Author’s response to reviews

Title: Dengue Score as a diagnostic predictor for pleural effusion and/or ascites: External validation and clinical application

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Author’s response to reviews:

Reviewer #1

In the title ‘diagnostic predictor’, the term predictor may not be applied in this study because 2 of them (Hemoconcentration => 15.1 and albumin < 3.49) are the evidence of plasma leakage. Plasma leakage had occurred sometimes so they are not the predictors? The other parameters, platelet count <= 49,500 is usually the helpful indicator for plasma leakage. AST ratio => 2.51 is the common findings in dengue infections. It is found in both DF and DHF, so it may not be a
good predictor of plasma leakage. The higher ratio may be used instead. The term 'parameter' may be used instead of 'predictor'.

Response:

Prediction models can be used as a diagnostic model or a prognostic model. Prediction models estimate the risk (absolute probability) of the presence or absence of an event (in this study, ‘event’ refers to patients with pleural effusion and/or ascites). Depending on the time frame of the study, prediction research can be diagnostic (outcome or disease present at this moment) or prognostic (outcome occurs in the future) [1]. The design of the present and previous studies [2] are that of the diagnostic model to determine the probability of pleural effusion and/or ascites (detected by abdominal USG) in dengue-infected patients based on four variables: Hct increase≥15.1%, serum albumin≤3.49 mg/dL, platelet count≤49,500/μL and AST ratio≥2.51.

The results of studies on diagnostic testing are presented as sensitivity, specificity, positive and negative predictive values. In addition, predictive values have been suggested to estimate the probability of disease in the clinical setting, as the sensitivity and specificity of a test have limited clinical usefulness because they cannot be used to estimate the probability of disease in an individual patient [3]. This is why we stated “at a cutoff of ≥2, the Dengue Score had a positive predictive value (PPV) of 79.20% and a negative predictive value (NPV) of 90.36% for the diagnostic prediction of pleural effusion and/or ascites” (Lines 35-37). Several studies report the diagnostic model as “diagnostic predictor” [4-6]. Thus, we believe that the term 'diagnostic predictor' in this study is used correctly.

Clinical application of these 3 parameters (except AST ratio) may be to late for many patients (Hemoconcentration, low serum albumin and platelet < 49,500) are usually found late in the course of DHF illness. Earlier signs/parameters to predict plasma leakage in dengue patients are best for clinical application, not a late signs/parameters that used in this study.

Response:

The clinical applications of the present study are as follows:
1. Patients with Dengue Score≤1 are likely to have dengue fever (DF), the mildest form of dengue infection (line 160-161).

2. Patients with Dengue Score=2 have a high probability of plasma leakage and may therefore need to be closely observed in health care facilities (line 170-173).

3. Patients with Dengue Score≥3 are more likely to have severe dengue and a prolonged hospital stay (line 199-203).

Why Hemoconcentration => 15.1% is used (instead of => 20%) and o AST ratio of => 2.51 were used as the dengue score?

Response:

We used Hemoconcentration =>15.1% and AST ratio of =>2.51 based on a previous study [2]. Analyses of four variables to diagnose pleural effusion and/or ascites are presented in Table 1.

Table 1. Final multiple logistic regression model to predict pleural effusion and/or ascites

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariate adjusted</th>
<th>Coefficient</th>
<th>Odds ratio (95% CI)</th>
<th>p Value</th>
<th>Dengue Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of hemoconcentration</td>
<td>≥ 15.1%</td>
<td>1.13</td>
<td>3.11 (1.41-6.88)</td>
<td>0.005</td>
<td>1</td>
</tr>
<tr>
<td>Lowest albumin concentration at critical phase</td>
<td>≤3.49 g/dL</td>
<td>1.50</td>
<td>4.48 (1.87-10.77)</td>
<td>0.001</td>
<td>1</td>
</tr>
<tr>
<td>Lowest platelet count</td>
<td>≤ 49,500/µL</td>
<td>1.28</td>
<td>3.62 (1.55-8.49)</td>
<td>0.003</td>
<td>1</td>
</tr>
<tr>
<td>Elevated ratio of AST</td>
<td>≥ 2.51</td>
<td>0.98</td>
<td>2.67 (1.19-5.97)</td>
<td>0.017</td>
<td>1</td>
</tr>
</tbody>
</table>

AST: aspartate aminotransferase; CI: confident interval
Please give more detail on NS1 Ag used in this study. Many cases especially those who came late to the hospital, especially those with shock, the NS1Ag are usually not detected? What brand, sensitivity and day of fever that NS1Ag was done in each patients?

Response:

Patients who were included in our study visited the hospital on median day 3 of fever (IQR 2-4). NS1Ag was assessed in each patient on the day of admission. Patients developed shock during hospitalization. The NS1 used in this study was from SD BIOLINE Dengue Duo, Standard Diagnostics, Korea; based on the manufacturer’s information, the sensitivity is 92.4% and the specificity 98.4%. We have added these information in the Method section (line 88) and the Results (line 131-133 and table 2)

Table 1 - please add all parameters that were used for dengue score: Hemoconcentration => 15.1%, alb <= 3.49, platelet <= 49,500 and AST ratio => 2.51.

Or add one more table to show each parameter that were found in all study groups, group dengue score =< 1, = 2 and => 3.

Response:

We have added another table, Table 2, to show each parameter of all study groups.

Please use only group dengue score =< 1, = 2 and => 3. On line 179, 190, 208, the authors used the term group =< 2! Which is equal to group =< 1? This had made the readers confused!

Response:

We have made correction on the nomenclature (line 174, 185 and 203).
Reviewer #2

This manuscript seeks to perform external validation of the Dengue Score (intended to predict plasma leakage, and based upon AST, albumin, HCT, and platelet count). The Dengue Score was retrospectively applied to data from ~200 inpatients in a Jakarta hospital over a 5-year period.

MAJOR COMMENTS.

As currently performed, this analysis does not appear to add much to the literature regarding risk factors for plasma leakage or the clinical evaluation of dengue infection in general. The major finding of this study is that Dengue Score was found to correlate with hemoconcentration, thrombocytopenia, and severe dengue (which includes plasma leakage and organ damage) - each of these items is reflected to some degree within the calculation of the Dengue Score, therefore their correlation is not surprising.

Response:

Research on the prediction model ideally follows three steps, namely, development, validation, and impact/implementation [1].

Several facts regarding plasma leakage in dengue-infected patients are known:

1. Hematocrit of ≥20% and serum albumin ≤3.5 g/dL are criteria of plasma leakage [7, 8].

2. Elevated hepatic transaminase levels are associated with plasma leakage [9].

3. In clinical practice, clinicians often detect pleural effusion and/or ascites in patients with elevated hematocrit values of less than 20%, a cut off used to define hemoconcentration as recommended by the WHO [10].

4. Previous studies reported albumin levels<3.5 g/dL in dengue fever (DF) [11, 12].

5. Pleural effusions and/or ascites as visualized by ultrasonography (USG) are sensitive and specific for determining plasma leakage [10, 13]. However, USG is not widely available in resource-limited areas.
The Dengue Score (previously published in BMC Infect Dis) [2] adds:

1. The cutoff point of the laboratory parameters (degree of hematocrit, platelet count, serum albumin level and elevated ratio of transaminase levels) for diagnosing pleural effusion and/or ascites as the gold standard.

2. Calculating the AST ratio to address differences between laboratories regarding the reference limits for AST.

3. Development of a dengue scoring system as a diagnostic predictor of pleural effusion and/or ascites.

Additional steps in prediction model research are validation and impact/implementation [1]. Thus, the novelty of this study is to validate the previously published Dengue Score and its clinical application (line 25-26 and line 83-84).

The author's state that the Dengue Score may be useful in identifying which patients may need to be admitted to the hospital, however the applied measurements (presumably maximum HCT concentration, minimum PLT measurement) are derived from later in the hospitalization. Their analysis does not support these conclusions.

Response:

We deleted the statement regarding the application of the Dengue Score to determine need for hospital admission (line 161) and reworded the conclusion (line 43-44 and line 209-212).

MINOR COMMENTS.

Despite the above comments, this is an interesting cohort with seemingly abundant clinical data available. Perhaps a more valuable analysis would consider how laboratory or other clinical factors on admission may predict plasma leakage.

Response:
The aim of this study is to externally validate the previously published Dengue Score and its clinical application. Therefore, our data cannot be used to elaborate laboratory or other clinical factors on admission for predicting plasma leakage.

This reviewer is not familiar with application of the Hosmer Lemeshow test for calibration; recommend statistical review as indicated.

Response:

The performance of prediction models can be assessed using the area under the curve (AUC) to evaluate discrimination and the Hosmer-Lemeshow goodness-of-fit to evaluate calibration. All statistical analyses were performed using STATA, version 14.0 (line 113-120).

Page 5, line 56: it is a little confusing (circular?) to state that length of stay affects management of dengue.

Response:

We have corrected this statement (line 83).

References


