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PREDICTORS FOR SEVERE DENGUE IN ADULTS: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Dengue infection inflicted a huge burden towards health problem in tropical and subtropical countries. Reported cases were more than 1.2 million in 2008, which increased to over 3.2 million in 2015, involving the Americas, South-East Asia, and Western Pacific regions. Published studies regarding predictors of severe dengue have been inconsistent and therefore accurate methods to predict severe dengue is needed. This review was performed to synthesise from the relevant studies regarding predictors of severe dengue.

Methodology: A systematic literature search was performed using PubMed, ScienceDirect, and Google Scholar for articles published from 2015 until 2019. The search was based on the inclusion criteria and keywords, including 'predictors', 'factors associated', 'severe dengue' and 'dengue haemorrhagic fever' and 'dengue shock syndrome'. The inclusion criteria were all observational studies with full articles and written in English. Reviewed articles, systematic review and meta-analysis articles were excluded. Study on children and solely involved biomolecular components were also excluded. Unpublished literature was not searched in this review.

Result: After multistage screening conducted based on inclusion and exclusion criteria, 9 out of 1312 initially searched articles, were assessed and reviewed in the final stage. The significant predictors were reported to increase risk of severe dengue significantly includes sociodemographic (age), medical history (secondary infection, pre-existing comorbid), clinical presentation (warning signs, fluid accumulation, bleeding tendency, low blood pressure), laboratory profile (increase haematocrit, low platelet count, raised ALT, raised lactate), secondary dengue infection and as well as the delayed hospitalisation and late seeking treatment.

Conclusion: In conclusion, older age group, presence of comorbid and the number of comorbid, secondary infections, presence of warning signs, abnormal haematocrit rise and platelet count drop, were independent risk factors of severe dengue. These factors may be useful to guide triage at the presentation of adult dengue patients who are at higher risk of severe dengue.

Keyword: predictors, severe dengue, dengue haemorrhagic fever, dengue shock syndrome, systematic review

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1.0 Introduction

Dengue infection inflicted a huge burden towards health problem in tropical and subtropical countries. In earlier years (prior to 1970), there were only nine countries that had reported severe dengue epidemics. Presently, all regions are affected worldwide, and in the year 2019 alone, it has reported the most significant number of dengue cases. In Asia, Philippines, Vietnam, Malaysia and Bangladesh had reported 420,000, 320,000, 131,000 and 101,000 dengue cases, respectively (World Health Organization, 2020). The top three most affected regions are America, South-East Asia, and Western Pacific regions (World Health Organization, 2020).

Dengue virus has four serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) which belongs to the category Flavivirus of the family members Flaviviridae. The virus is spread via the bites of female Aedes mosquitoes, mainly the Aedes aegypti mosquitoes. Dengue illness arrays from asymptomatic or self-limiting dengue fever (DF) to severe Dengue defined by plasma leakage that can cause life-threatening severe dengue (World Health Organization, 2020).

Based on the 1997 WHO definition, four criteria need to be fulfilled before diagnosing DHF: 1) having high-grade fever for 2-7 days; 2) having thrombocytopenia (platelet count less than 100,000 cells/μ; 3) having spontaneous bleeding into the skin, or bleeding from the nose, periodontal, intestinal tract or vaginal canal; and 4) having plasma leakage specified as a rise in haematocrit (HCt) ≥ 20% over normal values or presence of fluid accumulation including pleural effusion or ascites. Given the different spectrum of dengue clinical features, DHF severity was further divided into four different grades. Grade I DHF was specified as a person having spontaneous bleeding right into the skin manifested by petechiae, ecchymosis or a favourable tourniquet examination. Grade II DHF was defined as a patient having spontaneous bleeding from the nose, gums, stomach tract or vagina. Meanwhile, the grade III DHF was specified as a patient having hypotension shown up by pulse pressure less than 20 mmHg or a systolic high blood pressure less than 90 mmHg. The grade IV DHF was specified as a DHF individual having shock, evidenced by low blood pressure and poor perfusion (World Health Organization, 1997).

On the other hand, according to the 2009 WHO definition, severe dengue was categorised as those having 1) severe plasma leak, defined as having plasma leakage with shock or respiratory system distress as manifested by a breathing rate > 24 breaths/minute and/or need for oxygen supplementation; 2) having significant clinical bleeding defined as spontaneous blood loss from the intestinal tract and/or vaginal area and/ or needing a blood transfusion and/or getting various other acute monitoring for controlling active blood loss such as nasal packing or a dental splint; and 3) having serious organ involvement defined as an aspartate aminotransferase (AST) level ≥ 1,000 IU/l and/or an alanine aminotransferase (ALT) degree ≥ 1,000 IU/l and/or a serum creatinine > 1.2 mg/dl (World Health Organization, 2009). Severe dengue could progress and worsen, which put the severe dengue patients at higher risk of death. Prompt appropriate therapy, vector control, and curriculum are the only present approaches to reduce mortality and also global illness concern (Chevillon & Failloux, 2003; E. Khan et al., 2007; Erum Khan et al., 2010).

Published studies regarding signs and symptoms that are related to severe dengue have reported mix findings. As an example, a study showed that male DF clients were more probable to advance into DHF (OR: 2.3, 95% CI: 1.1-4.5) (E. Khan et al., 2007), while there was no evidence with severe Dengue reported in other research studies (Erum Khan et al., 2010). The number of signs and symptoms of vomiting/nausea, abdominal discomfort, skin breakouts, and also bleeding was likewise discovered to be associated with severe Dengue. The clinical manifestations stated earlier could be used as early predictors for severe dengue with the help from other findings such as viral factors, differing host immune conditions, host immune responses, and research laboratory examinations can predict severe dengue (Pawitan, 2011). Given the inconsistent records, more precise methods are needed to predict severe dengue. This review was performed to synthesise from the relevant studies regarding predictors of severe dengue.

2.0 Methodology

2.1 Search protocol

A systematic review was conducted to analyse articles related to the studied topic. NCBI PubMed, ScienceDirect, Google Scholar and WHO Dengue bulletin of reference lists of articles were searched for suitable studies published from January 2015 to December 2019 with language limit to English. Searches were done in June 2019 until December 2019. PICO strategy was used for searching the articles. The terms P (Population) were 'dengue patients' OR 'dengue patient' AND 'adults' OR 'adult'. Because severe dengue is also classified as DHF and DSS, for the term P (Problem), we used the following keywords for searching: 'dengue fever' OR 'DF' OR 'dengue haemorrhagic fever' OR 'DHF' OR 'dengue shock syndrome' OR 'DSS' OR 'Severe dengue'. No term search for I (Intervention) and C (Comparison). For O (Outcome), the terms searched were 'Factors associated' OR 'Predictors' OR 'Determinants' or 'Risk Factors'. The inclusion criteria were all observational studies with full articles and written in English. Reviewed articles, systematic review and meta-analysis articles were excluded. Study on children and solely involved biomolecular components were also excluded. Unpublished literature was not searched in this review.

2.2 Study selection

Articles were screened based on titles initially. Then, the chosen articles were randomly allocated to two reviewers based on the abstracts and keywords. Both reviewers need to get to an agreement in order for the study to be accepted right into the next phase of screening. If both of them unable to agree, a third reviewer will be included in the screening process, and the articles will be accepted by consensus. Nevertheless, no third reviewer was required during the screening.

Subsequently, selected articles were screened based on the full articles obtained by another two reviewers. The inclusion and exclusion criteria as stated in 2.1. PRISMA 2009 flow diagram portrays the flow of literature search, as shown in Figure 1.

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2.3 Quality Assessment of Articles

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (23) was used for quality assurance analysis. This tool includes 34 items with sub-items to assess the articles. Several items in the checklist (items 6a, 6b, 12d, 14c, 15) are only relevant to particular research study design (case-control or cohort research study). Each thing in the selected articles was classified as either 'adequately reported' or 'inadequately reported'. Nevertheless, if an item did not apply to the research design, it was scored as 'not applicable' and not included in the overall score. Only articles scored more than 70% of all the requirements would be selected in final information extraction. The report is summarised in Table 1.

2.4 Data Extraction

Data were elicited from the articles by using a standardised table that includes the authors' name, publication year, location of study, study design, sample size, study population and results. The summary of the findings is tabulated in Table 2.

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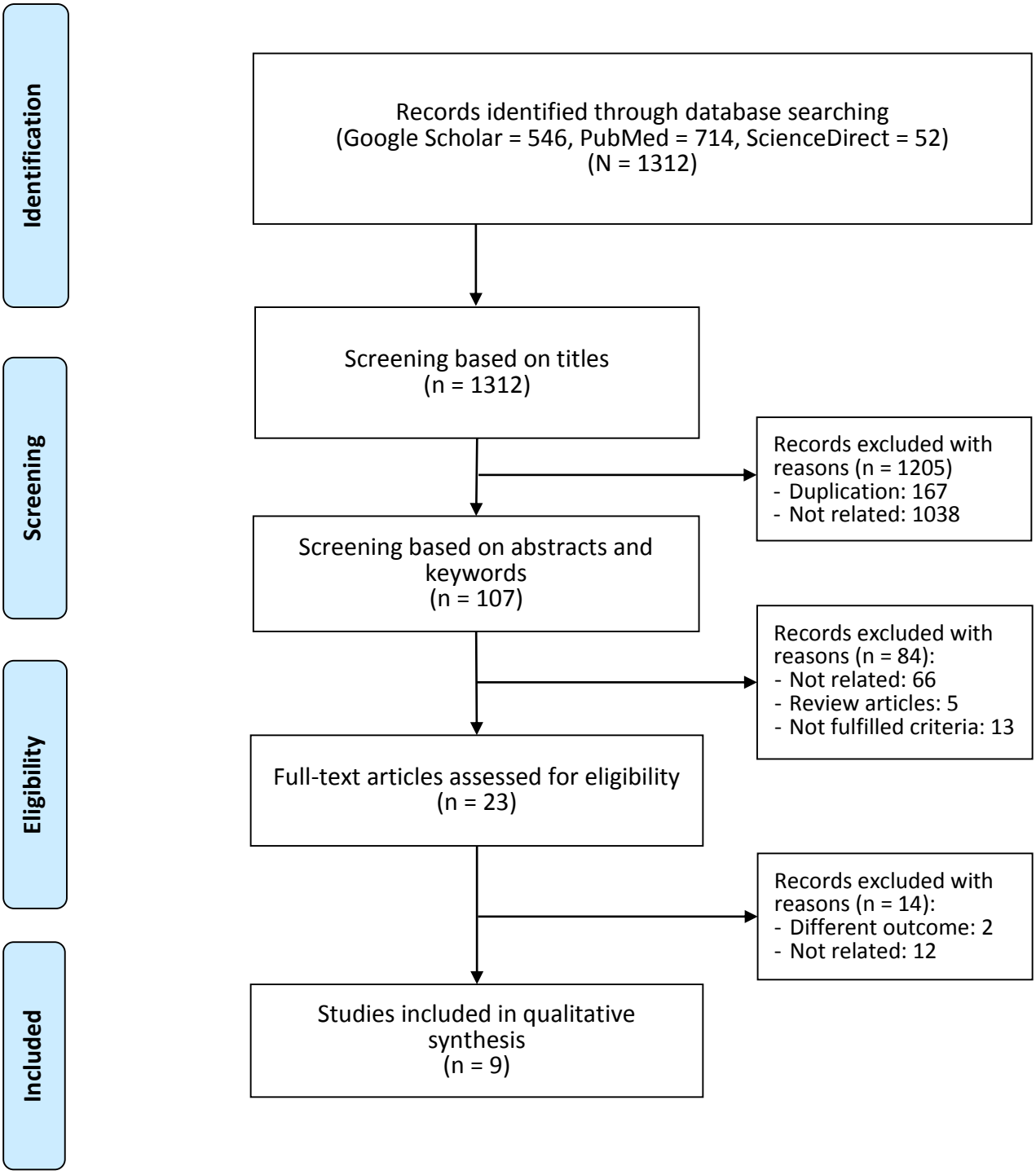

Figure 1: PRISMA 2009 Flow Diagram for Predictors of Severe Dengue Among Adults

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Table 1: Quality Assessment of Selected article based on STROBE checklist

Items	Authors	Teixeira et al., 2015	Thanachartwet et al., 2015	Mallhi et al., 2015	Tamibmaniam et al., 2016	Pang et al., 2017	Jain et al., 2017	Agrawal et al., 2018	Temprasertrudee et al., 2018	Ahmad et al., 2018
	Title and Abstract									
1a	Study design was described	Y (Case Control)	Y (Cohort)	Y (Cross Sectional)	Y (Cross Sectional)	Y (Case Control)	Y (Cohort)	N (Cohort)	Y (Cohort)	Y (Cross Sectional)
1b	Abstract: informative and balanced summary	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Introduction									
2	Explain about background	Y	Y	Y	Y	Y	Y	Y	Y	Y
3	Specific objective	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Methods									
4	Study design	Y	Y	Y	Y	Y	Y	Y	Y	Y
5	Setting including location, period of recruitment, data collection, follow-up and exposure	Y	Y	Y	Y	Y	Y	Y	Y	Y
*6a	Participant and selection criteria	Y	Y	NA	NA	Y	Y	Y	Y	NA
*6b	Matching	N	N	NA	NA	Y	N	N	N	NA
7	Define variable	Y	Y	Y	Y	Y	Y	Y	Y	Y
8	Data Sources and measurement	Y	Y	Y	Y	Y	Y	Y	Y	Y
9	Method assess risk of bias	Y	Y	Y	Y	Y	Y	Y	N	Y
10	Explain on study size was created	Y	Y	N	Y	Y	N	N	Y	N
11	Method on quantitative variable were categorised	Y	Y	Y	Y	Y	Y	Y	Y	Y
12a	Statistical method	Y	Y	Y	Y	Y	Y	Y	Y	Y
12b	Statistical method on interaction and measurement of subgroup	Y	Y	N	N	N	N	N	N	N
12c	Missing data	Y	Y	Y	Y	Y	Y	Y	N	Y
*12d	Follow-up, matching and sampling strategy	Y	Y	NA	NA	Y	Y	Y	Y	NA
12e	Sensitivity analysis	N	N	N	N	N	Y	N	N	Y

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	Result									
13a	Number of participants at each stage of study	Y	Y	Y	Y	Y	Y	Y	Y	Y
13b	Reason for non-participants	Y	Y	Y	NA	Y	Y	Y	NA	Y
13c	Flow diagram used	N	Y	N	Y	N	N	Y	N	N
14a	Descriptive statistic	Y	Y	Y	Y	Y	Y	Y	Y	Y
14b	Number of missing data	Y	Y	Y	Y	Y	Y	Y	Y	N
*14c	Follow-up time	Y	Y	NA	NA	Y	Y	Y	Y	NA
*15	Outcome data	Y	Y	NA	NA	Y	Y	Y	Y	NA
16a	Main result	Y	Y	Y	Y	Y	Y	Y	Y	Y
16b	Category boundaries reported	Y	Y	Y	Y	Y	Y	Y	Y	Y
16c	Translating relative risk into absolute risk	Y	Y	Y	Y	Y	Y	Y	Y	Y
17	Additional analysis	N	N	N	N	N	N	N	N	Y
18	Summary key result	Y	Y	Y	Y	Y	Y	Y	Y	Y
19	Limitation	Y	Y	Y	Y	Y	Y	Y	Y	Y
20	Overall interpretation	Y	Y	Y	Y	Y	Y	Y	Y	Y
21	Generalizability	Y	Y	N	Y	Y	Y	Y	Y	N
22	Funding and role of funder	Y	Y	Y	N	Y	Y	Y	N	Y
	Scoring	**88.2%**	**91.2%**	**79.3%**	**82.8%**	**85.3%**	**85.3%**	**82.4%**	**75.6%**	**82.8%**

*Applicable for case-control and cohort study design; Y (adequate); N (inadequate); NA (not applicable)

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Table 2: Articles on Predictors for Severe Dengue/Dengue Haemorrhagic Fever/Dengue Shock Syndrome

No.	Author/Title	Location	Objective	Description	Result
1.	Teixeira et al., 2015/ Arterial Hypertension and Skin Allergy Are Risk Factors for Progression from Dengue to Dengue Hemorrhagic Fever: A Case Control Study	Brazil	To investigate whether specific morbidity due to chronic illnesses increased the risk of progression from DF to DHF/DSS	An unmatched concurrent case-control study conducted There were 490 cases of DHF and 1,316 controls.	**Predictors for DHF** • Hypertension (aOR: 1.6; 95% CI: 1.1, 2.1) • Skin allergy (aOR: 1.8; 95% CI: 1.1, 3.2)
2.	Thanachartwet et al., 2015/ Identification of clinical factors associated with severe Dengue among Thai adults: a prospective study	Thailand	To identify the clinical factors associated with the development of severe Dengue according to the WHO's 2009 definition	A prospective cohort study of adults with Dengue 154 samples with confirmed Dengue were included	**Predictors for SD** • Age >40 years old (aOR: 5.215, 95% CI: 1.538,17.689), • Persistent vomiting (aOR: 4.817, 95% CI: 1.375, 16.873) • Absolute atypical lymphocytes >300 cells per µL (aOR: 3.163, 95% CI: 1.017, 9.834) • Lactate levels ≥2.0 mmol/L (aOR: 7.340, 95% CI: 2.334, 23.087)
3.	Mallhi et al., 2015 / Clinico-laboratory spectrum of dengue viral infection and risk factors associated with Dengue haemorrhagic fever: a retrospective study	Malaysia	To evaluate dengue cases for better understanding of clinic-laboratory spectrum to combat this disease	A retrospective cross-sectional study A total 667 dengue patients were reviewed	**Predictors for DHF** • Age > 40 years (aOR: 4.1, p <0.001) • Secondary infection (aOR: 2.7, p <0.042) • Lethargy (aOR: 3.1, p: 0.005) • Thick gallbladder (aOR: 1.7, p = 0.029) • Diabetes mellitus (aOR: 2.8, p <0.041) • Delayed hospitalization (after 3 days of onset of illness) (aOR: 2.3, p = 0.037)

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No.	Author/Title	Location	Objective	Description	Result
4.	Tamibmaniam et al., 2016 / Proposal of a Clinical Decision Tree Algorithm Using Factors Associated with Severe Dengue Infection	Malaysia	To look at the laboratory and clinical determinants in patients that is associated to severe dengue.	A retrospective cross-sectional study. This study included 657 patients.	**Predictors for SD** • Vomiting (aOR: 2.65, 95% CI: 1.16, 6.05) • Pleural effusion (aOR: 33.33, 95% CI: 10.00, 111.06) • Systolic blood pressure < 90mmHg (aOR: 9.42, 95% CI: 2.18, 40.61)
5.	Pang et al., 2017 / Diabetes, cardiac disorders and asthma as risk factors for severe organ involvement among adult dengue patients: A matched case-control study	Singapore	To characterise and identify risk factors that predispose dengue adults at risk of progression with severe organ involvement.	A retrospective matched case-control study involved 174 dengue patients who had progressed with severe organ involvement and 865 dengue patients without severe organ involvement.	**Predictors for SD** **Age and Comorbid** • Age group ≥ 60, (aOR: 2.75; 95% CI: 1.3, 5.8, compared to age group 12–29) • Any pre-existing co-morbidity (aOR: 1.63; 95% CI: 1.07, 2.49) • Two or more existing co-morbidities (aOR: 2.90, 95% CI: 1.66, 5.07) • Pre-existing diabetes (aOR: 2.21; 95% CI: 1.10, 5.02) • Pre-existing cardiac disorder (aOR: 4.30; 95% CI: 1.45, 12.78) • Pre-existing asthma (aOR: 2.14; 95% CI: 1.04, 4.42) **Sign and Symptoms** • Abdominal pain (aOR: 2.02; 95% CI: 1.40, 2.93) • Clinical fluid accumulation (aOR: 26.2; 95% CI: 2.51, 274.3) • Haematocrit rise and rapid platelet count drop (aOR: 6.67; 95% CI: 3.98, 11.17) • Nausea or vomiting (aOR: 1.65; 95% CI: 1.08, 1.87)

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No.	Author/Title	Location	Objective	Description	Result
					• Plasma leakage at presentation (aOR: 6.19; 95% CI: 4.09, 9.40)
6.	Jain et al., 2017/ Predictors of Dengue-Related Mortality and Disease Severity in a Tertiary Care Center in North India	India	To identify predictors of dengue related mortality and disease severity during the 2015 outbreak in India.	This prospective observational study (cohort study) included confirmed adult dengue patients hospitalised between August and November 2015 in a tertiary care centre in New Delhi, India. Data of 369 patients were analysed.	**Predictors of SD** • Late presentation to the hospital (≥5 days after onset) (aOR: 1.1, 95% CI: 1.0, 1.2; p = 0.03) • Dyspnea at rest (aOR: 5.1; 95% CI: 1.6, 15.7; p = 0.005)
7.	Agrawal et al., 2018 / Clinical profile and predictors of Severe Dengue disease: A study from South India	India	The aim of the study was to investigate the clinical symptoms, laboratory findings and mortality in severe dengue.	A prospective cohort study, which prospectively recruited 400 patients with primary presumptive diagnosis of dengue	**Predictors of SD** • Diabetes (aOR: 2.12; 95% CI: 1.34, 4.65; p<0.0001), • Elevated hematocrit (aOR: 3.14; 95% CI: 2.17, 6.14; <0.0001), • Skin rashes (aOR: 1.99; 95% CI: 1.11, 3.55; p<0.0001), • Melena (aOR: 2.59; 95% CI:1.40, 4.93; p<0.0001), • Low platelet count (aOR: 6.71; 95% CI:4.12, 13.6; p<0.0001), • Lymphadenopathy (aOR: 3.12 95% CI: 1.91, 7.85; p<0.0001) • Delayed admission (aOR: 2.40; 95% CI:1.31, 3.41; p<0.0001)
8.	Temprasertrudee et al., 2018 / A Multicenter Study of Clinical Presentations and	Thailand	To determine the clinical presentations of dengue in adults and to identify	A retrospective cohort study was performed in adults with dengue, as confirmed by a	**Predictors of SD** • Having cough (aOR: 8.07; 95% CI: 2.51, 30.16; p= 0.001)

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No.	Author/Title	Location	Objective	Description	Result
	Predictive Factors for Severe Manifestation of Dengue in Adults/ Thailand		predictive factors for severe dengue	positive NS1 antigen test result. A total of 357 patients were enrolled.	• ALT > 120 U/L (aOR, 3.51; 95% CI: 1.11, 11.14; p= 0.033)
9.	Ahmad et al., 2018/ The Sensitivity, Specificity and Accuracy of Warning Signs in Predicting Severe Dengue, the Severe Dengue Prevalence and Its Associated Factors/ Malaysia	Malaysia	To study Malaysian dengue clinical practice guideline (CPG) warning signs (WS) in predicting severe dengue (SD) and its associated factors among confirmed cases presented to a teaching hospital in north-eastern Malaysia in 2014	A cross-sectional study was performed using secondary data acquired from the hospital records. 700 patients were selected.	**Predictors of SD** • Persistent vomiting (aOR: 2.41; 95% CI: 1.16, 4.99; p=0.018) • Mucosal bleeding (aOR: 4.73, 95% CI: 2.09,10.69; p<0.001) • Haematocrit rise with rapid platelet drop (aOR: 2.74, 95% CI: 1.21,6.19; p=0.015)

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3.0 Results and Discussion

A total of 9 articles published from year 2015 until 2019 (5 years) were included in the final stage with all involving adult population. The final collection consists of four cohort study, two case control study and three cross sectional studies. The summary of the predictors of severe dengue is depicted in Table 3.

Table 3: Summary of Predictors for Severe Dengue

Predictors	Findings	Author
Sociodemographic	Age (Older age group)	- Pang et al., 2017 - Mallhi et al., 2015
Co-morbidities / previous medical history	- Presence of any	Pang et al., 2017
	- Presence of two or more	Pang et al., 2017
	- Diabetes	- Agrawal et al., 2018 - Mallhi et al., 2015
	- Cardiac disorder	Pang et al., 2017
	- Asthma	Pang et al., 2017
	- Hypertension	Teixeira et al., 2015
	- Skin Allergy	Teixeira et al., 2015
	- Secondary dengue infection	Mallhi et al., 2015
Warning Signs	- Persistent vomiting	- Ahmad et al., 2018 - Pang et al., 2017 - Tamibmaniam et al., 2016 - Thanachartwet et al., 2015
	- Lethargy	Mallhi et al., 2015
	- Abdominal Pain	Pang et al., 2017
	- Clinical Fluid Accumulation	- Pang et al., 2017 - Tamibmaniam et al., 2016
	- Haematocrit rise and rapid platelet drop	- Ahmad et al., 2018 - Agrawal et al., 2018 - Pang et al., 2017
	- Bleeding (mucosal/malaena)	- Ahmad et al., 2018 - Agrawal et al., 2018
Other clinical findings	- Cough	Temprasertrudee et al., 2018
	- Skin Rashes	Agrawal et al., 2018
	- Lymphadenopathy	Agrawal et al., 2018
	- Dyspnoea at rest	Jain et al., 2017
	- Low systolic BP	Tamibmaniam et al., 2016
	- Thick gallbladder	Mallhi et al., 2015
Laboratory Profile	- Raised ALT	Temprasertrudee et al., 2018
	- Raised Lactate	Thanachartwet et al., 2015
	- Raised lymphocyte	Thanachartwet et al., 2015
Time related to Dengue Management	- Delayed hospitalisation	- Agrawal et al., 2018 - Mallhi et al., 2015
	- Late presentation to hospital	Jain et al., 2017

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3.1 Dengue Classifications

The extent of dengue infection in these research studies was reviewed using the 1997 WHO interpretation and the revised 2009 WHO interpretation. Seven articles reported to use WHO Dengue Classification 2009 (Agrawal et al., 2018; Ahmad et al., 2018; Jain et al., 2017; Pang et al., 2017; Tamibmaniam et al., 2016; Temprasertrudee et al., 2018; Thanachartwet et al., 2015) and two articles used WHO Dengue Classification 1997 (Mallhi et al., 2015; Teixeira et al., 2015). The 1997 WHO case classification method for dengue was revised because of variations across the wide geographical locations and the age groups impacted by dengue. The 2009 categorisation is regarded as being much more responsive in capturing serious condition with observed sensitivities of up to 92% compared to 39% the 1997 standards (Basuki et al., 2010; Narvaez et al., 2011).

In addition, a multi-centre study across 18 countries done in 2011 had shown that around 14% of dengue cases could not be categorised using the 1997 WHO dengue classification as opposed only 1.6% when using the revised 2009 methods. (Barniol et al., 2011). Furthermore, implementation of guidelines to diagnose and manage dengue is varied between nations and regions, based on the WHO criteria for DF/DHF/DSS (Santamaria et al., 2009). Therefore, this variation marked the need for standardising case category and management, at least for the local adaptation (Barniol et al., 2011).

3.2 Hospital based studies

In general, participation in hospital based study tends to be higher than that of population based as hospital setting may increase participation (Ruano-Ravina et al., 2008). Most of selected studies in this review were hospital based. This is probably since most of severe dengue cases were managed at the hospitals and the medical records are readily available for data extraction. The used of readily available data is not only convenient but also saves time. However, there are some limitations by using the secondary data in which it could introduce information bias or selection bias if the study is not designed and conducted correctly.

3.3 Severe dengue predictors

This review revealed the most common demographic predictors which is age. Three articles in this review showed that older age was significantly related to severe dengue (Mallhi et al., 2015; Pang et al., 2017; Thanachartwet et al., 2015). Even with different serotypes circulating in the study period, in all years, the proportion of elderly individuals presenting severe dengue was higher than the sample average (Vicente et al., 2017).

Based on earlier studies, gender was found to be a significant factor in which female was found to be significantly associated with severe dengue (Carrasco et al., 2014; Kabra et al., 1999; Lai et al., 2013; Shekhar & Huat, 1992). It was suggested that immune responses in females are more competent than in males, resulting in a more excellent production of

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cytokines, or the capillary bed of females is prone to increased permeability (Guha-Sapir & Schimmer, 2005). Besides, dengue severity could be influenced by the difference in health seeking behaviour between genders (Vicente et al., 2017).

Presence of certain co-morbidities like diabetes mellitus, hypertension, chronic kidney disease, allergies, asthma, ischemic heart disease and hepatic anomalies might place some patients at high risk of developing severe dengue. Increased capillary fragility and permeability due to activation of T-lymphocytes and release of cytokines in DM are some possible factors of development of DHF (Mahmood et al., 2013; Pang et al., 2017).

This review revealed that late presentation to the hospital and delayed admission were significantly associated with severe dengue. Reports has stated that patients with mild disease more often seek medical attention somehow 2–4 days after the onset of illness (Asia-Pacific Dengue Prevention Board, 2009; Pan American Health Organization, 1994). In dengue, severe manifestations often appear late, around 4 to 5 days after onset during defervesant period. Thus, patients are more likely to present late, waiting for severe symptoms to appear if they are not well verse on the dengue situation; and recognise early signs and symptoms of dengue fever. Delay in seeking treatment, admission or even diagnosis could result in increased risk for mortality and complications (Chowell et al., 2007).

Severe dengue rarely results from primary dengue infection (Guzman et al., 2013; Halstead & Lum, 2009). The antibodies that develop as a result of dengue infection confer immunity against that particular dengue virus type but are non-neutralizing for infections caused by other dengue virus serotypes. Such infections by alternate dengue virus serotypes combined with cross-reactive T cells are believed to cause most of the manifestations of DHF/DSS (Heymann, 2009; Olkowski et al., 2013). Secondary infections are thus more frequently associated with severe dengue. Differentiation thus requires detection of IgM and/or IgG antibody. During acute phase of the disease, the presence of DENV IgM antibody alone suggest primary infection and the simultaneous detection of DENV IgM and IgG antibodies is suggestive of secondary infection.

Several warning signs proposed by WHO 2009 for SD (World Health Organization, 2009) were identified as significant predictors. Abdominal distension, which was a good predictor of SD development and could be considered related to abdominal pain and vomiting that was also significant in the above studies. The concurrent increase in haematocrit and rapid decrease in platelet were found to be statistically significant in predicting severe haemorrhage and severe plasma leakage (Ahmad et al., 2018; Pang et al., 2017).

Severe haemorrhage in severe dengue was not only caused by thrombocytopenia. A study has shown that the most substantial risk factors for haemorrhage in severe dengue were prolonged duration of shock and a haematocrit within the normal-low range at the time of shock, suggesting that patients with prolonged shock not only had plasma leakage but also bleeding (Lum et al., 2002). Multiorgan failure in severe haemorrhage was most likely related to the duration of hypoperfusion. Thus, the prevention of haemorrhage in severe dengue should be directed at early recognition of shock and prompt correction of circulatory status.

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The variation of definition for warning signs alone can be observed between regions. It is undeniable that warning signs help to determine the dengue severity. However, utilisation of warning signs excessively as determining factors for triage and management in hyperendemic nations, for instance, Malaysia as well as Indonesia might contribute to unnecessary admissions.

The use of WHO Dengue Classifications 2009 might not be perfect in detecting and managing dengue, but it has been shown to have better capability to detect severe dengue cases. Comprehending the predictor of severe dengue development would undoubtedly provide details to determine individuals at higher risk and otherwise, give sufficient time to medical professionals for reducing dengue associated morbidity and also mortality. Appropriate utilisation of laboratory findings in dengue diagnosis combined with public health education and surveillance by public health sectors could go a long way in combating dengue. Therefore, these findings could aid national dengue control bodies to plan and carried out the national program to deter, control and provide effective treatment to illness such dengue.

4.0 Conclusion

In conclusion, older age group, presence of comorbid and the number of comorbid, secondary infections, presence of warning signs, abnormal haematocrit rise and platelet count drop, were independent risk factors of severe dengue. These factors may be useful to guide triage at the presentation of adult dengue patients who are at higher risk of severe dengue.

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Declaration

The authors declare that this manuscript has never been published in any other journal.

Authors contribution

Author 1: information gathering and manuscript drafting
Author 2: editing and review of manuscript

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