Protocol of systematic review and meta-analysis on the epidemiology and risk factors of dengue shock syndrome

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2. Review purposes

This study aims to analyze existing information on the epidemiologic risk factors, clinical signs, and biomarkers of dengue shock syndrome in human.

3. Introduction

Dengue infection is caused by an arthropod-borne human viral pathogen with four serotypes (dengue virus-1: DENV-1, DENV-2, DENV-3, and DENV-4), belongs to the genus Flavivirus of the family Flaviviridae. The dengue disease ranges from asymptomatic to severe dengue characterized by severe bleeding, plasma leakage, shock and/or severe organ impairment (dengue hemorrhagic fever, DHF or dengue shock syndrome, DSS) that can lead to a life-threatening syndrome [1]. The dengue infection is well established as a major health problem in Southeast Asia and Western Pacific Regions. Each year, more than 250,000 cases of DHF/DSS are reported from an estimated 50 million dengue infections [2]. So far, there is no effective vaccine or antiviral drug against the disease, early appropriate treatment and vector control are the only ways to reduce mortality and global burden [1,3]. Therefore, the World Health Organization (WHO) encourages research on the development of new tools to find out risk factors that can be avoided and dengue severity markers that can reduce healthcare burden in endemic countries. Since severe forms such as organ impairment occur less frequently without shock syndrome, there is a need to study the epidemiology, molecular, biochemical, and immunological aspects of DSS to develop vaccines and new treatments.

Several risk factors and biomarker have been reported in individual studies [4], however, the associations are not observed consistently across studies in some factors. Therefore, we conducted to estimate overall associations between reported factors and DSS by systemic review and meta-analysis of relevant studies to identify important risk factors and biomarkers for DSS.

4. Search strategy and study selection

We will conduct electronic searches in PubMed, Scopus, EMBASE, LILACS via Virtual Health Library, Google Scholar, WHO Dengue bulletin, and the Cochrane Library to identify relevant articles. There is no restriction regarding to language, publication period, patient age (children or adult), or study design.

Search term:

-PubMed, EMBASE and Scopus: "dengue AND (shock OR DSS OR severity OR severe OR "grade IV" OR "grade III")"

-LILACS and Cochrane Library: "dengue"

-Advanced Scholar Search: we use "dengue" to fill in the field "with all of the words", "shock OR DSS OR severity OR severe OR "grade IV" OR "grade III"" to fill in the field "with at least one of the words", and "where my words occur" in the field "title of article"

-manual search of articles in WHO Dengue bulletin, reference lists and citation list using the Scopus databases, factor-specific searches by adding the factor terms beside "dengue"

Two independent reviewers (Huy and Giang) initially scan primary titles and abstracts (when available) to select potential full text articles for further scrutiny. When the title and abstract cannot be rejected by any reviewer, the full text of the article is obtained via Nagasaki University Library and carefully reviewed for inclusion by the two reviewers (NTH, TVG). Inclusion or exclusion of each study is determined by discussion and consensus between the two reviewers. Discussion and consensus with the third reviewer (DHDT) will be carried out when disagreement happen.

5. Inclusion criteria and exclusion criteria

Inclusion criteria

- Reported epidemiology, clinical signs and laboratory parameters for dengue infected patients with shock compared with DHF

Exclusion criteria

- No control group such as DHF, non-shock
- Animal studies, case reports or studies with less than three cases for each group, scientific correspondence, poster, conference, thesis
- Impossible extraction of data.
- In case of overlapping data, selected the largest data.

6. Data extraction

Data are extracted by one of two investigators (NTH, TVG), and then checked by at least two of three reviewers (NTH, TVG, DHDT), disagreement is solved via discussion and consensus between the three authors. A data extraction form (including quality assessment) in excel file is developed by two authors (NTH, TVG), based on a pilot review, extraction, and calibration

of twenty random included studies.

① *Extraction of study characteristic:*

-first author

-country, city and hospital where patients recruited

-year of publication

-year of patient recruitment (the midpoint of the study's time period)

-study design (all case or case-control)-

-data collection (prospective or retrospective)

-assignment of the patient (consecutive or random)-

-characteristic of patient population (infant, children, adult)

-criteria of dengue infection (confirmed or clinical diagnosis)

-criteria of DSS and DHF

-number of included individuals (DSS and control DHF)

-including DF patients in the DHF group

-description of blinded interpretation of factors, gender, and age at examination of included individuals.

② *Formats of data input for factors.*

Format of data input for factors

Dichotomous data (number of events)

- Events and sample size in each group

- Non-events and sample size in each group

- Events and non-events in each group

- Event rate and sample size in each group

- Chi-squared and total sample size

Continuous data

- Mean, standard deviation (SD), and sample size in each group

- Difference in means, common SD, and sample size

- Cohen' s d (standardized by pooled within-groups SD) and sample size

- Mean, sample size, and t-value

- Difference in means, sample size, and t-value

- Sample size and t-value

- Mean, sample size, and p-value

- Difference in means, sample size, and p-value

- Sample size and p-value

③ *Selection of data for meta-analysis (this modification was added after we find out that multiple data and/or methods were available in included studies)*

If several types of data or several methods are presented for one particular factor, we extract all but use the one with the least significant association (the nearest odds ratio at one) if that factor is significantly associated with DSS after meta-analysis. Otherwise, the data with lowest and highest are pooled separately to get minimal and maximal odd ratios, respectively. When data are available at different day of the course of disease, values at day 4, 3, 5, 2 and 6 are favored in that order for analysis.

④ *Calculation of data (this modification was added after we find out that multiple data set reported the case or control group into two subgroups)*

If the data set reported the DSS (or DHF) group in two separated groups (such as DHF grade III and IV for DSS, and DHF grade I and II for DHF), combined mean and standard deviation (SD) are calculated as shown in the following equation [5]: .

$$n \lfloor x \rfloor^{\top} \tilde{n} \; \acute{x}$$

Mean   =

whereas n_1, n_2 are patient number of two group; x_1, x_2 are mean of two groups.

whereas SD_1, SD_2 are SD of two groups

⑤ *Estimation of data*

When the included study only reported the mean/median, range, and the sample size, the mean and SD are estimated according to Hozo *et al* [6] as follow:

Estimation of mean

- $mean = \dfrac{min + 2median + max}{4}$ when sample size ≤25

- $mean = median$ when sample size >25

Estimation of SD

-

    when sample size ≤25

-     when 25 <sample size ≤70

-     when 25 <sample size >70

When the published study only reported the mean, the estimated SD is derived from linear regression of log(published SDs) against log(published means) according to van Rijkom *et al* [7]. The published SDs and means are derived from other includes studies.

7. Risk of bias

Papers published by same research group and studying the same factors are checked for potential duplicate data based on the year of patient recruitment and hospital where the patients are recruited. When it happens, the largest data set is used for meta-analysis.

Two reviewers (NTH, TVG) independently evaluate the risk of bias in selected studies by assessing the quality of studies. Disagreement is also solved by discussion and consensus by two authors (NTH, TVG). The quality of selected studies are assessed using a combined criteria suggested by Pai *et al.*[8] and Wells *et al* [9], because these criteria can affect the accuracy of the effect size. The quality of each study included in the meta-analysis is determined across nine metrics: study design, full description of characteristic of patient population (infant, children, adult), data collection (prospective or retrospective), assignment of the patient (consecutive or random), inclusion criteria, exclusion criteria, method quality (description and same method for DSS and DHF groups), blinded interpretation of factors, and full description of dengue diagnosis. The score system is fully described in the Table 1. The effect of each criteria and total quality score on the pooled effect size and the heterogeneity across studies is performed by meta-regression analysis and subgroup analysis where there are ten or more studies assessing a particular factor [10].

Table 1: Quality assessment of selected studies

Criteria	0 point	1 point
study design	case or no description	all case
characteristic of patient population	or no description	full description

(infant, children, adult)		
data collection	retro or no description	prospective
assignment of the patient	not consecutive, random, nor description	consecutive or random
inclusion criteria	no description	full description
exclusion criteria,	no description	full description
method quality		description and same method for DSS and DHF groups
interpretation of factors	not blinded or no description	description of blinded method
dengue diagnosis		full description

8. Meta-analysis

Meta-analysis for a particular factor is performed using Comprehensive Meta-analysis software version 2.0 (http://www.meta-analysis.com) where there is more than one study.

-The odds ratio (OR) is computed together for both dichotomous and continuous variables when there are two groups of DSS and DHF.

-The rate of event (prevalence) is pooled for the proportion of DSS among DHF/DSS; we only include studies with the design of all cases (cross-sectional) and not including DF patients in the DHF groups for this analysis of DSS prevalence

Model: We use fixed-effects model with weighting of the studies if there is no evidence of significant heterogeneity ($p > 0.10$), and use random-effects model with weighting of the studies when there is heterogeneity between studies ($p \leq 0.10$) [11].

Publication bias: we carry out Begg's modified funnel plot and Egger's regression test where there are five or more studies assessing the association of a particular factor. If publication bias is found (Egger's regression test: $p<0.1$), the trim and fill method of Duvall and Tweedie is performed to add "missing studies" to improve the symmetry. The pooled effect size and

its 95%CI are adjusted after the addition of potential missing studies.

Sensitivity analysis: The effect of each study on the pooled effect size is tested by meta-analysis after removing each study. Cumulative meta-analysis is carried out to test effect of few largest studies on the effect size by repeatedly meta-analyses each time adding a new study according to its sample size.

Meta-regression analysis and subgroup analysis: The effect of covariates on the pooled effect size and the heterogeneity across studies is performed using meta-regression analysis and subgroup analysis where there are ten or more studies assessing a particular factor. The effect of covariates on the pooled effect size is considered significant when the p-value is <0.05 or its 95%CI is not overlapped with the original one.

Analysis of factor-specific relationship (this modification was added after we find out that several data sets reported three or more categories for a particular factor): Analysis of factor-specific relationship with the DSS is also performed where there are three or more categories reported for a particular factor. The midpoint of each category for particular factor is assigned to plot against natural logarithm of OR or rate of event. We use a mixed-models analysis to test a potential nonlinear factor-specific relationship of infection by using polynomial, sin wave and exponential regression models. When the candidate models are nested, we use likelihood ratio tests (F-test) to test whether the more complex model is a better fit. When comparing two non-nested models, we use the Akaike information criterion (AIC), which indicates the likelihood of the model minus the number of parameters of the model.

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