Abstract of Dissertation submitted by TRAN QUANG THACH

Title: Predictive markers for the early prognosis of dengue severity: A systematic review and meta-analysis

Japanese title: 論文名 デング熱重症化の早期予後予測マーカーに対する評価：系統的レビューとメタ解析

Tran Quang Thach, Heba Gamal Eisa, AlMotsim Ben Hmeda, Hazem Faraj, Tieu Minh Thuan, Manal Mahmoud Abdelrahman, Mario Gerges Awadallah, Nam Xuan Ha, Michael Noeske, Jeza Muhamad Abdul Aziz, Nguyen Hai Nam, Mohamed El Nile, Shyam Prakash Dumre, Nguyen Tien Huy, 平山 謙二教授

（PLOS NEGLECTED TROPICAL DISEASES・15(10): e0009808・2021）
doi: 10.1371/journal.pntd.0009808
〔Total Page Number: 25〕

Department of Infection Research,
Nagasaki University Graduate School of Biomedical Sciences

Supervisor: Professor Kouichi Morita, MD, PhD

Introduction:

Predictive markers represent a solution for the proactive management of severe dengue. Despite the low mortality rate resulting from severe cases, dengue requires constant examination and round-the-clock nursing care due to the unpredictable progression of complications, posing a burden on clinical triage and material resources. Accordingly, identifying markers that allow for predicting disease prognosis from the initial diagnosis is needed. Given the improved pathogenesis understanding, myriad candidates have been proposed to be associated with severe dengue progression. Thus, we aim to review the relationship between the available biomarkers and severe dengue.

Materials and Methods:

We performed a systematic review and meta-analysis to compare the differences in host data collected within 72 hours of fever onset amongst the different disease severity levels. We searched nine bibliographic databases without restrictive criteria of language and publication date. We assessed risk of bias and graded robustness of evidence using NHLBI quality assessments and GRADE, respectively. This study protocol is registered in PROSPERO (CRD42018104495).

Results:

Of 4000 records found, 40 studies for qualitative synthesis, 19 for meta-analysis. We identified 108 host and viral markers collected within 72 hours of fever onset from 6160 laboratory-confirmed dengue cases, including hematopoietic parameters, biochemical substances, clinical symptoms, immune mediators, viral particles, and host genes. Overall, inconsistent case classifications explained substantial heterogeneity, and meta-analyses lacked statistical power. Still, moderate-certainty evidence indicated significantly lower platelet counts (SMD -0.65, 95% CI -0.97 to -0.32) and higher AST levels (SMD 0.87, 95% CI 0.36 to 1.38)

in severe cases when compared to non-severe dengue during this time window.

Discussion:

The major concern in dengue fever is the abrupt occurrence of severe complications, for which only close monitoring of patients is the treatment scheme. Thus, the markers managing to predict the subsequent progression of complications—in the early stage of disease course—could alleviate the clinical management burden. Ideally, the predictors foretell the outcomes before the severe complications occur—usually on days 4–7 following fever onset. Alongside the findings shown above, we put forward four points that medical care may find helpful. First, the main inconsistency in our findings regarding clinical signs was the existence of different case classifications. Given that the updated WHO classification, which includes broader clinical outcomes, is more sensitive to detecting severe cases than the 1997 guideline, the estimated effect of the markers defined was larger. Second, bias and inconsistency may arise from the measurements of abdominal pain and vomiting. The effects could vary in terms of a "dose-response" relationship—referring to the resulting progressions of different clinical manifestations. Indeed, the patients presented with different vomiting episodes per day and different abdominal manifestations in that individuals who have a greater number of vomiting episodes are more likely to experience complicated dengue, and different clinical manifestations could speak to the different progressions. Third, there was evidence that hepatomegaly is more prevalent in complicated dengue; however, the hepatomegaly rate was lower than expected in our study. Hence, the samples in our analysis were shorter than the required size to provoke a precise point estimate. The modest detection rate of hepatomegaly requires a re-evaluation of ultrasound benefits in the early stage. The relationship between plasma leak signs—detected by ultrasound—and complicated dengue is undeniable. However, the sonographic hallmarks allow for reliable prediction mostly around the critical phase or later. Hence, although the differences between severe and non-severe dengue were detected during the first 3 days, a high false-negative prediction rate may occur. Fouth, there is a need for larger studies to confirm the relatedness of hyaluronan in severe dengue. In conclusion, our review highlights two topics which merit further consideration. First, platelet and AST require establishing quantitative diagnostic values and additional validation through prospective studies. Finally, decreased platelet counts could serve as an independent warning sign, instead of combining with elevated hematocrit detectable when plasma leak has implicitly occurred, often on day 3 or around the critical phase.