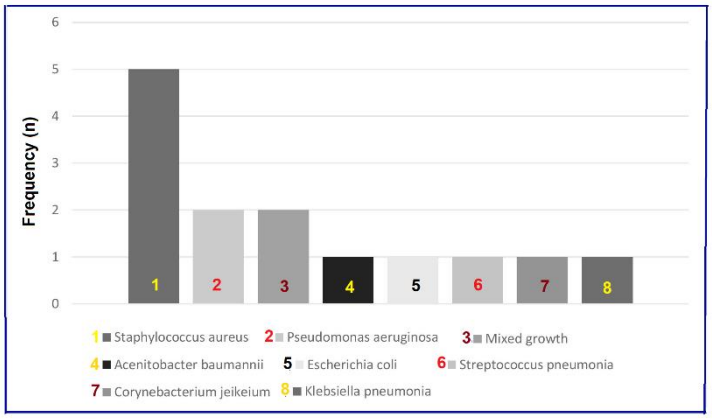

Figure 1: The frequency of microorganisms isolated from blood and other cultures on ICU admission in patients with severe fengue

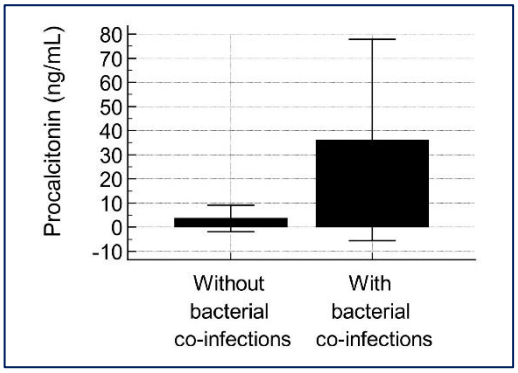

Figure 2: Baseline serum PCT (ng/mL) in severe dengue patterns with and without bacterial coinfection on ICU admission.

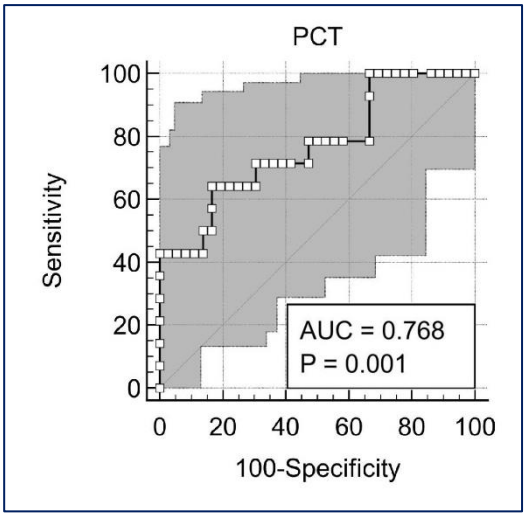

Figure 3: ROC curve of baseline procalcitonin for discrimination of severe dengue patients with and without bacterial coinfection on ICU admission.

without the bacterial coinfection. A significantly higher proportion of participants with bacterial coinfection had respiratory compromise due to severe plasma leakage, required mechanical ventilation and required blood products administration in the first 24 hours of ICU admission compared to those without (71.4 % vs 36.1 % respectively, P = 0.024). Of note, all enrolled participants were in the febrile phase of dengue.

With regard to baseline laboratory characteristics, only CRP was found to be significantly higher in those with bacterial coinfection compared to those without (82.4 ± 68.9 vs 41.1 ± 52.4 mg/L, P = 0.027). There was no significant difference in the clinical outcome between the two groups.

The mean difference in the level of baseline PCT between those with and without the bacterial coinfection is shown in Figure 2. On admission to ICU, severe dengue patients with bacterial coinfection had significantly higher PCT compared to those without (36.2 ± 41.8 vs 3.6 ± 5.6 ng/mL, P = 0.012).

Analysis of the ROC curve showed that PCT was a good biomarker in discriminating patients with severe dengue with and without bacterial coinfection. The AUC was 0.768 (95% CI 0.627 - 0.875, P = 0.001) (Figure 3). At the cut-off point of 0.5 ng/mL, the sensitivity of PCT was 100% (95% CI 76.8 – 100), specificity was 27.8% (95% CI 14.2 – 45.2), positive LR was 1.38 (1.1 – 1.7) and negative LR was less than 0.1. In our severe dengue cohort, the ideal cut-off point of PCT for diagnosing bacterial coinfection was more than 4.6 ng/mL. At this value, the sensitivity was 64.3% (95% CI 35.1 – 87.2), specificity was 83.3% (95% CI 67.2 – 93.6), positive LR was 3.9 (1.7 – 8.8) and negative LR was 0.4 (95% CI 0.2 – 0.9).

On further analysis, PCT had a higher AUC compared to CRP; the latter had a value of 0.700 (95% CI 0.554 – 0.822, P = 0.014) (Figure 4). However, comparison of the ROC curves was not statistically significant with difference between areas of 0.067 (95% CI -0.122 – 0.257, P = 0.484). The ideal cut-off point of CRP for discriminating severe dengue patients with and without bacterial coinfection was at more than 37 mg/L. At this cut-off point, the sensitivity was 64.3 % (95% CI 35.1 – 87.2), specificity was 72.2 % (95% CI 54.8 – 85.8), positive LR was 2.31 (95% CI 1.20 – 4.46) and negative LR was 0.49 (95% CI 0.24 – 1.03).

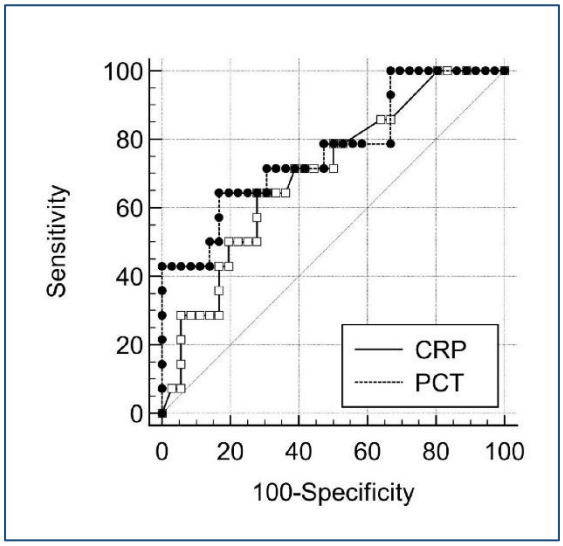

Figure 4: Comparison of the ROC curves of baseline procalcitonin vs C-reactive protein for discrimination of severe dengue patients with and without bacterial coinfection on ICU admission.

4. Discussion

In this cross-sectional study of 50 patients with severe dengue, we found that serum PCT measured on ICU admission was significantly higher in the presence of bacterial coinfection. Evaluation of the ROC curves showed that PCT had a good performance for predicting bacterial coinfection in severe dengue with AUC of 0.768. The ideal cut-off point of PCT for discriminating severe dengue patients with bacterial coinfection in this study was more than 4.6 ng/ml, higher than the well-established value of 0.5 ng/mL.[10] At this cut-off point, PCT test was 64.3% sensitive, 83.3% specific and more useful to rule out rather than to rule in the bacterial coinfections, as indicated by the positive LR of 3.9 and the negative LR of 0.4. Using the cut-off point of 0.5 ng/mL, we found that PCT was 100% sensitive but poorly specific with specificity of 27.8%. Comparison to the routinely used CRP indicated that PCT was a better marker in terms of its discriminative ability, sensitivity, and specificity for bacterial coinfections in severe dengue.

Review of the previous literature revealed that bacterial coinfection was observed in 4% to 25% of adults with dengue.[11] The prevalence of bacterial coinfection in our cohort of 28% was slightly higher than the reported range, possibly because our cohort was of higher dengue severity. In dengue, bacterial coinfection was reported to be particularly common among patients with severe plasma leakage.[11] In line with this finding, we found that patients who had bacterial coinfection had a higher prevalence of respiratory compromise and had greater requirements for mechanical ventilation as well as blood products administration in the first 24 h of ICU admission than those without the coinfection. On another note, half of these coinfected patients grew Gram-positive bacteria as compared to only 35.7% who grew Gram-negative bacteria. This finding correlates with previous works that Gram-positive infection had a higher frequency in ICU setting.[12] In term of the outcome, bacterial coinfection in dengue was associated with high

mortality and morbidity compared with dengue without the coinfections,[11] but this was not observed in our study which could be explained by the relatively small sample size.

In this study, we observed that up to 86.1 % of severe dengue patients without bacterial coinfection received antibiotic. The decision to start antibiotics in this cohort seems fairly understandable, given their high mean SOFA score of 4.8 at ICU admission. On the other hand, overuse of antibiotics is undesirable, because of the side-effects and the increasing antimicrobial resistance. PCT is now recognized as a good biomarker to guide the starting and stopping of antibiotics in the ICU.[13] However, the current study only evaluated the diagnostic performance of PCT for bacterial coinfection in severe dengue. It therefore remains unknown whether integrating measurement of POC PCT in the clinical decision-making regarding antibiotic initiation would improve the outcome of severe dengue patients. A further randomized controlled trial is therefore warranted to confirm or refute the clinical benefits of measuring PCT in severe dengue.

The strengths of our study were the cross-sectional design with prospective data collection and hence its associated advantages over the previous study which was retrospective in nature. In addition, all participants were enrolled during the febrile phase of dengue and assessment of PCT was done on admission to ICU; thus, our findings may help physicians to predict bacterial coinfection earlier among hospitalized patients with severe dengue. Furthermore, the PCT in this study was measured with a rapid POC analyzer, which increases its clinical applicability in a busy clinical setting.

5. Limitations

Although our results are encouraging, the study had several pertinent limitations. The relatively small sample size in this study was not powered to detect significant differences of many variables including the outcome. However, this was not the main aim of our study and with such a sample size, we were able to detect a significant difference in the level of PCT between the groups. Also, this study was conducted in only two centers in Malaysia, and as such the results may not be generalizable to external populations. In this study, the exact mechanism of elevated PCT in severe dengue has not been directly determined. This, together with the determination of the ideal cut-off point of PCT for bacterial co-infection in severe dengue, requires further validation in a larger prospective cohort study.

6. Conclusion

Procalcitonin measured at the time of admission to ICU offers early detection of bacterial coinfection in patients with severe dengue. Further studies are warranted to validate these findings especially in term of the ideal cut-off point and to assess whether point-of-care procalcitonin may be successfully integrated with physicians' clinical practice to improve early detection of bacterial coinfection as well as antibiotic stewardship in patients with severe dengue admitted to ICU.

7. Data availability

Numerical data related to this study is available with the authors.

8. Conflict of interest

Authors declare no conflict of interest in the conduct of this study.

9. Acknowledgement

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10, Authors' contribution

WNAWA: Concept, conduction of the study work, drafting manuscript

WFWMS: Concept, data analysis, drafting manuscript, reviewing final manuscript

MBMN, NFR, PS: Reviewing final manuscript

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