A STUDY ON DENGUE FEVER PRESENTATION AND OUTCOME IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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LIST OF SYMBOLS, ABBREVIATIONS OR NOMENCLATURE

DENV	Dengue virus
DF	Dengue fever
ED	Emergency department
SD	Standard deviation
OR	Odd ratio
CI	Confidence interval
SPSS	Statistical Package for the Social Sciences
KKM	Kementerian Kesihatan Malaysia
HCT	Haematocrit
AST	Aminotransferase
ALT	Alanine Transferase
DSS	Dengue shock syndrome
DHF	Dengue haemorrhagic fever
CNS	Central nervous system
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ELISA	enzyme-linked immunosorbent assay
NS1	Non-structural protein 1
PT	Prothrombin time
APTT	Partial thromboplastin time
ICU	Intensive Care Unit
HDW	High Dependence Ward
AOR	Adjusted odd ratio

ABSTRAK

Pengenalan

Demam denggi merupakan salah satu penyakit berjangkit yang paling endemik di Malaysia yang mana kadar jangkitan kian meningkat saban tahun. Pesakit boleh hadir dengan pelbagai gejala dan tahap jangkitan demam denggi, daripada demam denggi ringan sehingga tahap denggi parah (*severe dengue*). Tujuan kajian ini adalah untuk mengenalpasti gejala pesakit demam denggi serta risiko untuk mendapat komplikasi.

Kaedah Kajian

Kajian retrospektif ini melibatkan pesakit yang disahkan mengalami demam denggi berusia 12 tahun atau lebih di sebuah hospital pengajian tinggi di pantai timur Malaysia dari tahun 2016 hingga 2018. Data yang diperolehi adalah sosiodemografi pesakit (umur, jantina, berat, bangsa), gejala penyakit dan komplikasi penyakit demam denggi. Faktor-faktor yang mempengaruhi demam denggi parah seterusnya dikenalpasti.

Keputusan

Sejumlah 327 kes dikenalpasti, yang mana 66 pesakit (20.2%) mengalami demam denggi parah. Gejala yang paling kerap dialami adalah kurang selera makan (75.2%) disusuli demam (65.7%) dan muntah (55.7%). Komplikasi paling kerap pula adalah *dengue shock syndrome* (18.3%) disusuli masalah pernafasan (*respiratory distress*) (1.2%). Faktor prediktif untuk demam denggi parah yang dikenalpasti adalah sesak nafas (AOR 5.82, 95% CI 1.37-24.69, p=0.017), cirit-birit (AOR 0.49, 95% CI 0.27-0.91, p=0.023), kadar nadi yang tinggi (AOR 2.85,95% CI 1.59-5.10, p=0.001) dan pembengkakan hati (AOR 2.76, 95% CI 1.24-6.18, p=0.013).

Kesimpulan

Dengan mengetahui faktor prediktif untuk demam denggi parah, pasukan perubatan dapat mengenalpasti pesakit yang perlu diberi keutamaan dalam rawatan serta ciri-ciri pesakit yang mungkin akan merosot kepada demam denggi parah.

Kata Kekunci

Demam denggi, komplikasi, penyakit tropikal, penyakit berjangkit

ABSTRACT

Background:

Dengue fever is one of the most endemic infectious disease in Malaysia and the number of cases increases each year. Patients may present in various phases and forms of dengue, which can progress to severe dengue. The aims of this study were to determine the presentations of dengue infection and factors associated with severe complications.

Methods:

This retrospective study involved patients aged 12 years and above with positive dengue infection presented to emergency department in our tertiary, suburban hospital and admitted, from year 2016-2018. Patients sociodemographic patterns, presentation and complications of dengue were identified. Factors associated with severe dengue were determined.

Results:

A total of 327 cases were included, with 66 patients (20.2%) contracted severe dengue. Most common symptoms was loss of appetite (75.2%), followed by fever (65.7%) and vomiting (55.7%). Most common complication was dengue shock syndrome (18.3%) followed by respiratory distress (1.2%). Factors predictive of severe dengue include shortness of breath (AOR 5.82, 95% CI 1.37-24.69, p=0.017), diarrhoea (AOR 0.49, 95% CI 0.27-0.91, p=0.023), tachycardia (AOR 2.85,95% CI 1.59-5.10, p=0.001 and hepatomegaly (AOR 2.76, 95% CI 1.24-6.18, p=0.013).

Conclusions:

Identifying factors predictive of severe dengue may help physicians in prioritizing the patients care and anticipate deterioration and complications.

Keywords:

Dengue fever, severe dengue, complications, tropical disease , infectious disease

CHAPTER 1.0 INTRODUCTION

Dengue is one of the most important arthropod-borne diseases with high morbidity and mortality. Predominantly in urban areas, it affects tropical and subtropical regions around the world. Malaysia also experience increase of dengue incidence as it happened globally. Since the year 2000, the dengue incidence in Malaysia continues to rise from 32 cases per 100,000 population to 361 cases per 100,000 population in 2014. The dengue incidence rate is higher for age group of 15 and above. Most of the dengue cases reported were from urban areas (70%–80%) where factors such as high-density population and rapid development favours dengue transmission. With regards to case fatality rate, the national target is less than 0.2%. The case fatality rate has been reduced from 0.6% in year 2000 to 0.2% in year 2014. Most of the dengue mortality has been observed to be higher among age group of 15 years and above, with the highest recorded in 2004.[1]

Mosquito-borne flavivirus is the dengue virus responsible for dengue infection. It is transmitted by Aedes albopictus and Aedes aegypti.[2] There are four distinctive serotypes, which are DENV-1,2,3 and 4. Every episode of infection induced a life-long protective immunity to the specific homologous serotype but granted only partial and transient protection against other different serotypes. Secondary infection or re-infection by dengue virus from a different serotype is one of major risk factors for severe dengue infection due to antibody-dependent enhancement. Other important contributing factors are host genetic background, viral virulence, viral load, T-cell activation and auto-antibodies. At any one time in Malaysia, all of the four serotypes can be isolated. However, one particular dengue virus serotype is able to predominate for about two years before being replaced by other serotypes. The predominant serotype has switched two times in 2013-2014, which is from DENV-2 to DENV-1 and conversely in February and June 2014.[1]

Clinical course of Dengue fever follows 3 phases, which are febrile phase, critical phase and recovery phase.

In general, the management of dengue infection is symptomatic as well as supportive. Treatment issues vary according to the clinical course of the three phases. It is important to identify plasma leakage and early shock along with severe organ dysfunction. This can be attained by continuous clinical and laboratory monitoring and observation during the early febrile phase of infection.[1]

This study aims to determine the risk factors associated with severe complication in dengue infection in order to help physicians prioritize their management of high-risk dengue patients. This study also aims to identify the sociodemographic data, the presentation, as well as the prevalence of severe complication of dengue infection in adult population who were admitted to Hospital Universiti Sains Malaysia.

CHAPTER 2.0 STUDY PROTOCOL

2.1 PROBLEM STATEMENT AND STUDY JUSTIFICATION

1. Dengue infection is one of the common infectious disease in Malaysia with high morbidity and mortality which predominantly affects the urban areas. There is an increase of the incidence of dengue infection in our country from 32 cases per 100000 population in 2000 to 361 cases per 100000 population in 2014 with a mortality rate of 0.2%. Despite having the most dengue cases in Malaysia in year 2016, there is still inadequate data on dengue infection and its complication in Kelantan. Therefore, this study will elaborate on the sociodemographic data and presentation of patients with dengue infection in HUSM, Kelantan. With this knowledge, it is hoped that cases of dengue can be identified early based on their presentations, thus early treatment can be started to prevent further complications. The data can also be used to compare dengue cases in other regions. Other than that, this study will also determine the type of severe complications and its prevalence in dengue patients in HUSM.

2. The progression of the disease may be sudden and rapid causing severe complications that may eventually leads to morbidity and mortality of the patient. Early detection of high risk patients who may develop severe complications is fundamental in the management of dengue patients, in which fluid titration and further treatment can be outlined beforehand. This study will explore the factors that may predict severe complications of dengue in our population. The findings can be used as an effort to guide physicians in prioritizing high risk patients in the management of dengue.

3. Patients with dengue infection may present with various clinical findings as well as phases of the disease where it can mimic other infection and diseases. Moreover, rapid test for detection of NS-1 antigen may reduce in its sensitivity after day 4-5 of illness where the result may be false negative. This research will study the fashion of presentation of dengue fever so that it may help clinician in order to diagnosed dengue fever. Investigations results will also be included which can help to increase the awareness of clinician in having high index of suspicion for clinically suspected dengue infection.

2.2 BENEFIT OF THIS STUDY

1. Results from this study can be used as a guide for the attending doctors in terms of when to anticipate severe complications in dengue infection and to prioritize management by identifying the risk factors from the patients diagnosed with dengue fever.

2. Results from this study may also show recent sociodemographic data, presentation trends and complications from dengue in patients diagnosed with dengue fever/severe dengue hailing from Kota Bharu area as well as its vicinity.

2.3 RESEARCH QUESTIONS

1. What is the sociodemographic data and presentations of dengue patients in Hospital Universiti Sains Malaysia (HUSM)?

2. What are the complications of dengue in patients in HUSM?

3. What is the prevalence of severe complication in dengue patients?
4. What are the associated factors for developing severe complication in dengue patients?

2.4 OBJECTIVES

General objective

To determine the presentation and outcome of dengue patients admitted to Hospital Universiti Sains Malaysia

Specific objectives

1. To determine the sociodemographic data of patients with dengue infection in HUSM.
2. To determine the types of complications among dengue patients in HUSM.
3. To determine the prevalence of severe complication among dengue patients in HUSM.
4. To determine the factors associated with severe complications in dengue patients in HUSM.

Null hypothesis

1. There is no correlation between patient's sociodemographic characteristics, presentation, clinical findings and investigations with severe complication of dengue.

2.5 LITERATURE REVIEW

Dengue fever epidemiology

The World Health Organization approximate that more than 2.5 billion people in the world are at risk of dengue infection. Originally recognised in the 1950s, it has turned out to be a foremost cause of child mortality in several South American and Asian countries[2].The dengue infection incidence is higher in age group of 15 and above. A study has reported that the progression of urbanization process in Malaysia resulting in increased in incidence of dengue infection.[4]

Cases of dengue mortality in Malaysia has been observed to be highest in 2004 which mostly involved age group of 15 years and above.[1] According to Tee HP et al, there was almost equal gender distribution where female patients comprised of 52.4% and the median age was 27 years old where 60% of the dengue patients were less than 30 years old.[5]

Dengue fever clinical presentations

Dengue infection usually have an incubation period of 4-7 days (range 3-14 days). Patients may be asymptomatic or some may experience a vast spectrum of illness ranging from mild undifferentiated febrile illness to severe disease, with or without organ impairment and plasma leakage. Patients may present with vomiting, abdominal pain, symptoms of upper respiratory tract infection, pleural effusion, hepatomegaly and ascites. However, in a study done in Kuantan, Malaysia, only diarrhoea was found to be significantly associated with DHF or dengue shock syndrome (DSS) with the odd ratio of 2.41 (95% CI = 1.04-5.57).[5]

Symptomatic dengue infection is indeed a complex disease where a systemic and dynamic disease with clinical, serological and haematological profiles changing from daily basis. These changes may accelerate within hours or even minutes in the critical phase, mostly in patients with plasma leakage.[1]

Prevalence of Dengue Shock Syndrome and severe dengue infections

According to Tee HP et al, the demographic data between the groups of DHF/DSS and classical DF showed that development of DHF/DSS were significantly associated with patients aged 30 years and above where the OR was 2.37 (95% CI= 1.14-4.94). There was no significant association noted for variables such as gender and race however.[5]

In a study done in 2000-2010 in Malaysia, the annual incidence rate of DHF on average was 5.99 (with 95% CI=3.33-8.64) per 100000.[4] A meta-analysis study of 80 published studies of cross-sectional designs, showed that the proportion of DSS was 28.5% (95% CI: 24.7 – 32.6) which have high heterogeneity (heterogeneity of *p*-value is <0.001, I^2=95). Further sub-analysis has demonstrated that DSS prevalence in adults (17.7%; 95% CI: 10.1 – 29.4; where 11 studies have been recruited with only adults) was lower than in children significantly (37.4%; with 95% CI: 29.6 – 45.9; in 26 studies where only children recruited).[7]

Risk factors for developing severe dengue infections

Age-In regards of age, Karunakaran et al founds that age >40 is a risk factor for mortality (p = 0.002). In their study, those with age 40 and above were 9.3 times (95% CI; 1.9–44.4) more likely to have mortality when contracted by dengue fever.[6] Guzman *et al* had revealed an increased mortality in bipolar pattern, where young infants and the elderly aged 50 years and above had higher mortality and hospitalization rate.[9]According to Tee

HP et al however, older age group was 2.37 times more likely to develop DHF/DSS compared to the younger age group.[5]

Gender difference-Understanding male-female dissimilarity in infection severity and rates of disease is crucial for public health control programmes. A meta-analysis of 37 studies showed a significant association between DSS and female gender (OR: 1.37, 95% CI: 1.17-1.60).[7] However there was almost equal gender distribution in a study in tertiary hospital in Kuantan.[5]

Gastrointestinal symptoms-It is demonstrated in a meta-analysis study that nausea and vomiting are associated factors for developing DSS.[7]

Bleeding signs-According to a meta-analysis study, gastrointestinal bleeding was recognized as positive associated factor for DSS (pooled OR: 1.84, 95% CI: 1.42-2.39), whereas positive tourniquet test, petechiae, skin hemorrhages, hemoptysis and hematuria were not associated with risk of DSS. Based on this study, there were no associations between DSS and purpura/ecchymoses and nose or gum bleeding were found, further suggesting DSS were not associated with mucosal and skin bleeding.[7]

Haematocrit level-There are many literatures that indicate high haematocrit level correlates with risk to developed severe dengue or DSS. High haematocrit level means that percentage of red blood cells in the blood is increased above the upper limit and may indicate dehydration. In dengue pathophysiology *per se,* high haematocrit is the manifestation of third space loss of plasma volume due to an increased blood vessels and capillary permeability, which is the hallmark of critical phase in dengue fever clinical course.

In Tee HP et al study, in regards of analysing the association of DHF/DSS and haematocrit, the results had shown that haematocrit values of 47% and higher for male

(OR= 13.22, 95% CI= 3.35- 52.20), and 40% and higher for female patients (OR= 3.96, 95% CI =1.52-10.33) had strong association of developing severe dengue. Moreover, it also shown that haematocrit increased or fluctuation of more than 20% is strongly significant in association with DHF/DSS, with the odd ratio of 39.71 (95% CI= 13.90-113.48).[5]

Plasma leakage signs-All of the plasma leakage signs (pleural effusion, haemoconcentration, ascites, hypoproteinaemia and hypoalbuminemia), were strongly associated with DSS.[7]

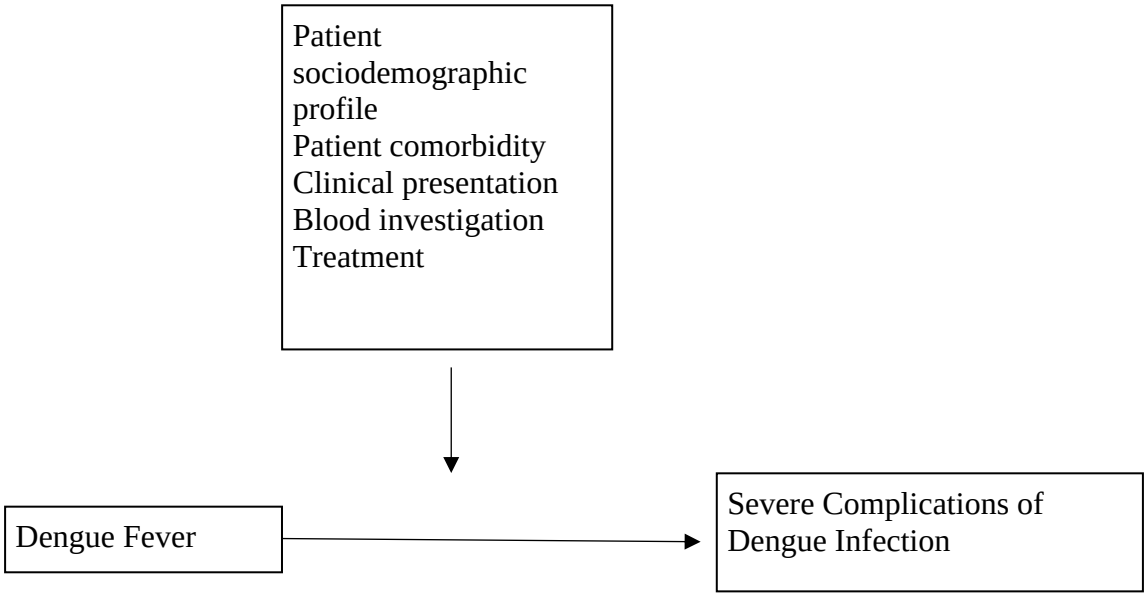
Comorbidities-Co-morbidities is one of the determinants of mortality identified.[6] Dengue patients with hypertension, diabetes mellitus, chronic obstructive pulmonary disease, asthma, congestive heart failure, other cardiovascular diseases, chronic kidney disease, chronic anemia and multiple co-morbidities were known to have higher incidence of mortality[6]. In a separate study, it is shown that type 2 diabetes mellitus dengue patients with additional comorbidity had significantly greater incidence of severe gastrointestinal bleed (5.8% vs. 0.2%; $P < 0.001$) and profound thrombocytopenia[8].

Thrombocytopenia-Tee HP et al found that those with platelet count less than 35,000/mm3 were associated with the risk of developing DSS/DHF (OR= 2.73; 95% CI= 1.26-5.89)[5]. Karunakaran et al suggested that platelet counts may be mortality predictors[6]. Thrombocytopenia was present in all of the patients who died of dengue in their study. Moreover, in pediatric population, the risk of death was 6 times higher in those with platelet count <50,000/μl.[6]

Coagulation-Prothrombin time prolongation has been associated with higher fatality[6]. There were positive association noted between DSS and prolonged prothrombin time (PT) as well as activated partial thromboplastin time (APTT)[7].

2.6 METHODOLOGY

2.6.1 CONCEPTUAL FRAMEWORK



2.6.2 RESEARCH DESIGN

This is a retrospective cross-sectional study which includes all patients that fulfil all inclusion and exclusion criteria who presented in emergency department and admitted in HUSM from January 2016 till December 2018 until sample size is achieved. Cases diagnosed of either confirmed or suspected DF will be identified from hospital database as all DF cases will be notified. Information regarding patient's name and registration number will be retrieved from the notification database and their case notes will be

collected from the Record Unit to be reviewed afterward. Relevant data will be extracted from patients' case notes and later to be analysed.

2.6.3 STUDY AREA

Emergency Department and Medical Wards Hospital Universiti Sains Malaysia (HUSM) Kubang Kerian, Kelantan

2.6.4 STUDY POPULATION

- Reference population: Dengue fever (DF) patients in Kelantan
- Source population: all patients diagnosed with DF who presented or admitted in HUSM
- Study participants: all confirmed DF who presented to emergency department and admitted to medical wards in HUSM who fulfilled the inclusion and exclusion criteria

2.6.5 SAMPLING FRAME

This study will be conducted from 2018 following ethics approval until May 2020.

2.6.6 SUBJECT CRITERIA

Inclusion criteria

- Patients diagnosed with dengue fever with classical symptoms of dengue
- Age 12 years old and above
- Positive Rapid Combo Test (RCT) – NS1 antigen test and dengue IgM/IgG antibodies

or

- Positive serology test for dengue infection- Dengue IgM capture enzyme-linked immunosorbent assay (ELISA)

Exclusion criteria

- Patients with other confirmed infections
- Cases with negative serology for dengue

2.6.7 SAMPLE SIZE ESTIMATION

Sample size is calculated using single proportion formula. According to Tee HP *et al*, based on a study done in Hopital Tengku Ampuan Afzan Kuantan, Pahang, the prevalence of severe complication in dengue fever was 20.8% (Tee *et al.*, 2009).

The following formula was used (Daniel, 1999):

Sample size, $n = \frac{Z^2 P(1-P)}{d^2}$

Z = Z statistic for level of confidence

P = expected prevalence

d = precision

Taking the Z score as 1.96 (for 95% confidence level), expected prevalence of severe complications in dengue fever is 20.8% and precision of 0.05, the sample size was

calculated to be 255. Considering drop-out rate of 10%, total sample required, N, was calculated:

N = 255 + 10% drop-out rate

= 280

Other variables are also calculated using single proportion formula severe complication of dengue fever using sample size calculator from statulator.com with 5 % absolute precision and 95% confidence with reference of Dhand. N. K. & Khatkar M. S. (2014).

Variables			Prevalence	Reference	Sample size calculation using single proportion formula
1	Age	> 30 y/o	29.2%	Tee HP et al	317
		< 30 y/o	15.4%	Tee HP et al	196
2	Gender	Male	14.9%	Tee HP et al	196
		Female	26%	Tee HP et al	296
3	Race	Malay	20.9%	Tee HP et al	255
		Non Malay	20%	Tee HP et al	246
4	Epigastric pain		23.5%	Tee HP et al	281
5	Vomiting		22.4%	Tee HP et al	264
6	Arthralgia		10%	Karunakaran et al	139
7	URTI		21.4%	Tee HP et al	255

8	Hepatomegaly	26.7%	Tee HP et al	303
9	Aneroxia	10%	Karunakaran et al	139
10	Ig G antibody (Primary dengue infection)	28.4%	Tee HP et al	317
11	Ig M antibody (Secondary dengue infection)	14.9%	Tee HP et al	196
12	Haematocrit fluctuation >20%	80%	Tee HP et al	246
13	Anemia	70%	Karunakaran et al	323
14	Thrombocytopenia	3%	A Mohd Hanief et al (Mohd Hanief Ahmad, 2018)	45

Based on calculation above, in conclusion total sample size for this study is 323. Considering drop-out rate of 10%, total sample required, N, was calculated:

N = 323 + 10% drop-out rate

= 355

Samples will be selected using convenient sampling method until sample size is achieved

2.6.8 OPERATIONAL DEFINITION

1. Diagnosis of dengue infection

    1.1. Based on World Health Organization (WHO) where a positive serology and presence of classical symptoms of dengue infection are needed for diagnosis

    1.2. Positive serology is defined as presence of either positive IgM or IgG or both

    1.3. Primary infection is defined as presence of IgM with negative IgG

    1.4. Secondary infection is defined as positive IgG regardless of IgM results

2. Classification of Dengue Fever and level of severity

    2.1. Based on 2009 WHO Dengue Classification and Level of severity(Deen *et al.*, 2009)

        2.1.1. Dengue with warning sign, when there is presence of any of the followings:

        - Abdominal pain or tenderness
        - Persistent vomiting
        - Persistent diarrhea
        - Clinical fluid accumulation
        - Mucosal bleed
        - Lethargy, confusion, restlessness
        - Tender liver

- Increase in HCT concurrent with rapid decrease in platelet count in laboratory findings

2.1.2. Severe dengue:

2.1.2.1. Severe plasma leakage leading to

- Shock (DSS)
- Fluid accumulation with respiratory distress

2.1.2.2. Severe bleeding

- Gastrointestinal bleeding
- As evaluated by clinician

2.1.2.3. Severe organ involvement:

- Liver AST or ALT > or 1000
- CNS impaired consciousness
- Heart and other organs

2.1.3. Severe complications of dengue infection includes complications developed in the criteria of severe dengue which are:

2.1.3.1. Severe plasma leakage leading to

- Shock (DSS)
- Fluid accumulation with respiratory distress

2.1.3.2. Severe bleeding

- Gastrointestinal bleeding

- As evaluated by clinician

2.1.3.3. Severe organ involvement

- Liver AST or ALT > or 1000
- CNS impaired consciousness
- Heart and other organs

2.7 DATA COLLECTION METHOD

Data will be collected from the patients' case note which will be retrieved from the Record Unit Hospital Universiti Sains Malaysia. Ethical approval from the Human Research Ethics Committee and permission from the hospital director will be obtained before reviewing patients' medical records. Any data collection will be carried out in such a way to ensure patients confidentiality. Case note retrieved will be from patient that visited HUSM from 2016 to 2018.

2.8 DATA ENTRY AND ANALYSIS

2.8.1. Variable

2.8.1.1 Independent variables

a. Patient's demography

- Age, Gender, Sex, Race and Educational background, weight, height, body mass Index (BMI) - obese/non-obese

b. Comorbidity

- hypertension, diabetes mellitus, heart failure, liver failure, renal failure, anaemia

c. Symptoms on presentation

- Day of fever on 1st presentation to healthcare

- Day of fever on presentation to HUSM

- Day of fever at 1st diagnosed as severe dengue/dengue fever with severe complications

- Epigastric pain, shortness of breath, nausea and vomiting, diarrhea, petechial rash,

headache, upper respiratory tract infection (URTI), lethargy, loss of appetite (LOA)

d. Clinical examination and features

-blood pressure, pulse rate, respiratory rate, temperature, peripheral perfusion status

(capillary refill time, pulse volume, skin temperature)

-Hepatomegaly

-Features of overload

-ascites, pleural effusion

e. Investigations

-IgM and IgG antibodies

-platelet count on admission

-haematocrit on admission

-haematocrit fluctuation>20%

e. Treatment

-blood product transfusion

-amount

-type -Packed cell (PC), fresh frozen plasma (FFP), Platelet (Plt)

-fluid administration – colloid, crystalloid infusion

2.8.1.2 Dependent variable

2.8.1.2.1 Severe complication of dengue infection

i. Severe plasma leakage leading to

1. Shock (DSS)

2. Fluid accumulation with respiratory distress

ii. Severe bleeding

iii. Severe organ involvement

1. Liver AST or ALT > or 1000

2. CNS impaired consciousness

3. Heart and other organs

2.8.1.2.2 Length of stay in

i. ICU/HDW

ii. General ward

iii. Emergency department

2.8.2 Data Entry

Data will be entered and analysed using Statistical Package for Social Science (SPSS) for windows, version 22.0

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2.9 Statistical Analysis

For Objective 1 and 2, descriptive analyses will be expressed as frequencies, means with standard deviation and percentages and presented as bar chart, pie chart, or line graphs as seen appropriate. For Objective 3, prevalence will be stated in percentage. For Objective 4, simple and multiple logistic regression analyses will be applied to identify the risk factors associated with severe complications in dengue. A p-value ≤ 0.05 is considered as statistically significant for all statistical analyses in this study.

2.10 Dummy Tables

Table 1: Sociodemographic and Presentation of Patient with Dengue Fever

Variables	Category	Dengue fever ± warning sign, n (%)	Severe dengue, n (%)	Total dengue cases,

				n (%)
Age (mean, SD)				
Gender	Male Female			
Race	Malay Non-Malay			
Symptoms on presentation	Epigastric pain Shortness of breath Nausea Vomiting Diarrhea Petechial rash Loss of appetite			
Clinical examination and features	Hypotension Tachycardia Tachypnoeic Fever Peripheral perfusion status - prolonged capillary refill time - reduced pulse volume - cold peripheries Hepatomegaly Fluid overload - pleural effusion - ascites			
Investigations	IgG antibodies			

	-positive Platelet count on admission <150 ε150 Raised HCT on admission -HCT male < or 60 years -45% -HCT male > or 60 years -42% -HCT female (all age groups) -40% Haematocrit fluctuation>20%			
Treatment	Blood product transfusion -PC -FFP -Plt Colloid infusion			
Admission	Admitted Discharge home			
Length of stay (mean, SD)	Intensive care unit General ward Emergency ward			

Table 2 : Day of fever on presentation of patients

Variables	Category	Mean (+/- SD)
Day of fever on presentation	Day of fever on 1st presentation to healthcare	
	Day of fever on presentation to HUSM	

	Day of fever at 1st diagnosed as severe dengue/dengue fever with severe complications	
	Day of fever at death	

Table 3: Complications of dengue infection

Variables	Category	**n (%)**
Prevalence of severe compilations of dengue infection		
Type of complication	Dengue shock syndrome	
	Fluid accumulation with respiratory distress	
	Severe bleeding	
	Severe organ involvement - Liver AST or ALT > or 1000 - CNS - Heart and other organs	
	Death	
	Other complications	

Table 4: Factors Associated with Severe Dengue/DHF/DSS

OR Variables	Category	Severe Dengue/ Total (%)	OR (95% CI)	p-value
Age				
Gender	Male Female			
Race	Malay Non-Malay			
Symptoms on presentation	epigastric pain shortness of breath nausea vomiting diarrhoea petechial rash loss of appetite			
Clinical examination and features	Hypotension Tachycardia Tachypnoeic Fever Peripheral perfusion status - prolonged capillary refill time - reduced pulse volume - cold peripheries Hepatomegaly Fluid overload			