Researchers locate two compounds in blood that could identify patients at risk of severe dengue

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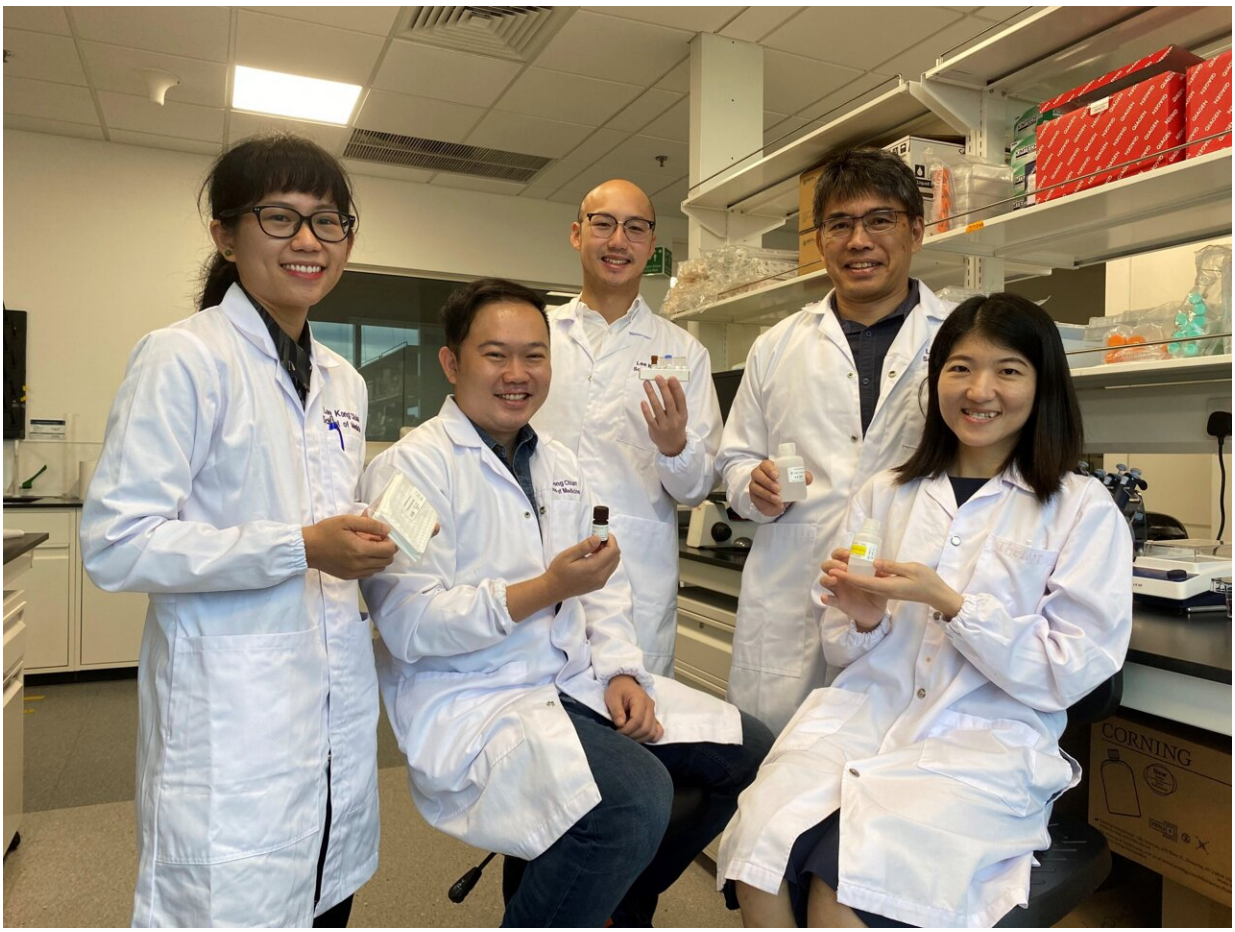

(L-R) Consultant at National Centre for Infectious Diseases (NCID) and Department of Infectious Diseases at Tan Tock Seng Hospital (TTSH), and National Healthcare Group-NTU Clinician Scientist Fellow at NTU's LKCMedicine Asst Prof Chia Po Ying; Dean's Postdoctoral Fellow from NTU's

LKCMedicine Dr Andrew Teo; Senior Resident at NCID and Department of Infectious Diseases at TTSH Dr Trevor Tan; NTU's LKCMedicine Assoc Prof Yeo Tsin Wen; and Research Assistant at NCID and Department of Infectious Diseases at TTSH Ms Diong Shiau Hui. Credit: Nanyang Technological University

Scientists and clinicians at Nanyang Technological University, Singapore (NTU Singapore) and the National Center for Infectious Diseases (NCID) have identified two compounds—sST2 and suPAR—in the blood of dengue patients that could determine if a patient is at risk of severe dengue in the early phases of the disease.

Dengue is often a mild disease. However, a minority of infections may progress to severe dengue, which could be life-threatening for patients that do not have access to close monitoring and specialized medical care.

While dengue infection is usually diagnosed based on a clinical assessment by a doctor and confirmed through blood tests to detect the dengue virus or antibodies against the dengue virus, there are currently no clinically available prognostic tests that are sensitive enough to predict or identify severe dengue infection in its early stages.

Symptoms like abdominal pain, vomiting and mild bleeding have a less than 20% accuracy in screening for severe dengue infection and are generally non-specific.

As lateral flow test kits for sST2 and suPAR are already commercially available and are used to test for heart failure, the researchers are working on validating and adapting these tests into a kit that could test for severe dengue.

sST2 and suPAR are proteins in the blood linked to heart health. High sST2 levels indicate heart stress and fibrosis, so they help assess heart failure severity. Elevated suPAR levels signal increased inflammation, which is associated with a higher risk of heart issues. Monitoring these proteins provides insights into heart health and disease progression.

The researchers estimate that this new method of monitoring the levels of the two compounds would bring a higher accuracy—55% to 60%—of predicting severe dengue than the traditional assessment approaches. The researchers said the test kits would greatly aid clinicians in distinguishing between non-life-threatening cases of dengue fever and severe dengue, which requires hospitalization.

The scientists and clinicians discovered the importance of sST2 and suPAR in determining dengue severity during a study conducted between 2016 and 2019 involving 129 dengue patients treated in Tan Tock Seng Hospital, Singapore.

Lead author Dr. Andrew Teo, a Dean's Postdoctoral Fellow from NTU's Lee Kong Chian School of Medicine (LKCMedicine), said, "Dengue is endemic in Singapore, and one of the primary challenges faced by clinicians is the identification of patients who are at risk of developing severe dengue. The current frequently used biomarkers do not consistently predict individuals at risk of severe dengue.

"We have found that both sST2 and suPAR, which are present in early dengue cases, show more promise in identifying those at risk of severe dengue. Furthermore, the availability of point-of-care test kits using these biomarkers would improve the user experience, in contrast with laboratory testing that often has a longer turnaround time."

Contributing author Assistant Professor Chia Po Ying, Consultant at the National Center for Infectious Diseases, and Department of Infectious

Diseases, Tan Tock Seng Hospital, who led the clinical recruitment for this study, said, "A rapid, prognostic test or biomarker would be invaluable in the management of dengue patients, especially in the febrile phase, the initial stage of an illness characterized by the presence of fever. This could transform dengue care and management and improve patient outcomes." Asst Prof Chia is also a National Healthcare Group (NHG)-NTU Clinician Scientist Fellow at NTU's LKCMedicine.

The study, which represents an advance in diagnosing severe dengue fever infections, reflects NTU's commitment to responding to the needs and challenges of healthy living and aging, one of humanity's grand challenges that the University seeks to address through its NTU 2025 strategic plan.

The findings from the study are published in the *Journal of Infection* and *Clinical Infectious Diseases* in October.

Breaking down dengue: How the test 'feverishly' detects severity

During a dengue infection, the body's immune response is triggered and elevates the levels of sST2 and suPAR. The team from NTU's LKCMedicine and NCID quantified the levels of the two compounds in patients' blood and found that most severe dengue cases tended to have higher levels while non-severe cases had lower levels. The researchers observed that when sST2 and suPAR levels exceeded specific values, it was associated with a strong likelihood of developing severe dengue.

With half of the world's population—approximately 4 billion people—in more than 129 countries at risk of dengue, according to the World Health Organization, the research team said there is a need for an inexpensive and accurate test. The researchers will validate their findings

by adapting lateral flow format test kits, like the Antigen Rapid Test kits used to detect COVID-19 infections, to measure sST2 and suPAR levels.

Senior author Associate Professor Yeo Tsin Wen from NTU's Lee Kong Chian School of Medicine, a clinician-scientist who is also an infectious diseases specialist, said, "The tests, which we aim to validate through collaboration with other clinicians, would serve as an easy and inexpensive point-of-care tool to help health care professionals worldwide avoid unnecessary hospitalization of patients suffering from mild dengue, relieving the health care burden and costs during dengue outbreaks. The test would also improve the management of dengue cases as it would help prioritize health care resources for severe cases, helping to confirm if certain cases of dengue fever are severe."

Dr. Andrew Teo added, "In time to come, these test kits would help answer a major unmet need of dengue, which is an affordable, easy to use early-phase dengue prognostic tool in detecting those at risk of severe dengue. This would ultimately contribute to improved patient outcomes and the management of this challenging disease, which is set to increase in prevalence worldwide due to more widespread habitats for the insects that carry this disease."

The researchers plan to validate their findings by recruiting patients in the earlier dengue disease phase to test for sST2 and suPAR levels, and to follow up on these patients if they develop severe dengue.

More information: Andrew Teo et al, Performance of soluble suppressor of tumorigenicity-2 as a prognostic marker for severe dengue in adults, *Journal of Infection* (2023). DOI: 10.1016/j.jinf.2023.10.003

Andrew Teo et al, Febrile Phase Soluble Urokinase Plasminogen Activator Receptor and Olfactomedin 4 as Prognostic Biomarkers for Severe Dengue in Adults, *Clinical Infectious Diseases* (2023). DOI:

10.1093/cid/ciad637