STUDY PROTOCOL

REVISED Clinical prognostic models for severe dengue: a systematic review protocol [version 2; peer review: 2 approved]

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Abstract

Background: Dengue is a common mosquito-borne, with high morbidity rates recorded in the annual. Dengue contributes to a major disease burden in many tropical countries. This demonstrates the urgent need in developing effective approaches to identify severe cases early. For this purpose, many multivariable prognostic models using multiple prognostic variables were developed to predict the risk of progression to severe outcomes. The aim of the planned systematic review is to identify and describe the existing clinical multivariable prognostic models for severe dengue as well as examine the possibility of combining them. These findings will suggest directions for further research of this field.
Methods: This protocol has followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta – Analyses Protocol (PRISMA-P). We will conduct a comprehensive search of Pubmed, Embase, and Web of Science. Eligibility criteria include being published in peer-review journals, focusing on human subjects and developing the multivariable prognostic model for severe dengue, without any restriction on language, location and period of publication, and study design. The reference list will be captured and removed from duplications. We will use the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) checklist to extract data and Prediction study risk of bias assessment tool (PROBAST) to assess the study quality.
Discussion: This systematic review will describe the existing prediction models, summarize the current status of prognostic research on dengue, and report the possibility to combine the models to optimize the power of each paradigm.
PROSPERO registration: CRD42018102907

Keywords

decision support techniques, dengue, dengue hemorrhagic fever, dengue shock syndrome, severe dengue, model, forecasting, prediction, prognosis

Open Peer Review

Reviewer Status ✓ ✓

	Invited Reviewers	
	1	**2**
REVISED **version 2** published 02 Aug 2019	✓ report	✓ report
version 1 published 24 Jan 2019	? report	✓ report

1 **Bushra Khalid**, International Institute for Applied Systems Analysis, Laxenburg, Austria

2 **Olaf Horstick**, University of Heidelberg, Heidelberg, Germany

Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: Dao Phuoc T: Methodology, Project Administration, Writing – Original Draft Preparation, Writing – Review & Editing; **Khuong Quynh L**: Methodology, Project Administration, Writing – Original Draft Preparation, Writing – Review & Editing; **Vien Dang Khanh L**: Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; **Ong Phuc T**: Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; **Le Sy H**: Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; **Le Ngoc T**: Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; **Phung Khanh L**: Conceptualization, Methodology, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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First published: 24 Jan 2019, **4**:12 (https://doi.org/10.12688/wellcomeopenres.15033.1)

REVISED **Amendments from Version 1**

The introduction has been updated with some additional characteristics of severe dengue as well as fixing grammatical and sentence structure errors for the entire protocol.

See referee reports

List of abbreviations

CHARM: the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies

DF: Dengue Fever

DHF: Dengue Hemorrhagic Fever

DSS: Dengue Shock Syndrome

PRIMA: the Preferred Reporting Items for Systematic Reviews and Meta – Analyses

PRISMA-P: the Preferred Reporting Items for Systematic Reviews and Meta – Analyses Protocol

WHO: World Health Organization

Introduction

Dengue is the most common mosquito-borne viral infection globally and a considerable public health burden in many tropical countries[1]. Globally, the number of dengue infection has increased rapidly within the past two decades, and it is estimated that the incidence of dengue went up six-fold from 1990 to 2013[2]. The disease has a wide-spectrum of clinical manifestations, from self-limited mild illness to severe dengue[3]. Although only a small proportion of dengue-infected patients develop severe dengue, it is responsible for an average of over 9,000 deaths per year over the same time period, globally[2]. The current WHO's guidelines suggests 2 levels of severity: dengue with/without warning signs and severe dengue[4]. While the former is usually a mild illness with considerable morbidity but low mortality, the latter is associated with uncompensated plasma leakage which may lead to hypovolemic shock, organ dysfunction and several complications including death[3].

Disease management is mainly based on early supportive treatment, since there is no specific antiviral drugs available[3,5,6]. Therefore, identifying early patients who are at risk of developing severe outcomes based on simple and readily available risk factors plays an important role in dengue case management. Potential predictors could be ranged from clinical features and standard laboratory tests, including hematocrit and platelet count to viral and immunological markers as well as novel markers of endothelial activation and vascular functions[7]. To accurately evaluate the risks of a specific clinical outcome for individual patients, a single predictor is hardly adequate, hence, there is a need to develop a multivariable prognostic model using multiple prognostic variables[8]. Building a prediction model, which comprises three typical elements including suggested predictors, an outcome and a statistical model, is the third step of a 4-step recommended design for prognostic research[9].

Recently, many clinical prognostic studies for severe dengue have been published. However, there remains no widely accepted paradigm to predict disease severity. This may be due to the heterogeneity in the study populations and design, clinical definitions of "severe" dengue, candidate predictors and analytical approaches between studies. It is, therefore, necessary to conduct this systematic review to provide a general and detailed description of the status quo of clinical prediction models for severe dengue, and to suggest further development in this emerging field of research.

Research aims

The primary aim of this systematic review is to identify and evaluate currently available multivariable prognostic models for severe dengue. To the authors' knowledge, this is the first time that multivariable prognostic models for severe dengue have been reviewed systematically. The secondary purpose is to establish if there is any possibility to combine these models. Furthermore, some suggestions will be given on how to develop robust and applicable clinical prediction models for severe dengue.

Methods

This protocol has been prepared using the Preferred Reporting Items for Systematic Reviews and Meta – Analyses Protocol (PRISMA-P)[10]. The PRISMA-P checklist is available as part of the Reporting guidelines[11].

Selection criteria

Study design. We will include all published articles on developing, validating or updating the multivariable prognostic models aiming to predict the risk of death or severe dengue based on the WHO 1997 and 2009 dengue case classification. There is no restriction on language, time of publication, country in which the study was conducted or study setting. Book chapters, commentaries, conference abstract, reviews, editorials, guidelines and letters will be excluded.

Population. This review will include studies published in peer-reviewed journals and conducted on patients who were diagnosed with dengue infection based on clinical features and/or dengue diagnostic tests such as but not limited to detection of antigen (NS1), serological test (total IgM, IgG ELISA), nucleic acid detection (RT-PCR, real-time RT-PCR) and virus isolation with the aim to develop, validate or update the multivariable prognostic models to predict the risk of occurrence of severe dengue. "Severe dengue" term for this study entails: Dengue Hemorrhagic Fever (DHF), Dengue Shock Syndrome (DSS) of the 1997 WHO dengue case classification and Severe Dengue of 2009 WHO dengue case classification, and mortality.

Types of multivariable prognostic models. Each included studies must be conducted to develop, validate or update a clinical multivariable prognostic model in order to predict the risk of occurrence of severe dengue for patients who have any symptoms relating to dengue infection or diagnosed with dengue infection. The developed model must involve at least two predictors. We will take into consideration all types of prognostic model

development studies (e.g. with or without external validation in independent data, and with or without model updating).

Primary and secondary outcomes

The primary outcomes of this systematic review will be the number of currently available clinical multivariable prognostic models for severe dengue and their properties including: study designs, outcomes, candidate predictors, statistical approach, validation status, and model performance. The secondary outcome of this systematic review is the possibility to combine these identified models into a more comprehensive prediction model.

Search strategy

We will conduct a comprehensive search to identify all related publications. The following bibliographic databases will be searched by individual search strategies created specifically for each database: PubMed, Embase, and Web of Science. PubMed, developed by the US National Library of Medicine, National Institutes of Health, covers the majority of biomedical journals published from 1950, and unlimited keywords allowed[12]. Embase and Web of Science also includes diverse published journals[13], with languages and keyword supported search. While Embase covers extensive Europe journals, Web of Science provides articles published from 1900, and citation analysis[12].

Since the patient characteristics are broad, to build up the search strategy, we will focus our keywords on two main parts: (1) "prognostic model" for clinical multivariable prognostic model, and (2) "severe dengue" for outcome relating to DHF, DSS of the WHO 1997, severe dengue of the WHO 2009 dengue case classification and mortality. The search strategies will be designed by combining index terms and text words relating to two main parts mentioned. All possible synonyms of these terms will be identified and included to cover more comprehensively the review subject. We will use Boolean operator "OR" to link all index terms, text words, and synonyms into particular groups relating to main keywords and Boolean operator "AND" to link all groups into the final search string. Search fields will be applied to make the search string more appropriate to each database. We will only focus on the articles relating to human subjects. The Boolean operator "NOT" will be also used to exclude book chapters, documents, editorials, review and guidelines. There is no restriction on language and publication date. The sample search strategy developed for PubMed, Embase and Web of Science as Extended data[11].

Selection of studies

Study selection will be conducted by following the PRISMA flow diagram. We will capture the reference lists from each database and then import them into Mendeley software to remove duplications. The BibTex file containing all filtered references will be then exported. We will import the BibTex file into JabRef software to create the Excel file as the reference list. The recorded data will be managed by the reference lists throughout the review process. Two independent reviewers will screen simultaneously all titles and abstracts based on the following broad screening criteria: (1) focusing on human subjects, (2) focusing on developing the clinical prognostic model, (3) focusing on severe dengue outcome (DHF, DSS of the 1997 WHO dengue case classification and Severe Dengue of 2009 WHO dengue case classification, and mortality). We will exclude articles that do not meet the screening criteria above. Any discrepancies reported during the study screening will be resolved through discussion with a third reviewer. Full-texts of identified abstracts will be retrieved and reviewed to check for more detailed criteria: (1) focusing on developing a multivariable model relating to severe dengue, (2) focusing on patients who were diagnosed with dengue infection based on clinical features and/or dengue diagnostic test. Identified publication will be excluded if full-text is not available. If any disagreements occur, we will reach a consensus by consulting a third reviewer. The reasons for excluding the articles will be reported in detail. Attempts will be made to translate the non-English articles into English.

Data extraction

Extracting data will be performed by two independent reviewers to collect essential data from full texts. The form for extracting data will be designed based on the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS). The CHARMS checklist was developed by Moons *et al.* to provide guidance on framing of systematic data extraction forms with eleven specific domains[14]. Additional data on article information, source of data, candidate predictors, sample size and model characteristics will also be extracted as suggested in the Cochrane Methods Prognosis Template[15]. All data retrieved from identified full-texts will be imported into the in-depth form. Any discrepancy will be resolved by discussing with the third reviewer to reach a consensus.

We will extract the following data as a minimum:

- Article information: author, year of publication, country of publication, location
- Source of data: study design (e.g. prospective or retrospective, case – control, etc) , follow-up time, study context (in primary or secondary health care center)
- Participants: patient characteristics, for example, age, gender, dengue diagnosis criteria, comorbidity, given treatment, etc. recruitment method, number of study centers, patient inclusion, and exclusion criteria.
- Outcome(s) to be predicted: severe dengue definition, for example, DHF, DSS, and severe dengue of 1997 and 2009 WHO dengue case classification, mortality, shock recurrence; method for outcome measurement, time of outcome occurrence
- Candidate predictors: number and type of predictors, definition and collection method of predictors, timing of measurement, measures of association and predictive performance (e.g. risk ratio, odds ratio, hazard ratio or mean difference), handling of predictor in model

- Sample size: total number of participants, ratio of participants to candidate predictors,
- Missing data: number and percentage of missing value in total and for each predictor, extend of loss to follow-up, method of dealing with missing data (e.g. imputation)
- Model development: modelling method (e.g. statistical model, machine learning techniques), variable selection method (e.g. best subset, stepwise selection), selection criteria (e.g. P-value, AIC, BIC)
- Model performance: calibration (e.g. calibration slope), discrimination (e.g. AUC, C-statistic, D-statistic) and classification measures (accuracy, sensitivity, specificity, predictive values)
- Model evaluation: internal and external validation
- Model presentation: how the final model was presented (e.g. nomogram, score chart)
- Model applicability and interpretation: strengths, limitations and applicability in clinical setting

Assessment of study quality

All identified studies meeting the eligibility criteria will be assessed based on the domains suggested by Prediction study Risk Of Bias Assessment Tool (PROBAST), the currently recommended tool for assessing the risk of bias in prognostic studies[16]. This tool was built up by experts in the field on the basis of the Delphi process comprising five domains: participant selection, predictors, outcome, sample size, and participant flow and analysis, with detailed guidance for determining potential items that could possibly be biased[16]. The quality of identified studies will be evaluated by two independent reviewers. Discrepancies will be resolved by discussing with the third reviewer.

Data synthesis

We will descriptively analyze all clinical multivariable prognostic models by describing and narratively synthesizing the article and model information. No formal meta – analysis will be conducted to summarize the model performance across identified articles. The percentage and frequency of each item will be summarized and tabulated. Each model will be narratively synthesized in terms of sample size, candidate predictors, development method, performance and evaluation, presentation, applicability in clinical practice and risk of bias. From the retrieved information, we will describe the clinical heterogeneities in study participants, candidate predictors, outcomes as well as the methodological heterogeneities in the sources of data, missing data, and statistical approaches. If data on measures of association and predictive performance is insufficient, we will estimate this data using the approaches suggested by Cochrane Collaboration and Parmar *et al.*[17,18]. We will also explore the possibility of combining identified prediction models into a more comprehensive model using a recent meta-analysis approach[19]. The trend in the development of prognostic models for severe dengue from the identified publications throughout years will be reported to make suggestions for further research in this field.

Dissemination of information

Our research findings will be presented at scientific conferences and published in peer-reviewed scientific journals. We will also disseminate the findings on popular science newspapers.

Study status

The publication search has been completed. Currently, we are conducting screening identified publications.

Discussion

The early and proper identification of patients who are at risk of severe dengue requires processing inputs from a variety of clinical signs, examination results, and epidemiological characteristics. While clinicians may find it challenging and overwhelming to utilize such a volume of information, prediction models can help as handy tools to support in monitoring, decision making and treating dengue patients. Given the emerging prediction models in dengue infection and heterogeneous characteristics of models and algorithms, we hope this review will provide a systematic evaluation of the existing literature in the field. From our review, recommendations could be made on how to develop and report prediction models for severe dengue, how to use these models and where to focus for research in the field in near future.

Declarations

Data availability

Underlying data. No data is associated with this article.

Extended data. We have submitted our extended data into Havard Dataverse

Harvard Dataverse: Extended data "Clinical prognostic models for severe dengue: a systematic review protocol"; https://doi.org/10.7910/DVN/MU4QLJ[11].

Reporting guidelines

Harvard Dataverse: PRISMA-P checklist for "Clinical prognostic models for severe dengue: a systematic review protocol" https://doi.org/10.7910/DVN/MU4QLJ[11].

Grant information

This work was supported by the Wellcome Trust through the Viet Nam Major Overseas Programme core grant [106680] which supports PKL

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 20 August 2019

https://doi.org/10.21956/wellcomeopenres.16820.r36128

✔ **Olaf Horstick**
Heidelberg Instititue of Global Health, University of Heidelberg, Heidelberg, Germany

Good now and good luck with the research.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Arbovirus and high level evidence

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 09 August 2019

https://doi.org/10.21956/wellcomeopenres.16820.r36129

✔ **Bushra Khalid**
Evolution and Ecology Program, International Institute for Applied Systems Analysis, Laxenburg, Austria

I would recommend the protocol for indexing.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: disease prognostic models, process based models, dengue fever transmission models

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 14 February 2019

https://doi.org/10.21956/wellcomeopenres.16401.r34670

Olaf Horstick
Heidelberg Instititue of Global Health, University of Heidelberg, Heidelberg, Germany

This is a very good protocol for the systematic review. I would only suggest to include searches on google scholar, with a modified search strategy on this database, and also searches of grey literature. The topic may well be in national guidelines, etc. and not in published scientific literature only.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Arbovirus and high level evidence

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 30 Jul 2019

Thang Dao Phuoc, University of Medicine and Pharmacy, Ho Chi Minh City, Vietnam

I thank you for your helpful comments. Your suggestions are great and worth considering. However, we currently do not have enough time to search for more databases as well as grey literature.

Competing Interests: No competing interests were disclosed.

Reviewer Report 12 February 2019

https://doi.org/10.21956/wellcomeopenres.16401.r34669

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Bushra Khalid
Evolution and Ecology Program, International Institute for Applied Systems Analysis, Laxenburg, Austria

This is a study protocol for identifying the clinical prognostic models for dengue management. Authors intend to identify already developed prognostic models for dengue management and check the possibility of combining them in order to increase the efficiency in predictability for an early treatment. This is an interesting study design especially from the perspective of combining several prognostic models however the first part of the study requires more description to fully understand what authors want to carry out in this work.

1. There are several grammatical and sentence structure errors in the document.
2. “The number of dengue infection has increased…” this sentence in the introduction does not state the region (any particular continent/global/particular region) on increase of dengue infection. The period 1990-2013 for citing in the current research is quite old. New research may be cited from the scientific literature.
3. “it is responsible for an average of over 9,000 deaths per year….” this sentence does not state the region of 9,000 deaths per year.
4. After mentioning the rate of dengue, the severity of dengue has been stated all of a sudden. It requires mentioning more information beforehand regarding the severity of dengue fever. Authors should consider maintaining a rhythm of the topic of concern.
5. Introduction section should be revised considerably to inform the background of the intended study.
6. The objective of the study does not clearly mention whether the study intends to identify the severe dengue within an individual patient or is it a collective term for a severe dengue incidence within a region?
7. Authors should describe the term “multivariate prognostic”.
8. Authors should revise the methods section and eliminate repetition in the text.
9. Authors may consider introducing any such multivariate prognostic models, if they exist.
10. Authors may consider discussing a little bit of prognostic variables and their importance in the transmission of severe dengue to highlight the importance of conducting this study.
11. As authors stated that “there remains no widely accepted paradigm to predict disease severity…” how do authors defend carrying out this study based on the various global disease predictive models which are not well-designed/functional? Why and how this study would be useful and applicable in reality for policy making or treatment.
12. Various prognostic models may have used various variables, how do authors think to compare the different situational/regional/global models with each other since every region/situation cannot be comparable.

Is the rationale for, and objectives of, the study clearly described?
Partly

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: disease prognostic models, process based models, dengue fever transmission models

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 30 Jul 2019

Thang Dao Phuoc, University of Medicine and Pharmacy, Ho Chi Minh City, Vietnam

I thank you for your helpful comments. We have edited some details based on your suggestions and have some of the following responses to your suggestions.

1. There are several grammatical and sentence structure errors in the document.
We have checked again our protocol and identified some grammatical errors and sentence structure errors. We have already fixed it in our revision.

2. “The number of dengue infection has increased…” this sentence in the introduction does not state the region (any particular continent/global/particular region) on increase of dengue infection. The period 1990-2013 for citing in the current research is quite old. New research may be cited from the scientific literature.
This is a global trend, from data of 76 countries and 1636 case reports of dengue, following the cited reference. To clarify that, we have modified the sentence to: “Globally, the number of dengue infection has increased …”. Even though the period 1990-2013 seems quite old, this research was published in 2016 and according to our knowledge, this is the standard and most up-to-date reference on this topic.

3. “it is responsible for an average of over 9,000 deaths per year….” this sentence does not state the region of 9,000 deaths per year.
Similar to question number 2, the number of deaths per year was estimated throughout data of 130 countries over the world. To clarify that, we have modified the sentence to: “it is responsible for an average of over 9,000 deaths per year over the same time period, globally.”

4. After mentioning the rate of dengue, the severity of dengue has been stated all of a

sudden. It requires mentioning more information beforehand regarding the severity of dengue fever. Authors should consider maintaining a rhythm of the topic of concern.
We have added this sentence to briefly mention about dengue severity after the sentence about global rate of dengue:
“"The disease has a wide-spectrum of clinical manifestations, from self-limited mild illness to severe dengue [reference: Simmons *et al.* (2012)]"”

5. Introduction section should be revised considerably to inform the background of the intended study.
As presented in our protocol, the introduction is divided into 3 main parts, namely:
1/ Global epidemiology of dengue – Paragraph 1: line 1 – line 14
2/ Difficulties of dengue management and the importance in early predicting severe dengue progression – Paragraph 2: line 15 – line 30
3/ Limitations of clinical prognostic studies – objectives of systematic review
Unless there is any specific background information you suggest that we should add, we believe that this structure and the presented introduction section provide adequate and appropriate information as background of our study.

6. The objective of the study does not clearly mention whether the study intends to identify the severe dengue within an individual patient or is it a collective term for a severe dengue incidence within a region?
As mentioned in our protocol, our objective is to describe in detail the status of existing clinical prediction models, mainly focusing on prognosis, for predicting risk of severe dengue progression, and to suggest possible development for this field of research. To our knowledge, “clinical prognostic model” or “clinical prediction model” are current standard terms that refer to models aiming to predict the risk of future clinical outcomes in individual patients (Reference: Steyerberg EW *et al.* (2013) Prognosis Research Strategy (PROGRESS) 3: Prognostic Model Research. Plos Med, 10(2): e1001381, URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3564751/.

7. Authors should describe the term “multivariate prognostic”.
Of note, we did not use the term “multivariate prognostic” but rather the term “multivariable prognostic models” in our manuscript (we believe that statistically, there are major differences between these two terms, “multivariable” and “multivariate”). “Multivariable prognostic models” refers to prognostic models which are multivariable, which in turn is a standard term that refers to statistical regression models with more than one predictor (independent variables) (Reference: Hidalgo B and Goodman M (2013) Multivariate or Multivariable Regression?. Am J Public Health, 103(1):39-40).

8. Authors should revise the methods section and eliminate repetition in the text.
We have checked the methods section multiple times for repetition. Even though there are some words/phrases look similar to each other, they are actually different and refer to different things. Therefore, we still keep this section as it currently stands.

9. Authors may consider introducing any such multivariate prognostic models, if they exist.
We have introduced a recent such model in the first sentence of the fourth paragraph in the introduction. The sentence now reads as “Recently, many clinical prognostic studies for severe dengue have been published, such as the Early Severe Dengue Identifier, a simple 4-predictor algorithm to predict individual risk of severe dengue [Reference: Tuan NM *et al.* (2017) An

Evidence-Based Algorithm for Early Prognosis of Severe Dengue in the Outpatient Setting. Clinical Infectious Diseases, 64(5): 656–663]".

10. Authors may consider discussing a little bit of prognostic variables and their importance in the transmission of severe dengue to highlight the importance of conducting this study.
In the second paragraph of the manuscript, we already briefly mentioned about considered prognostic variables of severe dengue: "Potential predictors could be ranged from clinical features and standard laboratory tests, including hematocrit and platelet count to viral and immunological markers as well as novel markers of endothelial activation and vascular functions".
Transmission of dengue plays an important role in dengue diagnosis and public health intervention; however, "transmission of severe dengue" seems not to be very relevant to our study. Even though there is some evidence to suggest that specific dengue serotype (especially serotype DENV-2) is more associated with severe dengue than other serotypes [Simmons C *et al.* (2012) Dengue. NEJM, 366(15):1423-32], severe dengue is rather a consequence of a complex interaction between viral and host factors than a separated entity which can be transmitted.

11. As authors stated that "there remains no widely accepted paradigm to predict disease severity…" how do authors defend carrying out this study based on the various global disease predictive models which are not well-designed/functional? Why and how this study would be useful and applicable in reality for policy making or treatment.
The fact that "there remains no widely accepted paradigm to predict disease …" does not mean that current predictive models in the field are "not well-designed/functional". We believe that this fact generally means two things: (1) the topic is still an open field for research and exploration, and (2) a high heterogeneity in how research is conducted and reported is expected. High heterogeneity in research design and report makes it extremely difficult to aggregate research findings in order to draw overall conclusions or develop a care management policy that is applicable. For this reason, we conduct this systematic review to identify this heterogeneity by detailed describing of published research and carefully assess their quality. Our findings would then be the basis for further attempts to harmonize and standardize how prognostic models for severe dengue are developed and reported. Together with other similar movements (such as the CONSORT statement for reporting randomized controlled trials), this piece of research would be one of the important factors to maintain and improve the quality of research as well as facilitate research progress in this field.

12. Various prognostic models may have used various variables, how do authors think to compare the different situational/regional/global models with each other since every region/situation cannot be comparable
Heterogeneity in included predictors is a big issue for any attempt to compare or combine different prognostic models. In terms of comparison, we acknowledge this heterogeneity and thus focus more on comparing study designs, methods for model development and model presentation. In terms of combination, we will first explore the possibility to combine published models using approaches described in Debray *et al.* (2014) Metaanalysis and aggregation of multiple published prediction models. Statistics in Medicine, 33(14):2341-62, namely "model averaging" and "staked regressions", which allow combining models with different sets of predictors.

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