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Original Article

Evaluating the importance of clinical manifestations and laboratory parameters associated with progression to severe dengue in children

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Abstract

Background The ability to predict the progression to severe dengue is crucial in managing patients with dengue fever. Severe dengue is defined by one or more of the following signs: severe plasma leakage, severe bleeding, or severe organ involvement as it can be a life-threatening condition if left untreated.

Objective To identify clinical manifestations and laboratory parameters associated with dengue hemorrhagic fever disease progression in children by systematic review and meta-analysis.

Methods We searched six medical databases for studies published from Jan 1, 2000, to Dec 31, 2020. The meta-analysis used random-effects or fixed-effects models to estimate pooled effect sizes. We assessed heterogeneity using Cochrane Q and I2 statistics, publication bias by Egger's test and LFK index (Doi plot), and categorized subgroup analysis by country. This study was registered with PROSPERO, CRD42021224439.

Results We included 49 papers in the systematic review, and we encased the final selected 39 papers comprising 23 potential predictors in the meta-analyses. The other 10 papers were not included because the raw data could not be calculated for the effect measure in the meta-analysis. Among 23 factors studied, seven clinical manifestations demonstrated association with disease progression in children, including neurological signs, gastrointestinal bleeding, clinical fluid accumulation, hepatomegaly, vomiting, abdominal pain, and petechiae. Six laboratory parameters were associated during the early days of illness, including elevated hematocrit, aspartate aminotransferase [AST], and alanine aminotransferase [ALT], low platelet count, low albumin levels, and elevated activated partial thromboplastin time. Dengue virus serotype 2 (DENV-2) and secondary infections were also associated with severe disease progression.

Conclusion This review supports the use of the warning signs described in the 2009 WHO guidelines. In addition, monitoring serum albumin, AST/ALT levels, identifying infecting dengue serotypes, and immunological status can improve the prediction of further risk of disease progression. **[Paediatr Indones. 2023;63:102-18; DOI: https://doi.org/10.14238/pi63.2.2023.102-18**].

Keywords: *children; dengue; risk prediction; severity; warning sign; meta-analysis*

Dengue fever is still a major public health concern across the globe. The global incidence is estimated to be 390 million individuals infected each year, with mortality rates ranging from 10,000 to 20,000 per year.[1,2] Dengue infection can affect all ages, including adults and children. Dengue mortality increases as the disease progresses to severe dengue or dengue shock syndrome, especially in children with comorbid factors. Although most patients have mild symptoms, in general, a small proportion progress to severe dengue or dengue hemorrhagic fever, which can be life-threatening. This progression to severe disease commonly occurs after the febrile phase, between days 4 and 6 of illness.[3]

During hospitalization, clinical and laboratory monitoring for these patients should always be carried out. Serial hematocrit and platelet examinations have become the standard examinations in various health care centers. To assist clinicians in the early detection of severe disease progression, the WHO has issued guidelines for dengue, namely, the 1997 and *2009 WHO Dengue Guidelines*.[3,4] Clinical symptoms

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such as persistent vomiting, abdominal pain, bleeding manifestations, and fluid accumulation are warning signs associated with the occurrence of severe dengue. Several laboratory parameters associated with dengue disease severity include hematocrit, platelets, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and serum albumin.[5]

This systematic review was done with the aim of identifying whether specific clinical manifestations and laboratory parameters have a strong, moderate, or low association with severe dengue. In addition, we hope that our results could help early decision making to optimize patient management and improve the quality of care for children.

Methods

This systematic review was conducted according to the *Preferred Reporting Items for Systematic Review and Meta-Analysis* (PRISMA) Statement6 and a guide to systematic review and meta-analysis of prognostic factor studies.[7] The protocol of this systematic review has been registered in *The International Prospective Register of Systematic Reviews* (PROSPERO) database (CRD42021224439).

We included observational studies of pediatric dengue patients who were clinically and serologically confirmed and were treated as inpatients or outpatients in a hospital, health center, or teaching hospital. Included studies used either the 1997 or 2009 WHO dengue classification,[3,4] showed an association between severe dengue prevalence and clinical manifestations and laboratory parameters, and had a minimum study size of at least twenty patients. To be included in the systematic review and meta-analysis, the studies had provided a summary measure or effect measure for severe dengue in the form of odds ratio (OR), risk ratio (RR), with P values or confidence intervals (CI), or had to give crude data that allowed for calculation of a measure. Severe dengue in our study was defined as a confirmed dengue patient in clinical shock due to plasma leakage, severe bleeding, or severe organ involvement. Published articles in the previous 20 years (2000 to 2020) were expected to provide novel updates on existing systematic reviews and meta-analyses. Only papers written in the English language were included. We excluded prognostic factors related to gene expression, cell receptor, virological studies, neutralizing antibodies, cytokines, and plasma proteins. We also excluded conference abstracts/papers, supplementary issues, review articles, seroepidemiological studies, adult population studies, and brief reports.

From December 2020 to February 2021, we conducted article searches from six electronic databases. The search strategy was to combine "dengue fever" and "children" with all possible synonyms. The search terms and the study selection process are shown in **Table 1** and **Figure 1**. We also searched for related studies through reference and citation checks. Bramer *et al*.[8] suggested that to get optimal results in a systematic review, the author should, at a minimum, search *Embase, MEDLINE/PubMed, Web of Science*, and *Google Scholar* to ensure adequate coverage. A small number of articles in languages other than English were not included. We also did not include papers from gray literature or unpublished studies that were not peer-reviewed. To confirm information in the articles, we contacted the corresponding authors by email when necessary

Zotero software was used to remove duplicate articles and export the listed articles to the Rayyan app for systematic review.[9] The titles and abstracts

Table 1. Search queries of the systematic review

Databases	Search query	Hits
PubMed	Dengue OR Severe dengue OR Complicated dengue OR Predictor OR Predictive OR Prognostic AND Pediatric NOT Adult Filters: Observational Study, Child: birth-18 years	1170
Embase	Dengue AND Children	102
Google Scholar	Dengue Prospective Cohort Children OR Pediatric OR Paediatric OR Pediatrics OR Paediatrics -Adult -Zika -Pneumonia -Vaccine -Economic -Chikungunya -Malaria -Sepsis	583
Web of Science	Dengue AND Children OR Pediatric OR Paediatric	7
EBSCO	Dengue fever OR dengue syndrome AND children OR adolescents OR youth OR child OR teenager OR teens OR young people OR kids OR paediatric OR pediatric	82
Scopus	Dengue AND Predictors AND Children	130

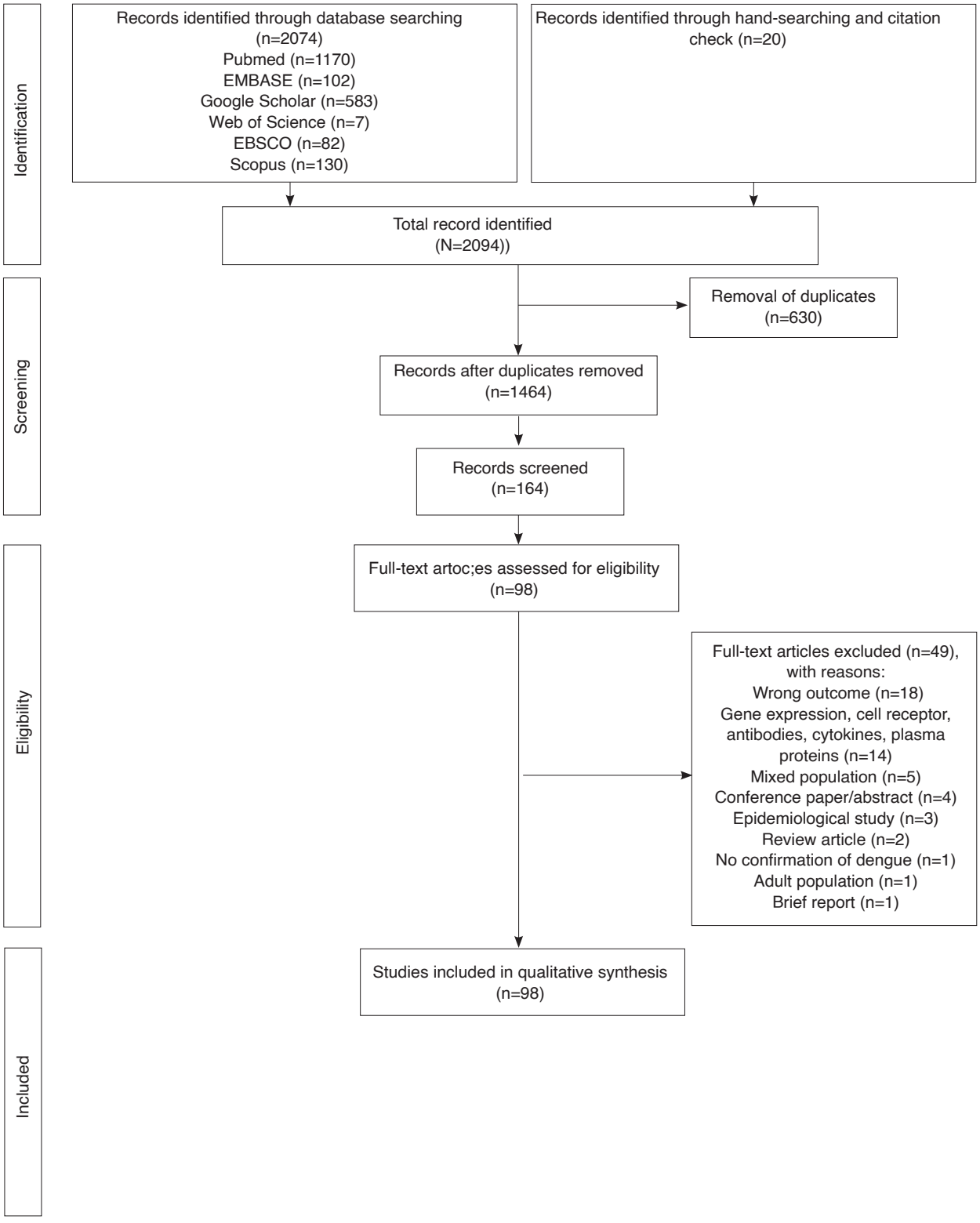

Figure 1. Systematic flowchart for articles selection

were independently reviewed by two authors (IS and BM) according to pre-determined eligibility criteria. After screening and removing irrelevant articles, we managed to list 98 articles. The same two authors conducted an overall text assessment after retrieving full-text papers from each publisher. Finally, the third reviewer (HL) resolved any differences between the two reviewers, with final decisions determined by consensus.

The primary information presented was the association between clinical manifestations and specific laboratory parameters with the severity of dengue infection. In addition, we extracted information about the location and health facilities where the study was conducted, time of the study, name of the first author, year of publication, study design and methods, sample size, and population characteristics in each study. Data from the included studies were extracted using a standardized, pre-piloted form and entered into *Microsoft Excel* by the two authors (IS, BM) independently. Disagreements were resolved by a third author (HL). Two authors (IS, HL) independently examined the risk of bias using the *Quality in Prognostic Studies* (QUIPS) tools.[10] Disagreements resolved by a third author (HH). *Microsoft Excel* was used to present the risk of bias assessment results.

All included studies were presented in a narrative and summary table. Each prognostic factor (clinical manifestation or laboratory parameter) evaluated in at least two studies was summarized in a forest plot and submitted to the meta-analysis. Meta-analysis was performed using *Comprehensive Meta-Analysis software version 3.0* (*Biostat*, USA) and *MetaXL version 5.3* (*EpiGear*, Australia). Combining the classification of dengue based on the *1997* and *2009 WHO Guidelines*, we divided the progression of dengue into two groups: patients with severe disease [dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS) according to *1997 WHO guidelines* or severe dengue according to *2009 WHO guidelines*] and patients without the severe disease forms [dengue fever (DF), non-severe dengue, and dengue with warning signs].

The pooled odds ratio indicates the strength of the association between certain prognostic factors and severe dengue. Dichotomous variables and continuous variables were analyzed to calculate the effect size (in the form of odds ratio or standardized mean difference) if there were DSS/DHF and DF groups (*1997 WHO criteria*) or severe dengue and non-severe dengue/dengue with warning sign groups (*2009 WHO criteria*). The standardized mean difference (SMD) value was then converted into the OR according to the Borenstein method.[11] The two variables (both dichotomous and continuous) were combined to obtain a pooled OR to increase the number of studies included in the analysis.[11-13]

Current guidelines for prognostic studies recommended reporting both crude and adjusted association measures.[14] The adjusted effect sizes can be obtained using a multivariate analysis approach. However, most of the eligible studies in our systematic review used univariate analyses, and only a small proportion used multivariate analyses. We decided to use only the crude measures of association in this meta-analysis. For the different predictors, we performed a meta-analysis with fixed effects and random effects to generate pooled estimates. To further investigate the robustness of pooled estimates, sensitivity analysis was also performed by removing studies with extreme effect size and heterogeneity. We also did subgroup analysis categorized by the country where the study was conducted.

The assessment of heterogeneity was conducted by using the Cochran Q statistic and I^2 statistic. Studies were considered heterogeneous if the P value for the Cochran Q was less than 0.1; the I^2 expressed the proportion of variation across studies that was due to heterogeneity. The level of heterogeneity was categorized as low (0-25%); low to moderate (25% to <50%); moderate to high (50% to <75%); and high (≥75%).[15,16] The agreement between reviewers in study selection was assessed with Cohen's kappa.

To detect any publication bias, we used Funnel plots and Doi plots. A symmetrical Doi plot indicates the absence of publication bias, while an asymmetric plot indicates the presence of publication bias, considering the *Luis Furuya-Kanamori* (LFK) index. In the funnel plot, Egger's test of $P<0.05$ indicates publication bias.[17] The LFK index up to ±1 indicated no asymmetry, values that exceeded ±1 but did not exceed ±2 indicated minor asymmetry, and values exceeding ±2 indicated major asymmetry. Unlike the Funnel plots that require a minimum of 10 studies, Doi plots can be used for a lesser number of studies.[16,18]

To enhance the symmetry, we also used Duval and Tweedie's trim and fill method to assess the sensitivity of the crude estimates to publication bias.[19] Factors that were only investigated in one study or for which raw data could not be combined, the association of these factors with disease progression was derived from the original study and presented narratively.

Results

Of the 2,094 papers identified, 49 were included in the systematic review (**Figure 1**),[20-68] with agreement between the two reviewers of 93% (Cohen's kappa=0.72). All included studies were observational (49; 100%). Among the studies, 38 (78%) were prospective cohort, 7 (14%) were retrospective cohort, 2 (4%) were case-control, and 2 (4%) were cross-sectional studies. Most of the included studies were conducted in Asia and Latin America and all were published between 2000 and 2020. The included studies were from India, Thailand, Indonesia, Vietnam, Sri Lanka, Paraguay, Nicaragua, Brazil, and the Philippines. Only one study took populations from seven dengue-endemic countries, namely, a study by Rosenberger *et al.*[36] Almost all of the studies were comprised of inpatient (hospitalized) populations and only one study by Tuan *et al.*[57] incorporated its outpatient study population.

The inclusion criteria for patients varied among studies, but generally included pediatric patients with symptoms of fever for 1-3 days (≤72 hours). About 57% (28/49) of the studies defined severity using the "1997 WHO classification," while the remaining studies [43% (21/49)] used the "2009 WHO classification." The supplementary information shows the details and summary of included studies (**Tables 1** and **2**).

A total of 93,628 patients in the 49 studies were included in this systematic review, with a pooled severe dengue prevalence of 30% (95%CI 25% to 34%). The management of dengue in pediatric patients followed the WHO guidelines, or at a more specific level, adjusted to the health service policy at the hospital where the study was conducted.

We used the QUIPS tool to examine the risk of bias in the six domains (**Figure 2**). Most studies had a low risk of bias for the aspects of study participation, study attrition, prognostic factor measurement, outcome measurement, statistical analysis, and reporting. In the confounding study domain, we found a moderate risk of bias. Details of the risk of bias assessment are presented in **Table 3**.

Twenty-three potential prognostic factors (reported in 39 studies) were evaluated in at least three studies and were included in the meta-analysis. An overview of prognostic factors evaluated is presented in **Table 2**, and the summary of crude and adjusted ORs of significant prognostic factors can be found in **Table 3**, as well as details of the risk of bias assessment.

The age profile of pediatric patients with severe dengue was no different from those without severe dengue. Heterogeneity in pooled results was very high (91%), and after removing studies with extreme effect sizes in sensitivity analysis, the heterogeneity remained unchanged. The OR value for the age factor was 1.00 (95%CI 0.83 to 1.20) and there was no evidence of publication bias (Egger's test P=0.86).

The association between gender and progression to severe disease was not significant. Moderate to high heterogeneity (I^2=60%) and publication bias was found in studies examining male gender as a predictor of severe dengue (Egger's test P=0.02). The result of the pooled OR was 1.04 (95%CI 0.88 to 1.24). We did a sensitivity analysis for this factor, with an OR of 1.21 (95%CI 1.05 to 1.39) and without evidence of heterogeneity (I^2=0%). Using the trim and fill method of Duval and Tweedie,[19] the OR was 0.89 (95%CI 0.57 to 1.05) and was not statistically significant.

Three studies reported an association between nutritional status and progression to severe dengue.[33,48,59] Baiduri *et al.*[33] showed a strong relationship between overweight-obesity and progression to severe dengue with an RR of 94 (95%CI 4.47 to 1989) through a multivariate analysis approach. Tantracheewathorn et al.[48] and Dewi *et al.*[59] found no association between normal nutritional status and progression to severe dengue. After including two studies in the meta-analysis, we obtained an OR of 1.02 (95%CI 0.60 to 1.75) with no heterogeneity (I2=0%).[33,48]

In terms of clinical manifestations, we found that neurologic signs were strongly associated with the progression of severe dengue. Neurological manifestations may include drowsiness, convulsions, decreased consciousness, or lethargy. Meta-analysis of

Table 2. Overview of prognostic factors evaluated

Factors	Number of studies	Number significant	Model	Association with severe dengue		Heterogeneity		Egger's 2-tailed bias	LFK index	Adjusted OR (95% CI)
				Pooled OR (95% CI)	P value	I^2	P value			
Normal nutrition[48,59]	2	0	Fixed	1.02 (0.60 to 1.75)	0.930	0	0.402	-	-	-
Male gender[20,22,24,28,33,38,39,41,42,48,54,56,59,61-63]	16	4	Random	1.04 (0.88 to 1.24)	0.641	60	0.001	0.02	4.40	[a]0.89 (0.57 to 1.05) [b]1.21 (1.05 to 1.39) I2=0%
Age[22,24,28,30,33,34,38,39,41,47,48,52,56,57,59,61-63]	18	6	Random	1.00 (0.83 to 1.20)	0.844	91	<0.001	0.86	1.23	[b]0.97 (0.81 to 1.17) I2=91%
Neurological sign[20,29,30,34,42,53,56,62,63]	9	4	Random	6.33 (2.34 to 17.13)	<0.001	68	0.002	0.04	1.76	[a]4.11 (1.59 to 10,65) [b]6.88 (2.91 to 16.25) I2=36%
Gastrointestinal bleeding[33,34,46,47,53,62,63]	7	2	Random	5.34 (1.67 to 17.01)	0.005	46	0.083	0.06	-3.30	[b]5.87 (2.03 to 16.98) I2=0%
Clinical fluid accumulation[20,21,25,26,28,29,33,34,42,47,48,56,61-63]	18	15	Random	4.66 (2.08 to 10.45)	<0.001	95	<0.001	0.04	2.43	[a] 3.86 (1.77 to 8,40) [b]3.03 (1.28 to 7.17) I2=95%
Hepatomegaly[20-22,24–26,29,30,33,34,42,47,48,53,56,59,61-63]	19	13	Random	2.64 (1.76 to 3.94)	<0.001	88	<0.001	0.008	3.78	[a] 2.09 (1.41 to 3.10) [b]2.28 (1.54 to 3.38) I2=88%
Vomiting[20,21,24-27,29,30,33,42,47,53,57,63]	14	8	Random	2.01 (1.54 to 2.64)	<0.001	48	0.021	0.52	0.47	-
Abdominal pain[20-22,24,26,27,29,30,33,42,46,53,57,59,63]	15	8	Random	1.91 (1.26 to 2.88)	0.002	82	<0.001	0.23	3.48	[b]1.58 (1.07 to 2.35) I2=81%
Petechiae[30,33,46,47,53,62,63]	7	4	Random	1.79 (1.29 to 2.49)	<0.001	44	0.097	0.14	4.09	[b]1.62 (1.31 to 2.02) I2=12%
Positive Tourniquet test[24,30,41,47,48,53,62,63]	8	4	Random	0.97 (0.46 to 2.05)	0.306	89	<0.001	0.74	0.37	-
Rash[25,26,53,56,61]	5	2	Fixed	1.09 (0.82 to 1.46)	0.536	74	0.004	0.13	-3.26	[b]0.71 (0.47 to 1.06) I2=55%
Elevated hematocrit[22-25,28,38,41-43,46–48,51,52,56,57,59,61,63,65]	20	11	Random	1.76 (1.50 to 2.07)	<0.001	89	<0.001	<0.001	7.04	[a] 1.17 (0.99 to 1.39) [b]3.14 (2.03 to 4.85), I2=81%
Low platelet count[22,24,25,28,33–35,38,41-43,46-48,51,52,56,57,59,61,63,65,68]	23	13	Random	2.01 (1.70 to 2.38)	<0.001	90	<0.001	<0.001	8.94	[a]1.48 (1.25 to 1.75) [b]1.76 (1.50 to 2.06) I2=89%
Higher WBC[28,33,41,43,46,48,52,57,59,61,63]	11	4	Random	1.01 (0.76 to 1.35)	0.940	66	0.001	0.68	-0.54	-
Low albumin levels[23,25,27,28,33-35,40,41,57,65]	11	7	Random	6.03 (2.34 to 15.53)	<0.001	96	<0.001	0.002	8.51	[b] 7.34 (3.29 to 16.38) I2=88%

Table 2. Overview of prognostic factors evaluated (continued)

Factors	Number of studies	Number significant	Model	Association with severe dengue		Heterogeneity		Egger's 2-tailed bias	LFK index	Adjusted OR (95% CI)
				Pooled OR (95% CI)	P value	I^2	P value			
Elevated ASTT[22,28,33-35,40,41,48,52,55-57,61,65,66]	15	10	Random	3.06 (2.00 to 4.69)	<0.001	91	<0.001	0.03	3.70	[a]3.63 (2.33 to 5.67) [b]3.08 (2.18 to 4.36) I2=68%
Elevated ALT[28,34,35,40,41,48,55,56,61,65,66]	11	5	Random	2.68 (1.59 to 4.51)	0.001	81	<0.001	0.21	2.14	[b]1.98 (1.27 to 3.08) I2=73%
Temperature[20,22,24,26,38,59,61,63]	8	3	Random	0.73 (0.43 to 1.22)	0.231	81	<0.001	0.012	-5.2	[a]1.08 (0.65 to 1.81) [b]0.58 (0.39 to 0.88) I2=0%
DENV-2 Serotype[47,54,58,64]	4	1	Fixed	1.66 (1.30 to 2.13)	<0.001	1	0.387	0.89	0.15	-
Activated partial thromboplastin time[33,47,51,55]	4	3	Fixed	8.74 (4.79 to 15.95)	<0.001	83	0.001	0.85	1.13	[b]4.59 (2.24 to 9.37) I2=70%
Secondary infection[48,54,55,62,64]	5	4	Fixed	2.02 (1.64 to 2.49)	<0.001	89	<0.001	0.14	4.56	[a]1.59 (1.31 to 1.93) [b]8.66 (4.99 to 15.04) I2=56%
Primary infection[54,55,62,64]	4	2	Fixed	0.52 (0.41 to 0.67)	<0.001	83	<0.001	0.54	-2.56	[b]0.62 (0.48 to 0.81) I2=0%

[a]Adjusted odds ratio by enhancing the symmetry using the trim and fill method of Duval and Tweedie[19]; [b]Adjusted odds ratio by sensitivity analysis

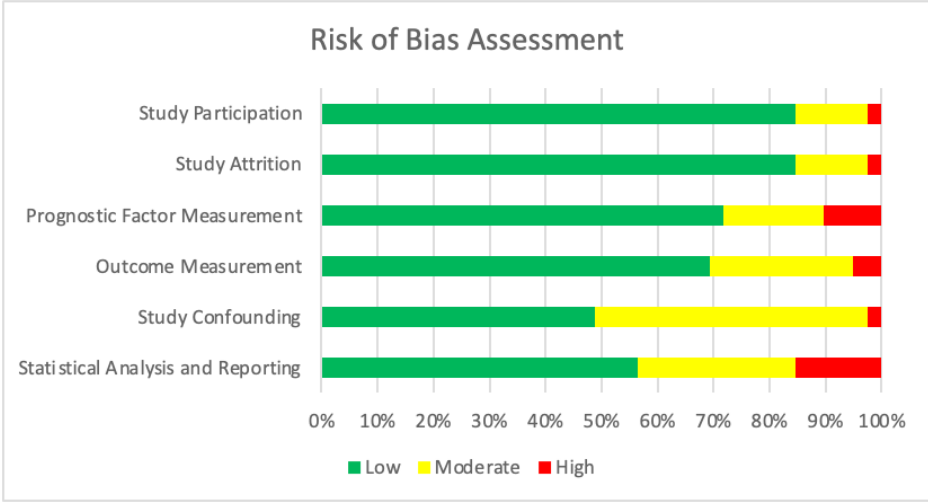

Figure 2. Risk of bias assessment according to the six domains of the Quality in Prognostic Studies (QUIPS) tool for the 39 observational studies included in the meta-analysis

nine studies yielded a high pooled OR of 6.33 (95%CI 2.34 to 17.13), with moderate to high heterogeneity (I^2=68%) and publication bias (Egger's test P=0.04). After removing two studies with extreme effect size and heterogeneity, the OR value was 6.88 (95%CI 2.91 to 16.25), with low to moderate heterogeneity (I^2=36%) and no asymmetry (LFK index 0.07).

Bleeding manifestations can be mild or severe. Almost all studies included petechiae as a predictive factor for disease progression and gastrointestinal bleeding either as melena or hematemesis as its severe form. Children with petechiae had an increased risk of developing severe disease, with an OR value of 1.79 (95%CI 1.23 to 2.49), low to moderate heterogeneity (I^2=44%), and no evidence of publication bias (Egger's test P=0.14), but with major asymmetry (LFK=4.09). The OR value of petechiae in the sensitivity analysis was 1.62 (95%CI 1.28 to 2.06), with low heterogeneity (I^2=12%) and no asymmetry (LFK index 0.07).

For children who presented with gastrointestinal bleeding, the risk of progression to severe dengue was increased, with an OR of 5.34 (95%CI 1.67 to 17.01), low to moderate heterogeneity (I^2=46%), without evidence of publication bias (Egger's test P=0.06). After we did sensitivity analysis of the gastrointestinal bleeding factor, the OR was 5.87 (95%CI 2.03 to 16.98) without evidence of heterogeneity (I^2=0%) and no asymmetry (LFK index 0.58).

For clinical fluid accumulation, whether pleural effusion or ascites, 18 studies were included in the meta-analysis, with OR value of 4.66 (95%CI 2.08 to 10.45), evidence of high heterogeneity (I^2=95%), and publication bias (Egger's test P=0.04). The positive relationship between clinical fluid accumulation and progression to severe disease was also consistent in sensitivity analysis with an OR of 3.03 (95%CI 1.28 to 7.17). Thus, the evidence of high heterogeneity in this factor remains, but no asymmetry was found (LFK index 0.87). Subgroup analysis of two studies in Thailand showed a stronger association (OR=12.09; 95%CI 4.62 to 31.66), without evidence of heterogeneity (I^2=0%). Subgroup analysis of four studies in Indonesia also showed a strong association (OR=6.28; 95%CI 2.17 to 21.30) with moderate to high heterogeneity (I^2=56%).

Hepatomegaly was moderately associated with severe dengue after pooling 19 eligible studies. High heterogeneity was found (I^2=88%) as well as publication bias (Egger's test p=0.008), with an OR of 2.64 (95%CI 1.76 to 3.94). We performed sensitivity analysis by removing three studies and obtained an OR of 2.28 (95%CI 1.54 to 3.38) without change in heterogeneity, and major asymmetry remained (LFK index 2.49). Using the trim and fill method, the adjusted OR of this factor was 2.09 (95%CI 1.41 to 3.10). Subgroup analysis of three studies in Thailand showed strong association (OR=3.37; 95%CI 2.06 to 5.52) without evidence of heterogeneity (I^2=0%). Subgroup analysis of four studies in Indonesia showed

Table 3. Summary of crude and adjusted odds ratios of significant prognostic factors submitted included in meta-analysis

Prognostic factor	Number of studies	Pooled OR (95%CI)	I^2(%)	LFK index
Neurological signs				
All studies	9	6.33 (2.34 to 17.13)	68	1.76 (minor asymmetry)
Sensitivity analysis	7	6.88 (2.91 to 16.25)	36	0.07 (no asymmetry)
Gastrointestinal bleeding				
All studies	7	5.34 (1.67 to 17.01)	46	-3.30 (major asymmetry)
Sensitivity analysis	5	5.87 (2.03 to 16.98)	0	0.58 (no asymmetry)
Clinical fluid accumulation				
All studies	18	4.66 (2.08 to 10.45)	95	2.43 (major asymmetry)
Sensitivity analysis	14	3.03 (1.28 to 7.17)	95	0.87 (no asymmetry)
Hepatomegaly				
All studies	19	2.64 (1.76 to 3.94)	88	3.78 (major asymmetry)
Sensitivity analysis	16	2.28 (1.54 to 3.38)	88	*2.49 (major asymmetry)
Vomiting				
All studies	14	2.01 (1.54 to 2.64)	49	0.47 (no asymmetry)
Abdominal pain				
All studies	15	1.91 (1.26 to 2.88)	82	3.48 (major asymmetry)
Sensitivity analysis	12	1.58 (1.07 to 2.35)	81	*1.60 (minor asymmetry)
Petechiae				
All studies	7	1.79 (1.29 to 2.49)	44	4.09 (major asymmetry)
Sensitivity analysis	5	1.62 (1.31 to 2.02)	12	0.07 (no asymmetry)
Elevated hematocrit				
All studies	20	1.76 (1.50 to 2.07)	89	7.04 (major asymmetry)
Sensitivity analysis	16	3.14 (2.03 to 4.85)	81	*2.63 (major asymmetry)
Low platelet count				
All studies	23	2.01 (1.70 to 2.38)	90	8.94 (major asymmetry)
Sensitivity analysis	20	1.76 (1.50 to 2.06)	89	*7.77 (major asymmetry)
Low albumin levels				
All studies	11	6.03 (2.34 to 15.53)	96	8.51 (major asymmetry)
Sensitivity analysis	10	7.34 (3.29 to 16.38)	88	-0.27 (no asymmetry)
Elevated aspartate aminotransferase				
All studies	15	3.06 (2.00 to 4.69)	91	3.70 (major asymmetry)
Sensitivity analysis	10	3.08 (2.18 to 4.36)	68	0.00 (no asymmetry)
Elevated alanine aminotransferase				
All studies	11	2.68 (1.59 to 4.51)	81	2.14 (major asymmetry)
Sensitivity analysis	9	1.98 (1.27 to 3.08)	73	0.24 (no asymmetry)
Elevated activated partial thromboplastin time				
All studies	4	8.74 (4.79 to 15.95)	83	1.13 (minor asymmetry)
Sensitivity analysis	3	4.59 (2.24 to 9.37)	70	0.68 (no asymmetry)
DENV-2 serotype				
All studies	4	1.66 (1.30 to 2.13)	1	0.15 (no asymmetry)
Secondary infection				
All studies	5	2.02 (1.64 to 2.49)	89	4.56 (major asymmetry)
Sensitivity analysis	3	8.66 (4.99 to 15.04)	56	*-1.75 (minor asymmetry)

*No further LFK index approaching zero beyond this point to eliminate the asymmetry

stronger association (OR=4.32; 95%CI 2.65 to 7.03) with evidence of low heterogeneity (I^2=18%).

We found that vomiting was associated with an increased risk of progression to severe dengue. However, the definition of vomiting is not clearly defined in most studies. A significant association between vomiting and disease progression was present with an OR of 2.01 (95%CI 1.54 to 2.63), low to moderate heterogeneity (I^2=48%), and no evidence of publication bias (Egger's test P=0.52). Abdominal

pain was also associated with progression to severe disease, with an OR of 1.91 (95%CI 1.26 to 2.88), evidence of high heterogeneity (I^2=82%), and no publication bias (Egger's test P=0.23). Sensitivity analysis on abdominal pain did not change the heterogeneity much, with an OR of 1.58 (95%CI 1.07 to 2.35) and minor asymmetry (LFK index 1.60). Subgroup analysis of four studies in Indonesia showed a strong association (OR=5.38; 95%CI 1.40 to 20.7), with evidence of moderate to high heterogeneity (I^2=67%). On the other hand, the subgroup analysis of two studies in Vietnam showed no association (OR=1.05; 95%CI 0.82 to 1.35) and no heterogeneity (I^2=0%).

Without evidence of publication bias, rash and positive tourniquet tests were not associated with progression to severe dengue. Heterogeneity was high in the positive tourniquet test and was moderate to high in the pooled results of positive rash signs. A high body temperature was not associated with progression to severe dengue, with evidence of high heterogeneity (I^2=81%) and publication bias (Egger's test P=0.012) (OR=1.73; 95%CI 0.43 to 1.22). In sensitivity analysis, high body temperature was inversely associated with the progression to severe dengue, with an OR of 0.58 (95%CI 0.39 to 0.88) and no evidence of heterogeneity (I^2=0%). Using the trim and fill method, the adjusted OR was 1.08 (95% 0.65 to 1.81) and was not statistically significant.

Hematological parameters of hematocrit, platelet count, and white blood cell count were included in the meta-analysis. Of those, hematocrit and platelet count were significantly associated with progression to severe dengue, while white blood cell count was not. By pooling 23 studies related to low platelet count, we obtained an OR of 2.01 (95%CI 1.70 to 2.38), with evidence of high heterogeneity (I^2=90%) and publication bias (Egger's test P<0.001). By removing three studies with extreme effect size and heterogeneity, the OR value was 1.76 (95%CI 1.50 to 2.06) with high heterogeneity (I^2=89%), and the asymmetry could not be further reduced (LFK index 7.77). Adding missing studies using the trim and fill method lowered the association (OR=1.47; 95%CI 1.24 to 1.73), but it was still significant. Subgroup analysis of six studies in Thailand showed a stronger association (OR=3.65; 95%CI 2.23 to 5.98), with evidence of low to moderate heterogeneity (I^2=48%). To further explore the potential effect modifiers, we performed a meta-regression of platelet factors with age as a moderator. The linear regression line showed a decrease of logOR at 22% (95%CI 0.10 to 0.35) for every 1-year increment of age.

Elevated hematocrit was positively associated with severe dengue. By pooling 20 studies related to hematocrit, we obtained an OR of 1.76 (95%CI 1.50 to 2.07), with evidence of high heterogeneity (I^2=89%) and publication bias (Egger's test P<0.001). In sensitivity analysis, hemoconcentration had a stronger association with disease progression, with OR=3.14 (95%CI 2.03 to 4.85), high heterogeneity (I^2=81%), and remaining asymmetry (LFK index 2.63). Using the trim and fill method, the hematocrit factor lost its significance (OR=1.17; 95%CI 0.99 to 1.39). Subgroup analysis of six studies from Thailand showed stronger association (OR=3.67; 95%CI 2.05 to 6.57), with evidence of low to moderate heterogeneity (I^2=47%). Subgroup analysis of five studies from India showed similar results with unadjusted estimates (OR=1.99; 95%CI 1.13 to 3.49) and moderate to high heterogeneity (I^2=63%). To further explore the potential effect modifiers, a meta-regression of hematocrit factors by age as a moderator showed a decrease of logOR at 19% (95%CI 0.07 to 0.30) for every 1-year increment of age.

Eleven studies were included in the meta-analysis of serum albumin. All studies consistently reported that children with lower albumin levels had an increased risk to develop severe dengue. Low albumin levels had an OR of 6.03 (95%CI 2.34 to 15.53), with evidence of high heterogeneity (I^2=96%) and publication bias (Egger's test P=0.002). In sensitivity analysis, the association was stronger with OR=7.34 (95% CI 3.29 to 16.38) and high heterogeneity (I^2=88%), but without asymmetry (LFK index -0.27). Subgroup analysis of five studies from India showed a strong association (OR=12.16; 95%CI 5.21 to 28.39), with moderate to high heterogeneity (I^2=71%). Subgroup analysis of two studies in Indonesia also showed a strong association (OR=9.99; 95%CI 2.61 to 38.19), with evidence of low to moderate heterogeneity (I^2=46%). A study by Kularatnam *et al.*[31] that was not included in the meta-analysis showed that the reduction in serum albumin levels seen on the third and fourth days of illness were valid predictors of entering into the critical phase in

dengue infection.

Fifteen studies were included in the meta-analysis of aspartate aminotransferase and eleven studies of alanine aminotransferase. This meta-analysis assessing for associations between disease progression and AST and ALT showed that higher enzyme levels were associated with progression to severe disease. Evidence of heterogeneity in the two factors was high, with publication bias on the AST factor (Egger's test P=0.003), but not on the ALT factor (Egger's test P=0.21). The pooled OR for AST was 3.06 (95%CI 2.00 to 4.69), and the results from the sensitivity analysis gave an OR of 3.08 (95%CI 2.18 to 4.36) with evidence of low to moderate heterogeneity (I^2=68%) and without asymmetry (LFK index 0). The pooled OR for ALT was 2.68 (95%CI 1.59 to 4.51), with evidence of moderate to high heterogeneity (I^2=73%) and without asymmetry (LFK index 0.24).

The assessment for an association between elevated activated partial thromboplastin time (aPTT) and disease progression showed a strong positive association. By including four studies, the pooled OR was 8.74 (95%CI 4.79 to 15.95), with evidence of high heterogeneity (I^2=83%) but without publication bias (Egger's test P=0.85). Removing one study from the sensitivity analysis still gave consistent results, with an OR of 4.59 (95%CI 2.24 to 9.37), moderate to high heterogeneity (I^2=70%), and without asymmetry (LFK index 0.68). The one study not submitted to the meta-analysis (Budastra *et al.*[60]) found that aPTT values may be used as a predictor for bleeding manifestation in dengue hemorrhagic fever using a Cox regression approach, with an RR of 2.02 (95%CI 1.92 to 3.90; P=0.02).

Secondary infection with different dengue serotypes was significantly associated with progression to severe dengue. In five studies, the pooled OR was 2.02 (95%CI 1.64 to 2.49), with evidence of high heterogeneity (I^2=89) but no publication bias (Egger's test P=0.14). The significant association remained in a sensitivity analysis which omitted two studies with extreme effect sizes and heterogeneity. The adjusted OR for this factor was 8.66 (95%CI 4.99 to 15.04), with moderate to high heterogeneity (I^2=56%) and minor asymmetry (LFK index -1.75). A study by Endy *et al.*[45] showed that cross-reactive memory humoral immune responses appear beneficial in symptomatic secondary DENV-3 infection, but not in secondary DENV-2 or DENV-1 infection. In addition, a secondary infection caused by DENV-1, which was considered to induce mild symptoms, involves the risk of severe manifestation, especially if DENV-2 was the cause of primary infection.

Primary infection with dengue virus was inversely associated with progression to severe dengue in the meta-analysis. The pooled OR of this factor was 0.52 (95%CI 0.41 to 0.67), with high heterogeneity (I^2=83%) and no publication bias (Egger's test P=0.54). Sensitivity analysis gave an OR of 0.62 (95%CI 0.48 to 0.81), with no evidence of heterogeneity (I^2=0%). The study by Poeranto *et al.*[67] showed that only DENV-3 could cause severe clinical manifestations in primary infection.

Studies included in the meta-analysis showed that the DENV-2 serotype was associated with severe disease progression. Pooling results from four studies gave an OR of 1.66 (95%CI 1.30 to 2.13), with evidence of low heterogeneity and no publication bias (Egger's test P=0.54). Consistent findings were also reported by Lovera *et al.*,[32] whose study showed that the DENV-2 serotype profoundly impacted clinical manifestations and dengue severity. The DENV-2 infections were more frequently associated with the requirement of fluid resuscitation, shock, and more prolonged hospital stay.[32]

Sirikutt *et al.*[44] showed that serum lactate and lactate dehydrogenase (LDH) were elevated in DHF and/or DSS patients. Lactate might be used as a predictor of DSS if the level was >2 U/L on day 0. Moreover, LDH can be used as a predictor of severe dengue or DSS if the level increased to approximately 1000 IU on day 0 of illness. Yacoub *et al.*[28] showed that initial venous lactates in dengue patients on the first day of ICU admission were associated with severe outcomes of recurrent shock and respiratory distress. Lactate levels correlated with the total amount of intravenous fluids received, but did not correlate with other hemodynamic parameters.

Chaiyaratana *et al.*[49] showed that a serum ferritin level ≥1200 ng/mL had a high sensitivity, but a relatively low specificity to predict the occurrence of severe dengue. Bongsebandhu *et al.*[50] showed that D-dimer was significantly associated with dengue severity. Early increasing D-dimer in the febrile stage could predict the severity of dengue infection during

Table 4. Summary of factors associated with progression to severe dengue

Association with progression	Factors
Very strong	Neurological signs, gastrointestinal bleeding, clinical fluid accumulation (ascites or pleural effusion), low albumin levels, elevated activated partial thromboplastin time
Moderate to strong	Hepatomegaly, elevated aspartate aminotransferase, elevated alanine aminotransferase
Weak to moderate	Vomiting, abdominal pain, petechiae, low platelet count, elevated hematocrit, secondary infection, DENV-2 serotype
No association	Normal nutritional status, male gender, age, temperature, positive torniquet test, white blood cells, viremia

the initial stage of the illness, with a 68.4% positive predictive value. Suvarna *et al*.[37] found that lipid profile changes accompanied dengue infection, some of which may indicate severity.

Regarding viremia, Tuan *et al*.[57] found that viremia magnitude was independently associated with severe dengue in a multivariate logistic model, but the viremia itself was not included in the final prognostic model of *Early Severe Dengue Identifier* (ESDI). The four factors included in the ESDI model were vomiting, platelet count, AST level, and NS1 rapid test status. Singla *et al*.[56] showed that dengue viremia was not associated with disease severity. Dengue viremia was indistinguishable between patients with non-severe dengue or severe dengue, either in primary or secondary infection. However, all secondary infections with recurrent bleeding had a significantly higher viremia compared to primary infections despite showing clinical improvement from severe dengue. Van Ta *et al*.[64] showed that DENV concentration/viremia within the first day of hospitalization (≤72 hours) could not be used as a prognostic factor of DSS. The DENV concentration was highest at day 2 of fever and higher in the secondary infection group, consistent with other studies.

Discussion

In this systematic review and meta-analysis, we found that age, gender, and normal nutritional status were not associated with the development of severe dengue. However, neurological signs, gastrointestinal bleeding, clinical fluid accumulation, hepatomegaly, vomiting, abdominal pain, and petechiae were associated with severe dengue. In addition, low platelet count, elevated hematocrit, low albumin levels, elevated AST/ALT, elevated aPTT, DENV-2 serotype, and secondary infection were also associated with progression to severe disease.

Age was not associated with progression to severe dengue in our study, similar to the findings reported by Zhang *et al.*[69] In another meta-analysis,[70] the factor of young age in children was associated with disease severity, and their interpretation may be more convincing because of its dose-response meta-analysis.

We found that most studies did not categorize nutritional status as malnourished, normal nutrition, overweight, or obese. Several studies determined body weight as a variable on a continuous scale. To more accurately determine the nutritional status of children, it is necessary to consider both their weight and height, or even other indicators, such as upper arm circumference or skinfold thickness.[71] In other words, the association between nutritional status and progression to severe dengue from this meta-analysis should be interpreted cautiously. A meta-analysis in the adult population showed that nutritional status was not associated with the occurrence of severe dengue.[70] Meanwhile, a study by Trang *et al.*[72] showed that children with normal nutrition were inversely associated with DSS compared to DHF (OR=0.87; 95%CI 0.77 to 0.99). Our review has not been able to find a sufficient number of articles related to obesity and dengue severity. A study conducted by Zulkipli *et al.*[73] seems to have conclusive findings that obesity is a risk factor for severe dengue in children.

Some clinical symptoms with a strong association to severe dengue included neurological signs represented by symptoms of drowsiness, convulsion, alteration in sensorium, or lethargy in most studies. Gastrointestinal bleeding, described in the form of melena or hematemesis, was also strongly associated with severe forms of the disease. Milder forms of bleeding such as petechiae that appear during early illness were also prognostic signs of disease

progression. Clinical fluid accumulation manifesting as ascites or pleural effusion can be particularly important considering the hallmark of plasma leakage in dengue pathophysiology. Thus, this prognostic sign can guide clinicians promptly for further patient management

We also found that clinical manifestations of vomiting and abdominal pain were associated with disease progression. These two subjective symptoms are frequent patient complaints and were reported to be significant in other studies.[5,69,70] The criteria for vomiting in most studies were not described clearly, although according to Vuong *et al.*,[74] the criteria for persistent vomiting should be two bouts of vomiting or more per day.

Numerous patients with severe dengue only exhibit evidence of severe plasma leakage. In contrast, a small proportion of patients who developed severe bleeding or severe organ dysfunction, often exhibited a higher degree of overlap with severe plasma leakage. In addition, patients with severe bleeding without leakage may have a predisposition to bleeding disorders.[36] Hence, this potential confounder should be considered because the predisposition to bleeding disorders does not appear to have been explored further in the included studies.

The association between secondary infection and disease progression is well documented and represents an antibody-dependent enhancement mechanism. A modeling study by Clapham *et al.*[75] found severe manifestations in 40% (95%CI 0.36 to 0.45) of secondary infections and in 18% (95%CI 0.16 to 0.20) of primary infections. The DENV-2 serotype was significantly associated with disease progression in children, and these findings were consistent with previous meta-analyses.[5,70]

Hepatic manifestations in dengue patients result from direct viral toxicity or dysregulated immunologic injury. The spectrum of hepatic involvement can be mild or even severe with transaminase elevation in the form of acute liver failure.[76] Our analysis showed that high AST or ALT levels in the early stages of illness were significantly associated with severe dengue. The studies included in our meta-analysis had varying cut-off AST/ALT concentrations, which might have caused the high heterogeneity. However, based on most of the mean AST and ALT reported in the included studies, we suggested that concentrations higher than three times the upper limit of normal were associated with severe disease progression.

In our study, albumin levels in the first days of illness were significantly lower in patients with severe dengue than in those with non-severe dengue. During plasma leakage, albumin was also extravasated. However, patients' nutritional status influenced their initial albumin levels, and albumin levels were generally lower in undernourished children.[77] In most of the included studies, low albumin levels were described as less than 3.5 g/dL. Our meta-analysis is in line with the recommendations of the *2011 SEARO Dengue Guidelines*, in which patients whose albumin levels are <3.5 g/dL or undergoing a decrease of 0.5 g/dL from baseline during the febrile phase, were considered to be associated with disease progression.[78]

Our meta-analysis had some limitations. As we searched for studies reported in the English language, some of the studies published in non-English languages had English versions, making them eligible for inclusion. However, some studies might have been excluded due to language limitations. In addition, we did not search studies from gray literature. Both criteria may have contributed to publication bias. The predisposing genetic factors were also not included in the meta-analysis because they have not been routinely analyzed along with the clinical outcomes. Analysis between clinical outcomes and predisposing genetic factors is quite challenging. Nevertheless, Pare *et al.*[79] evaluated multiple genetic variants that conferred a clinically prominent risk for disease progression. More than one-third of the prognostic factors had high heterogeneity, while others were moderate to high. However, in sensitivity analysis and subgroup analysis, the effect sizes were quite similar and consistent with evidence of lowered heterogeneity.

In our study, we find that neurological signs, gastrointestinal bleeding, clinical fluid accumulation, low albumin levels, elevated aPTT, hepatomegaly, elevated AST/ALT, vomiting, abdominal pain, petechiae, low platelet count, elevated hematocrit, secondary infection, and DENV- 2 serotypes are associated with disease progression in pediatric dengue patients. This finding supports the use of the warning signs (abdominal pain, persistent vomiting, clinical evidence of fluid accumulation, bleeding, lethargy and/or restlessness, liver enlargement, rise in hematocrit with rapid decrease in platelet count) described in the *2009 WHO Guidelines*. In

addition, monitoring serum albumin and AST/ALT levels, identifying infecting dengue serotypes, and immunological status could improve the prediction of risk of disease progression further.

Conflict of interest

None declared.

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