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Letter to the Editor

Performance of soluble suppressor of tumorigenicity-2 as a prognostic marker for severe dengue in adults

Background

We read with interest a recent Letter from Khurram et al. on COVID-19 and dengue co-epidemics may dilapidate healthcare systems.[1]

Dengue, an arthropod-borne viral disease, is spreading rapidly and has increased eightfold in the last two decades. Yearly an estimated 390 million infections occur resulting in 20,000 deaths.[2] In endemic regions, up to 10% of all febrile episodes are attributed to dengue, and the percentage of dengue cases admitted for inpatient management was 19% in Asia.[2]

Most symptomatic dengue is uncomplicated, but a minority of patients may develop severe disease. In the febrile phase of dengue, clinical symptoms last between 2 to 7 days. In the subsequent 24–48 h, some patients enter the critical phase, while others recover well with the resolution of symptoms.[3] Current stratification on the risk of severe dengue (SD) is based on features defined by the World Health Organization (WHO), termed warning signs.[4] Although warning signs are sensitive, they lack precision and may result in unnecessary hospitalisation. Reliable prognostic biomarkers that can be used in a variety of healthcare settings may thus reduce the strain on healthcare resources, especially during dengue outbreaks.

We previously demonstrated that soluble suppressor of tumorigenicity-2 (sST2), a biomarker for cardiac failure, to be elevated in proportion to dengue severity.[5] Others have also reported increased sST2 levels in paediatric with dengue haemorrhagic fever.[6]

In here, using an US-FDA approved cut-off value (35 ng/ml, for stratifying cardiac failure), we prospectively evaluated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of sST2 to predict SD.

Materials and methods

Details of participants recruitment were previously described.[5] Briefly, dengue patients were recruited and followed up from febrile, critical, early, and late recovery phases. Disease severities were assigned based on WHO 2009 classifications - dengue fever (DF), dengue fever with warning signs (DWS) and SD. The critical phase was defined according to the day with the lowest platelet count concurrent with the highest haematocrit and defervescence. Plasma sST2 levels were assayed by ELSIA based on manufacture's protocols. The area under the receiver operating curve (AUROC) and corresponding 95% confidence intervals (CI) were calculated. An optimal cut-off value to predict SD was determined by Youden's index. Together with the cut-off value and historical prevalence of SD, reported locally,[7,8] we determine the sensitivity, specificity NPV and PPV of sST2 as a prognostic biomarker of SD. This study was approved by the National Healthcare Group Domain Specific Review Board (E/2016/00982). Written informed consent was obtained from all patients prior to enrolment.

Results

Detailed baseline characteristics have been published.[5] There were 129 patients recruited for the study: 40 DF, 46 DWS, 13 SD and 30 controls, Table 1. For the DF, DWS and SD groups, 32, 34 and 7 patients, respectively, were enroled in the febrile phase.

Pasma sST2 levels were significantly increased in dengue patients in proportion to disease severity compared to controls in the febrile and critical phases.[5] The AUROC for sST2 in the febrile and critical phases to discriminate against SD were 0.78 [95% CI (0.53–1.00)] and 0.78 (0.62–0.96), respectively, Fig. 1. The Youden's index to differentiate severe from non-severe dengue was 35.2 ng/ml, a similar value to the US-FDA approved cut-off of 35 ng/ml to stratify cardiac failure.[9] The prevalence of SD in patients admitted to our hospital was previously reported as 16.5%.[8] Using this estimate and the cut-off value of 35 ng/ml, the sensitivity and specificity to predict SD in the febrile and critical phases were 99.6% and 86.7%, and 84.6% and 72.1%, respectively. The corresponding PPVs were 52.2% (febrile) and 41.2% (critical), while NPVs were 99.8% (febrile) and 95.3%. In an affiliated primary care facility, the estimated prevalence of SD occurrence was reported at 8.8%, discovery cohort.[7] In this setting, the sensitivity and specificity were 85.7% and 77.3% during the febrile stage, and 82.6% and 71.8% in the critical phase. The PPVs were 28.6% (febrile) and 24.4% (critical) and the corresponding NPVs were 98.1% (febrile) and 97.8% (critical).

Discussion

One of the most urgent needs in dengue management is reliable prognostic biomarkers to identify those at risk of SD in the febrile phase.[3,10] In our study of Asian adults with dengue, we are the first to demonstrate plasma sST2 to exhibit high sensitivity and specificity to predict the development of SD in the febrile phase.

Current practices on dengue hospitalisation are based on DWS.[4] Despite being sensitive, they lack specificity. An earlier study from our institution reported that displaying any one of the seven warning signs to be 95% sensitive and 18% specific in predicting SD in the febrile phase. Additionally, depending on the specific warning sign presented, the PPV ranged from 6% to 18% with an overall NPV of > 90%.[8] This is likely to result in over-hospitalisation if warning signs were the only criterion used for admission. Our observations suggest sST2 to be more sensitive and specific with a superior PPV compared to warning signs alone. Unnecessary hospitalisation can increase healthcare burden and costs, especially during an outbreak.

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Table 1
Baseline characteristics and disease outcomes.

	Controls (n = 30)	DF (n = 40)	DWS (n = 46)	SD (n = 13)	*p* value[a]
Male (%)	15 (50.0)	28 (70.0)	27 (58.7)	8 (61.5)	0.32
Median age (IQR) [range], years	44 (32–59) [23–75]	44 (29–55) [18–73]	48 (35–58) [21–80]	63 (45–68) [24–83]	0.12
Acute myocardial infarction, n (%)	0	0	1 (2)	2 (15.4)	**0.020**
Hypertension, n (%)	4 (13.3)	9 (22.5)	13 (28.3)	9 (69.0)	**0.001**
Days after first reported symptoms					
Median day of illness for febrile phase (IQR)	N.A.	4 (3–5)	4 (3–5)	5 (3–6)	0.87
Median day of illness for critical phase (IQR)	N.A.	6 (5–7)	6 (5–7)	6 (5.5–7)	0.28
Median day of illness for early recovery phase (IQR)	N.A.	8.5 (7–10.5)	8 (7–8)	8 (7–10)	0.19
Median day of illness for late recovery phase (IQR)	N.A.	20.5 (16–24.5)	17.5 (15–21.5)	18 (15–26)	0.10
Hospitalisation outcomes					
Length of hospital stay (IQR), days	N.A.	4 (3–5)[b]	5 (4–6)	7 (5–8)	**0.010**
ICU admission (%)	N.A.	0	0	2 (15.4)	0.14
Inotrope use (%)	N.A.	0	0	2 (15.4)	**0.018**

Data are presented in median (interquartile range) or no. (%) of patients, unless otherwise indicated. P values of < 0.05 were considered significant (in bold). Abbreviations: DF, dengue fever; DWS, dengue with warning signs; SD, severe dengue; IQR, interquartile range.

[a] P values tabulated by ANOVA/Kruskal-Wallis or chi-squared test/Fisher's exact for comparisons across groups.

[b] Includes 24 participants with dengue fever who were admitted during dengue illness.

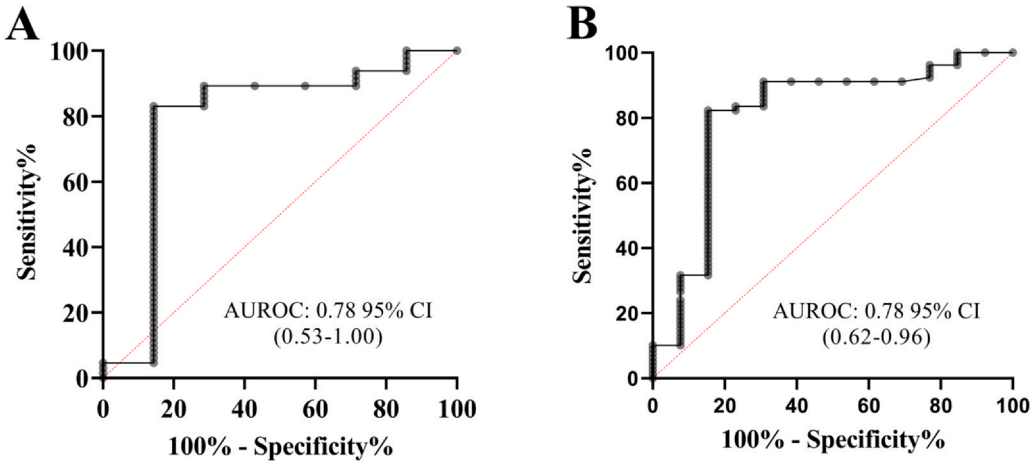

Fig. 1. Area under the receiver operating curve of plasma soluble suppressor of tumorigenicity-2 (sST2) in predicting severe dengue at febrile and critical phases. (A) In the febrile phase. (B) In the critical phase. Nonparametric AUROC with 95% confidence interval (CI) are presented.

Multiple studies have shown that a combination of host factors to be predictive of SD.[10] However, most procedures require specialised equipment and personnel to perform, which are less cost-effective or time-sensitive, especially in resource-limited settings or in smaller patient cohorts. Of note, Presage ST2 is an US-FDA-approved assay used to clinically prognose acute cardiac failure, and a quantitative lateral flow assay for sST2 is available, which may be a valuable point-of-care assay in primary care settings to identify those at risk of SD.[9] Together with the guidance of WHO warning signs, quantifying sST2 concentrations in the febrile phase may greatly reduce dengue hospital admissions without an increased risk of misdiagnosis of SD.

There are two limitations in our study. First, the study population was limited to older hospitalised adults and a relatively small number of patients enroled in the febrile phase progressed to SD.

In summary, febrile phase sST2 levels may be a reliable prognostic biomarker for adult SD. Further studies with cohorts from different geographical and age groups are needed to validate our findings.

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Declaration of Competing Interest

None.

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Contributors

Conceptualization of study: AT; investigation and data curation: AT, PYC; Formal analysis: TWY; writing original draft: TWY; edits and revision; AT, PYC, TWY.

All authors contributed to data interpretation, critically reviewed the manuscript, and approved the final manuscript for submission.

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