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

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AKU JANJI

Diperakui bahawa dissertasi yang bertajuk **A STUDY ON DENGUE FEVER PRESENTATION AND OUTCOME IN HOSPITAL UNIVERSITI SAINS MALAYSIA** merupakan kerja dan penyelidikan yang asli dari **ABDULLAH LUTFI BIN ISMAIL,** dari tempoh 2017 hingga 2020 adalah di bawah penyeliaan kami. Dissertasi ini merupakan sebahagian daripada syarat untuk penganugerahan Sarjana Perubatan Kecemasan, segala hasil dan data yang diperolehi adalah hak milik terpelihara Universiti Sains Malaysia.

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Tandatangan Pelajar

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Tandatangan Ketua Jabatan

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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. Faktor yang mempengaruhi pesakit untuk dijangkiti demam denggi parah adalah sesak nafas, cirit-birit, kadar nadi yang tinggi dan pembengkakan hati.

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. Factors associated with

severe dengue in this study were shortness of breath, diarrhea, tachycardia and hepatomegaly.

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 of dengue infection in order to help physicians in managing dengue patients. In Malaysian CPG provided by MOH, several pitfalls was elaborated in managing dengue patients, such as infrequent monitoring and infusion rate readjustments, inappropriate fluid therapy in patients with comorbidities, continuation and inappropriate intravenous fluid therapy in recovery phase, prolonged fixed and excessive fluid regime in stable patient and others. Inappropriate fluid therapy and inadequate monitoring of patient may lead to negative impact especially during critical phase, where patient may have worsening hemoconcentration, volume overload or failure to recognised compensated shock. Failure to recognised the phase of compensated shock due to inadequate and inappropriate monitoring and fluid therapy will ultimately lead to decompensated shock with a more complicated course of the disease as well as organ failures.[5] Adopting from WHO Dengue Guidelines, our Malaysian CPG provides criteria for in patient management where the dengue warning signs is utilised for these purposed, as dengue warning signs are good indicators of a higher risks to developed severe dengue.[6] In this study, we would like to unfold factors which can predict the development of severe dengue, including the dengue

warning signs. With this study, clinician may prioritize which patient is at higher risks of severe dengue and provides thorough care, monitoring and treatment as well as avoiding pitfalls as stated above. 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]

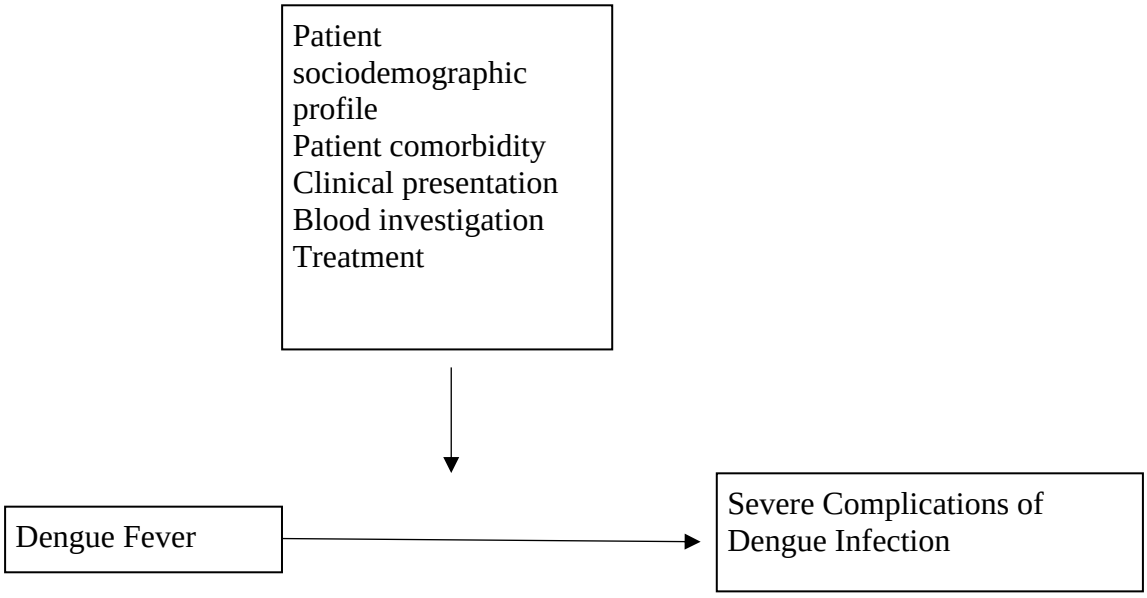
Comorbidities-Co-morbidities is one of the determinants of mortality identified.[6] Dengue patients with hypertension, diabetes mellitus, chronic obstructive pulmonary disease, asthma, congestive heart failure, other cardiovascular diseases, chronic kidney disease, chronic anemia and multiple co-morbidities 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

-paediatric patients is excluded as physiologically can be different specially on vital signs and presentations. Therefore this study were focused more on adult and teenagers population

- 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
- Patients referred from other facilities

2.6.7 SAMPLE SIZE ESTIMATION

Sample size calculation for Objective 3

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

Sample size calculation for Objective 4

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

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

-The first vital signs taken in the emergency department were included in the data as vital signs at presentation. Therefore, all the vital signs included were from triage.

However, the complications in the study included all complications detected throughout the patient's stay in the hospital during the visit

Clinical examination and feature includes:

-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	

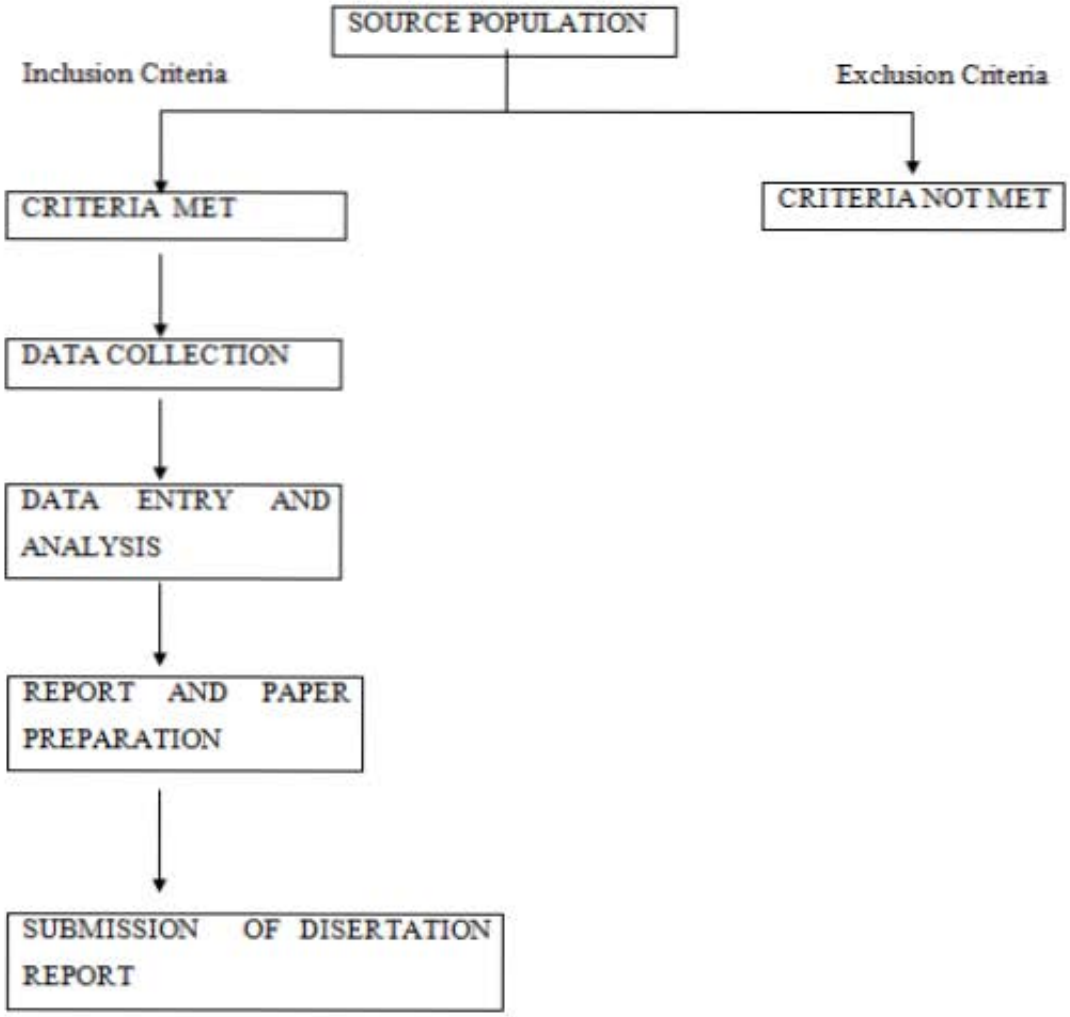
Table 4: Factors Associated with Severe Dengue/DHF/DSS

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 - pleural effusion - ascites			
Investigations	Positive IgG antibodies (secondary dengue) Platelet count on admission <150 ε150 Haematocrit on admission Normal HCT Raised HCT Haematocrit fluctuation>20%			

	Yes No			
Treatment	Blood product transfusion PC FFP Plt Colloid infusion			

2.11 FLOW CHART



2.12 GANTT CHART OF RESEARCH ACTIVITIES

Time / Project	2018							2019												2020				
	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M
1. Data Collection							→	→	→	→	→	→												
2. Data Entry & Analysis													→	→										
3. Report Preparation														→	→	→	→	→	→					
4. Submission of Draft																				→	→	→		

Milestone:

Semester 4: completion of data collection. Data entry and data analysis.

Semester 5: completion of data entry and data analysis.

Semester 5: Preparation of report.

Semester 6: Submission of draft.

2.13 ETHICAL CONSIDERATION

During the study, all data involving the samples will be held confidential and will only be accessible to the investigator and his team. Permission to retrieve the patient's data will be obtained from the Hospital Director. The investigator also declared no conflict of interest with regard to this study.

2.14 PRIVACY & CONFIDENTIALITY

All forms are anonymous and will be entered into SPSS software. Only research team members can access the data. Data will be presented as grouped data and will not identify the responders individually.

2.15 CONFLICT OF INTEREST

The investigators declare that they have no conflict of interests

2.16 PUBLICATION POLICY

No personal information will be disclosed and subjects will not be identified when the findings of the survey are published

2.17 REFERENCES

1. MOH (2015). Ministry of Health Malaysia clinical practice guidelines MOH/P/PPK/302.15(GU): Management of Dengue Infections in Adults (3rd Ed.). Ministry of Health Malaysia & Academy of Medicine Malaysia

2. Guha-Sapir D. & Schimmer B. Dengue fever: new paradigms for a changing epidemiology. *Emerg Themes Epidemiol*. 2005;2(1):1. Published 2005 Mar 2. doi:10.1186/1742-7622-2-1

3. WHO. Dengue Guidelines for Diagnosis, Treatment, Prevention and Control; WHO: Geneva, Switzerland, 2009. pp148

4. Mia, M.S., et al., Trends of dengue infections in Malaysia, 2000-2010. Asian Pacific Journal of Tropical Medicine, 2013. **6**(6): p. 462-466.

5. Tee, H.P., et al., Risk factors associated with development of dengue haemorrhagic fever or dengue shock syndrome in adults in Hospital Tengku Ampuan Afzan Kuantan. Medical Journal of Malaysia, 2009. **64**(4): p. 263-267.

6. Karunakaran, A., et al., Risk factors of mortality among dengue patients admitted to a tertiary care setting in Kerala, India. J Infect Public Health, 2014. **7**(2): p. 114-20.

7. Huy, N.T., et al., Factors associated with dengue shock syndrome: a systematic review and meta-analysis. PLoS Negl Trop Dis, 2013. **7**(9): p. e2412.

8. Lee I.K., et al., Diabetic patients suffering dengue are at risk for development of dengue shock syndrome/severe dengue: Emphasizing the impacts of co-existing comorbidity(ies) and glycemic control on dengue severity,Journal of Microbiology, Immunology and Infection,Volume 53, Issue 1(2020)Pages 69-78,ISSN 1684-1182
https://doi.org/10.1016/j.jmii.2017.12.005

9. Guzman MG, Halstead SB, Artsob H, Buchy P, Farrar J, Gubler DJ, Hunsperger E, Kroeger A, Margolis HS, Martínez E, Nathan MB, Pelegrino JL, Simmons C,Yoksan S, Peeling RW.Dengue: a continuing global threat. Nat Rev Microbiol. 2010 Dec;8(12 Suppl):S7-16. doi: 10.1038/nrmicro2460. PMID: 21079655; PMCID: PMC4333201.

10. Rajapakse S, Rodrigo C, Rajapakse A. Treatment of dengue fever. *Infect Drug Resist*. 2012;5:103-112. doi:10.2147/IDR.S22613

11. Hasan S, Jamdar SF, Alalowi M, Al Ageel Al Beaiji SM.2016. Dengue virus: A global human threat: Review of literature. *J Int Soc Prev Community Dent*. 2016;6(1):1-6. doi:10.4103/2231-0762.175416

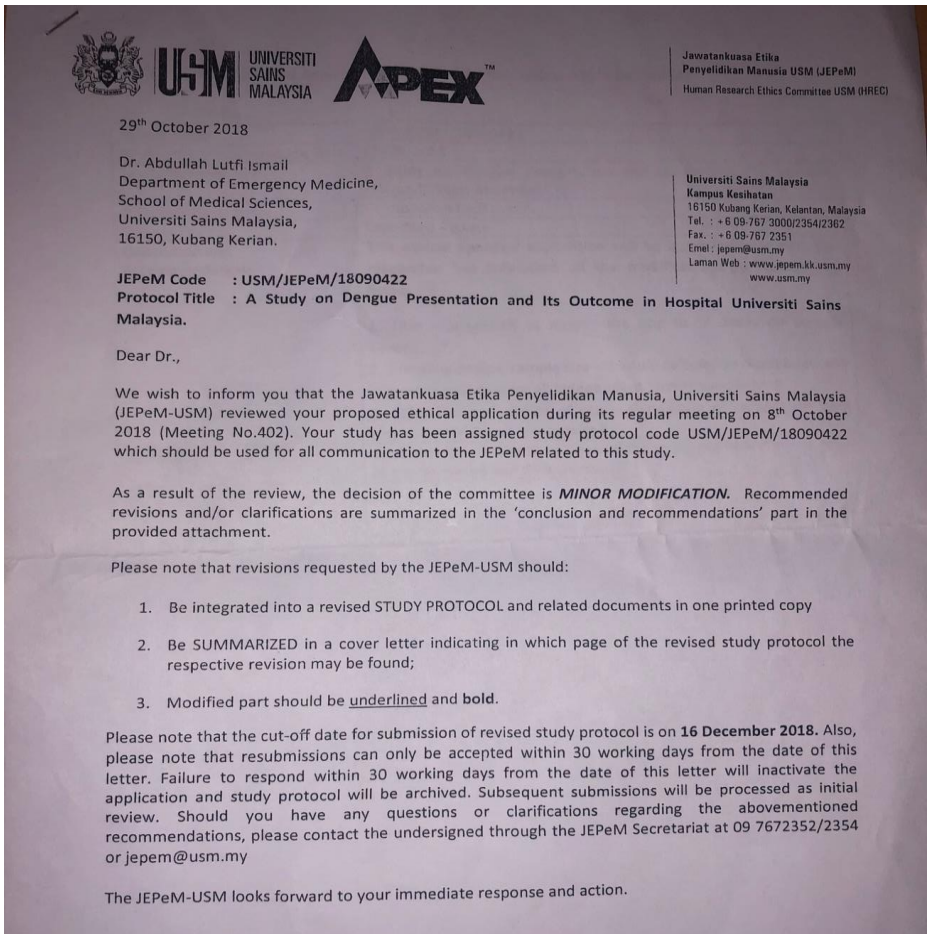
12. WHO (2020). Dengue and severe dengue (Fact sheet Updated 23 June 2020).https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue (accessed 26 October 2020)

13. MOH, 2020. Malaysian Health at a glance 2018. Ministry of Health Malaysia 2019

14. Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emerg Med J. 2003 Jan;20(1):54-60. doi: 10.1136/emj.20.1.54. PMID: 12533370; PMCID: PMC1726024.

15. Setia MS. (2016). Methodology series module 3: Cross-sectional studies. Indian J Dermatol. 2016. 61:261–264.doi: 10.4103/0019-5154.182410: 10.4103/0019-5154.182410PMCID: PMC4885177PMID: 27293245

18 ETHICAL APPROVAL LETTER



USM UNIVERSITI SAINS MALAYSIA APEX™

Jawatankuasa Etika Penyelidikan Manusia USM (JEPeM)
Human Research Ethics Committee USM (HREC)

29th October 2018

Dr. Abdullah Lutfi Ismail
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JEPeM Code : USM/JEPeM/18090422
Protocol Title : A Study on Dengue Presentation and Its Outcome in Hospital Universiti Sains Malaysia.

Dear Dr.,

We wish to inform you that the Jawatankuasa Etika Penyelidikan Manusia, Universiti Sains Malaysia (JEPeM-USM) reviewed your proposed ethical application during its regular meeting on 8th October 2018 (Meeting No.402). Your study has been assigned study protocol code USM/JEPeM/18090422 which should be used for all communication to the JEPeM related to this study.

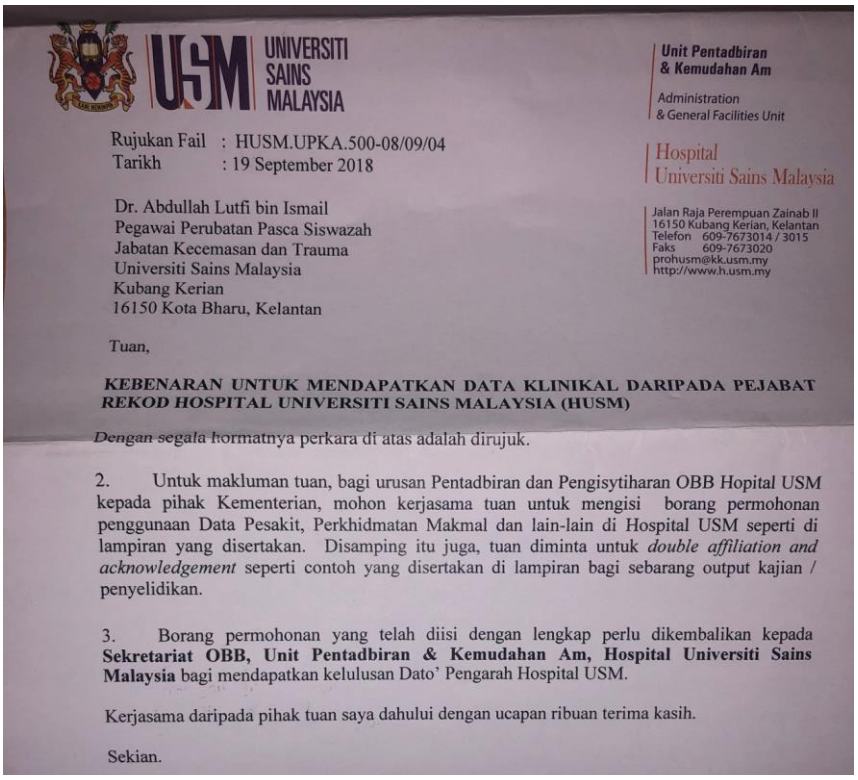
As a result of the review, the decision of the committee is ***MINOR MODIFICATION.*** Recommended revisions and/or clarifications are summarized in the 'conclusion and recommendations' part in the provided attachment.

Please note that revisions requested by the JEPeM-USM should:

1. Be integrated into a revised STUDY PROTOCOL and related documents in one printed copy
2. Be SUMMARIZED in a cover letter indicating in which page of the revised study protocol the respective revision may be found;
3. Modified part should be underlined and **bold**.

Please note that the cut-off date for submission of revised study protocol is on **16 December 2018.** Also, please note that resubmissions can only be accepted within 30 working days from the date of this letter. Failure to respond within 30 working days from the date of this letter will inactivate the application and study protocol will be archived. Subsequent submissions will be processed as initial review. Should you have any questions or clarifications regarding the abovementioned recommendations, please contact the undersigned through the JEPeM Secretariat at 09 7672352/2354 or jepem@usm.my

The JEPeM-USM looks forward to your immediate response and action.



UNIVERSITI SAINS MALAYSIA

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Rujukan Fail : HUSM.UPKA.500-08/09/04
Tarikh : 19 September 2018

Dr. Abdullah Lutfi bin Ismail
Pegawai Perubatan Pasca Siswazah
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Tuan,

KEBENARAN UNTUK MENDAPATKAN DATA KLINIKAL DARIPADA PEJABAT *REKOD* HOSPITAL UNIVERSITI SAINS MALAYSIA (HUSM)

Dengan segala hormatnya perkara di atas adalah dirujuk.

2. Untuk makluman tuan, bagi urusan Pentadbiran dan Pengisytiharan OBB Hopital USM kepada pihak Kementerian, mohon kerjasama tuan untuk mengisi borang permohonan penggunaan Data Pesakit, Perkhidmatan Makmal dan lain-lain di Hospital USM seperti di lampiran yang disertakan. Disamping itu juga, tuan diminta untuk *double affiliation and acknowledgement* seperti contoh yang disertakan di lampiran bagi sebarang output kajian / penyelidikan.

3. Borang permohonan yang telah diisi dengan lengkap perlu dikembalikan kepada **Sekretariat OBB, Unit Pentadbiran & Kemudahan Am, Hospital Universiti Sains Malaysia** bagi mendapatkan kelulusan Dato' Pengarah Hospital USM.

Kerjasama daripada pihak tuan saya dahului dengan ucapan ribuan terima kasih.

Sekian.

CHAPTER 3.0 MANUSCRIPT

3.1 TITLE PAGE

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

Running Title

Dengue presentation and factors associated with severe dengue complications

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3.2 ABSTRACT

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 and admitted 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. Factors associated with

severe dengue in this study were shortness of breath, diarrhea, tachycardia and hepatomegaly.

Keywords: Dengue fever, severe dengue, complications, tropical disease , infectious dis

3.3 INTRODUCTION

Dengue, which predominantly affecting the urban areas, is an endemic disease in Malaysia ever since the first major outbreak in 1973.[1] Currently, the disease has become one of the most prevalent infectious diseases in Malaysia, featuring high morbidity and mortality [2]. The causal agent of this acute disease is the dengue virus, which is a mosquito-borne flavivirus. It is transmitted by Aedes Albopictus and Aedes aegypti.[3]

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 possess only partial and transient protection against other serotypes. However, secondary infection or re-infection by dengue virus from a different serotype in certain sequence may be of major risk factors for enhance dengue illness.[4]

Clinical course of dengue fever (DF) has been described by many authors .[5,6] It follows three phases, which are febrile phase, critical phase and recovery phase. Critical phase usually occurs after the third day of fever or during defervescence, which is evidenced by an abrupt drop in temperature. Contrary to other viral diseases, where typically the patient's condition will improve as the temperature subsides, dengue patients conditions may deteriorate and manifest third space fluid accumulation, organ dysfunction and even profound shock during this phase. The progression of the disease may be sudden and rapid causing severe complications that may eventually leads to morbidity and mortality of patients. Patients may remain asymptomatic upon infection, but 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 symptoms considered to be warning signs for severe dengue, which are vomiting, abdominal pain, symptoms of upper respiratory tract infection, pleural effusion, hepatomegaly and ascites.[4,7,8]

Due to the lack of beneficial anti-viral drugs for dengue, the management of dengue infections is symptomatic as well as supportive in nature.[9] Treatment issues vary according to the clinical course of the three phases, emphasizing on the detection and identification of plasma leakage and early shock, along with severe organ dysfunction.[10] This can be attained through continuous clinical and laboratory monitoring and observation during the early febrile phase of infection. The importance of warning signs is for prediction of severe dengue.[7]

With the rapid increase in dengue cases throughout the world in 2019,[11] the overall strategy of dengue management readiness is imperative. In Malaysia there were 131,000 cases reported throughout the country in 2019. The number of cases and mortality rate (0.0 - 0.61 per 1000) in the State of Kelantan rose steadily during period of 2012-2016.[12] As a tertiary admission centre for dengue, HUSM has conducted profiling of the dengue prevalence and the various accompanying symptoms from admission record. The last exercise was done on records of patients in HUSM admitted in 2015.[7]

Therefore, this study was aimed to determine the sociodemographic, presentation and outcome of patients with dengue infection in our population. We also aimed to determine the prevalence of severe complication of dengue infection and the risk factors associated with severe complication in adult patients in order to help physicians prioritize their management of high-risk dengue patients.

3.4 METHODS

3.4.1 Sampling method and data collection

This retrospective cross-sectional study[13,14] included patients aged ≥12 years old diagnosed as dengue fever who visited our emergency department and admitted from January 2016 to December 2018. Patients with other confirmed infections were excluded.

Cases diagnosed as DF were identified from the hospital database and their medical records were then collected and reviewed after gaining ethical approval from the Human Research Ethics Committee and a written permission from the Hospital Director.

Throughout the study duration, the census of 355 patients were taken as sample. The data were extracted using a standardised data collection forms, which included the demographic of the patients and the symptoms of presentations, patients' vital signs, physical examinations and investigations as well as the duration and place of admission, whether patients need intensive care unit or general ward and most importantly, if patient had developed any complications of dengue.

3.4.2Variable definitions

Diagnosis of dengue infection was made in accordance to World Health Organization (WHO) guidelines where a positive serology and presence of classical symptoms of dengue infection are needed for diagnosis.[15,16] Positive serology is defined as presence of either positive IgM or IgG or both, where primary infection is defined as presence of IgM with negative IgG and secondary infection is defined as positive IgG regardless of IgM results. Classification of Dengue Fever and level of severity are based on 2009 WHO Dengue Classification and Level of severity [15,16] where dengue with warning sign is classified, when there is presence of any of the followings clinical findings: abdominal pain or tenderness, persistent vomiting, persistent diarrhoea, clinical fluid accumulation, mucosal bleed, lethargy, confusion, restlessness, tender liver and increased in haematocrit (Hct) concurrent with rapid decrease in platelet count in laboratory findings. Otherwise, severe dengue is classified if patient developed any of the following criteria: severe plasma leakage leading to Dengue Shock Syndrome (DSS) or fluid accumulation with respiratory distress, severe bleeding where it can be presented as gastrointestinal bleeding or as severe bleeding as evaluated by clinician, any severe organ involvement, where can

be defined as either liver Amino Transferase (AST) or Alanine Transferase (ALT) of 1000 or more, central nervous system (CNS) involvement such as encephalitis or impaired consciousness, heart involvement such as pericarditis and other organ involvements.[16] On the other hand, severe complications of dengue infection is defined as complications developed in the criteria of severe dengue which are described above. Haematocrit levels are in accordance to KKM clinical guideline, in which normal HCT for male aged 60 and below is less than 46%, male aged more than 60 is less than 42% while normal HCT for female is less than 40%[15]. Normal platelet level was taken as 150-400 x 10^9/L.

3.4.3 STATISTICAL ANALYSIS

Data were entered and analysed using Statistical Packages for Social Science (SPSS) version 24.0. Descriptive analyses were expressed as frequencies, percentages, and means with standard deviation. Prevalence of severe complications is stated in percentage. Simple logistic regression analyses were applied for identification of factors associated with severe complications. Factors with p-value <0.25 were selected for multiple logistic regression analysis. A p-value <0.05 is considered as statistically significant for all statistical analyses performed in this study.

3.4.4 ETHICAL CONSIDERATION

This study received ethical board approval from the Human Research Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/18090422). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the human research committees. Permission to use the data was obtained from the Hospital Director. No written consent was needed in this study.

3.5 RESULTS

A total of 354 cases were examined, however 27 (7.6 %) of them were excluded due to insufficient data, leaving a total number of 327 cases being analysed.

Demographic pattern and clinical presentation of patients

Majority of the patients were Malays (320 or 97.9%). The non-Malays comprised of five Chinese, and two foreigners (1 Pakistani and 1 Cambodian). The mean age was 32.28 (SD=15.34), ranging from 13 to 74 years old, where the mean age for severe dengue group was 30.3 years (SD=14.94), which slightly younger than classical dengue group, 32.77 years (SD=15.42). Gender wise, 160 (48.9%) were female and 167 (51.1%) were male patients. Majority of patients presented with symptoms of loss of appetite (246 or 75.2%), followed by vomiting which was found in 182 (55.7%) patients. Fever was the most common clinical finding (215 or 65.7% patients) followed by tachycardia (in 102 or 31.2%) while pleural effusion and ascites were the least common findings. The sociodemographic characteristics, presentation, and investigations in ED are presented in Table 1.

[Table 1: Sociodemographic characteristic, clinical presentation, investigations and treatment of patient with dengue infection]

Investigations and blood parameter

There were 46 patients (14.0%) with IgG positive in which 8 of them (17.4%) developed severe dengue complications while 38 (82.6%) only had classic dengue fever with or without warning signs. Raised in haematocrit were identified in 79 (24.2%) in which 11 (13.9%) developed severe dengue. Increased liver enzyme AST was common in dengue

patients in which 249 (76.1%) patients were affected. On the other hand, 171 (52.3%) patients had raised in ALT.

Treatment with blood product and colloid infusions

There were three patients who were transfused with blood products in which one patient was transfused with 2 pint packed cell, one patient was transfused with 4 units of fresh frozen plasma and 6 unit of platelet while the other patient was transfused with 1 whole blood and a total of 8 unit of platelets. Two of the patients developed severe dengue. Only two patients were given colloid infusion.

Admission and length of stay

A total of 20 patients were admitted to ICU with length of stay of 2 to 9 days with mean of 3.7 days (SD =2.17). Other patients were admitted to the general ward, and the duration varies from 1 day to 14 days with mean of 3.80 days (SD=1.63).

Day of fever on presentation of fever

The day of fever when patients first presented to any healthcare to seek treatment varies from day 1 of fever to day 10 of fever with median of day 3 and mean 3.30 days (SD=1.54). The median day of fever when patient visited our tertiary centre for treatment was at day 4 of fever with mean 4.41 days (SD =1.59). The median day of fever when patient developed complication of severe dengue was day 4 with mean of 4.09 days (SD=1.88).

Complications of severe dengue infection

The prevalence of severe complication of dengue infection was 66 out of 327 patients (20.2%). The complications comprised of dengue shock syndrome, n= 60 (8.3%), four patients with fluid accumulation with respiratory distress (1.2%), one severe bleeding (0.3%), two patients had elevated AST or ALT >1000 (0.6%), and dengue encephalitis in three patients (0.9%). There was no mortality out of all patients.

[Table 2: Complications of dengue infection]

Factors associated with severe dengue

A logistic regression analysis was used to examine the association between factors associated with severe dengue as summarized in Table 3. Factors included in the analysis were sociodemographic, sign and symptom, and investigation done in ED. Factors with p-value <0.25 from simple logistic regression analysis with clinical significance were included in multivariate logistic regression analysis as summarized in Table 4.

[Table 3: Simple logistic regression for factors associated with severe dengue]

[Table 4: Multiple logistic regression for factors predictive of severe dengue]

From the multivariate analysis, there were significant associations between severe dengue with 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).

3.6 DISCUSSION

In clinical practice, identifications of severe dengue risk factors has its important implications.[17] During an outbreak of dengue infection or dengue endemic, it will help the physicians to prioritize care and anticipate deterioration in managing the patients. It offer clues on which patient may progress to severe dengue and its complications.[18]

In our study there is observed prevalence of severe complications of 20.2%, which is lower than 28.5% from a meta-analysis study by Nguyen et al, where they studied a total of 198 papers where mostly from Asia (n=182) and others from Caribbean, south American and French Polynesia.[17] This lower prevalence probably due to our primary care setting, where index of suspicion is high for dengue infection when patient presented with fever especially from the endemic area, thus laboratory investigations to confirmed dengue infection is done early and diagnosis can be made early as well as its management prior to patient developing severe dengue, which were described in a study by Alexandra et al in 2019 in large tertiary hospital in Malaysia, where all the participants which consists of medical officer had good awareness and knowledge of dengue presentations and diagnosis.[32] Moreover, according to Hasan et al dengue patients can present with vast symptoms and signs, thus clinician can misdiagnosed them as other diseases such as upper respiratory tract infection, acute gastroenteritis and acute abdomen.[10] Study by Bingumal et al shown diagnostic dilemma in acute abdomen cases where dengue fever was not detected early causing surgical morbidity and prolonged hospital day and even mortality.[19] This shown that there may be difference in tendency to suspect and investigate for dengue infection especially in non-endemic country.

From this study we found out that dengue shock syndrome was the most common type of complication in severe dengue with prevalence of 18.3%. This corresponds to dengue fever in its critical phase where increased in capillary permeability may occur in some

patients which can lead to plasma leakage. This phase usually occurred after third day of fever or during defervescence which is evidenced by an abrupt drop in temperature.[16] Contrary to other viral infections where typically the patient's condition improves as the temperature subsides, dengue patients may deteriorate and manifest third space fluid accumulation, organ dysfunction and profound shock during this phase.[16] Coupled with reduced fluid intake due to symptoms such as loss of appetite in which majority of patients had in our study (75.2%) and fluid loss from vomiting or diarrhoea, may explained patient progression into developing dengue shock syndrome.

As an alternative explanation, Guzman et al explained that patients might having secondary dengue virus infections with a different type of dengue virus is risks of DSS.[4] This occurs through a mechanism known as antibody-dependent enhancement (ADE) of dengue virus infection.[4] From a meta-analysis study by Soo et al, it was reported that DENV-2 and DENV-4 from the South East Asia region were associated with secondary infection.[21] In Malaysia, domination of DENV-1 during the years 2014 to 2016 was followed by domination of DENV-2 in 2017, could be seen as a contributing factor to the increase in DSS. In addition, the higher prevalence DENV3-infected patients in 2014 (29.4%) could also be contributing factor for high prevalence of DSS.[22] This possibility is in line with the study by Soo et al.**,** who concluded that primary infection with DENV-3 SEA region and secondary infection with DENV-2, DENV-3, and DENV-4 which were also from the SEA , is a factor for evolution disease into severe dengue.[21]

Other common complications that arises from severe dengue were followed by fluid accumulation with respiratory distress whereby had almost similar pathophysiology as DSS; increased in capillary permeability causing extravasation of fluid, in this case particularly in the lungs. This process may be hastened by inappropriate and over-judicious intravenous fluids therapy, especially during critical and resolution phase

results in heart failure and pulmonary oedema as aftermath.[9] Symptoms of shortness of breath may represent this complication, in which the patients had 5.82 times the odds to developed severe dengue (95% CI =1.37-24.69, *p*-value 0.017).

There is no dengue death in this study. However there is reported 7.79% increment of dengue death each year from 2000 to 2010 in Malaysia.[23] As stated earlier, this may be due to improvement in detection and managing dengue fever in our country.

In this study, most common warning signs for severe dengue identified were gastrointestinal symptoms; highest were vomiting, followed by diarrhoea and epigastric pain. The results were almost similar to other study done previously.[7] Another study shown significant correlation between vomiting and abdominal pain with DSS.[17] In addition, study done in Vietnam shown prevalence of vomiting is higher in severe dengue group. Interestingly, they suggested that vomiting two times or more per day could be a good clinical sign which can predict severe dengue.[24] However out of all symptoms, only shortness of breath were significantly predictive of severe dengue at multivariable analysis. Those with diarrhoea were less likely to develop severe dengue in this study. This is probably due to a higher index of suspicion among the treating doctors in anticipating severe dengue in these patients, therefore more patients with diarrhoea were admitted. A study by Laurent et al also showed association of diarrhoea as a predictor for severe manifestation of dengue.[25]

Clinical examination of a dengue patient is crucial where the physician should look for signs of shock, plasma leakage and complications of severe dengue so that treatment and care could be started earlier and in concordance.[9] We found that patient with tachycardia and hepatomegaly had significant risks to developed severe dengue in our study. Tachycardia can be due hypovolemia due to reduced oral intake or gastrointestinal losses or due to plasma leakage, blood loss in haemorrhagic complication or manifestation of

heart involvement in severe dengue.[10] Higher risks of haemorrhagic complication in patients with hepatomegaly had been demonstrated in a study by Fadilah et al done in an urban area in Malaysia. It had been suggested that liver involvement in dengue viral infection was due to monocyte mobility and host broad immune response where marked activation of immunoregulatory T lymphocyte caused liver dysfunction and even fulminant hepatitis.[8] Meta-analysis study by Huy et al also shown hepatomegaly was strongly associated with DSS.[17]

The effect of age on severity of dengue infection is well known. It is proposed that ageing and waning of immunity response pose potential risks for mortality and morbidity in elderly patients with active infection.[29] However from our study, we noted that different in age is not an indicator for severe dengue. Karunakaran et al founds that age >40 is a risk factor for mortality ($p = 0.002$).[26] 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. According to Tee HP et al older age group was 2.37 times more likely to develop Dengue Haemorrhagic Fever (DHF)/Dengue Shock Syndrome (DSS) compared to the younger age group.[30]

Similar to a study done in a tertiary centre in Klang by Jamaiah et al, there were more males contracted with dengue fever compared to females. This can be explained due to the fact that males are generally more mobile and socially more interactive than females and tend to travel to high risks area especially for work purposes, causing them to be more susceptible to be infected.[20] On the hand, a study by Tee Hp et al in Kuantan showed more female patients with dengue infection, most likely due to their inclusions of paediatric patients, whereby their limited mobility results in no gender difference for susceptibility in paediatrics.[30]

Contrary to other viral infections where typically the patient's condition will improve as the temperature subsides, dengue patients may deteriorate and manifest third space fluid accumulation, organ dysfunction and even profound shock during this phase.[16] In our study however, physical examination signs of increased capillary permeability such as ascites and pleural effusion were not significantly associated with severe dengue. This contradict many other studies that showed otherwise. In a study for example, it was stated that all of the plasma leakage signs (pleural effusion, haemoconcentration, ascites, hypoproteinaemia and hypoalbuminemia), were strongly associated with DSS.[17] This may be due to only two samples had these signs in this study.

Limitation of our study includes missing data; such as height of patient was not documented in patients case note thus body mass index (BMI) can't be measured. This is a single centred study in a tertiary centre hospital, where usually treat and catered patients with more severe presentations unlike in government health clinic with more mild cases. In the future we may need another study which included cases from other facilities such as local health clinic as samples to have better picture of the presentation and complications of dengue fever in Kelatan population.

CONCLUSION

Our study provides information which may aid the physicians especially from emergency department to tailor their interventions more effectively as dengue patients can present with various chief complaints and presentations and at any stage and progression. It is crucial for physician to identify patients that may progress to severe dengue and its complications in timely manner, so it can be halted by appropriate treatment and care. Clinical Practice Guidelines from MOH provides clinician with criteria for hospital admission/referral which adopted from the 2009 WHO guidelines, which utilised dengue warning signs, such as epigastric pain, persistent diarrhoea, persistent vomiting, lethargy

and others.[5] WHO guidelines also recommend the usage of warning signs as a gauge of disease course as the patient either deteriorate to severe dengue or recuperated with treatment. From our study, we concluded that out of dengue warning signs criteria, shortness of breath, diarrhoea, tachycardia and hepatomegaly were predictors for severe dengue. We recommend clinicians to be more attentive and meticulous in treating this group of dengue patients and provide close monitor nursing care as they may progress to severe dengue. From this study, the majority of its outcome or complication was dengue shock syndrome. It is advisable for clinician to have good knowledge and awareness of fluid therapy in DSS as per CPG by MOH and preparation such as Dengue Unit or acute treatment setting in intensive care unit or high dependency unit specialised for dengue patient to be made available. With this information, it is hope that it will ease physician to identify potential of dengue patient who may develop severe dengue and its complications in future outbreak, so that they can prioritize care and anticipate deterioration and complications.

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3.9 DECLARATION OF CONFLICTING INTERESTS

We declare that there was no conflict of interests to the study, authorship and/or publication of this article.

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3.11 REFERENCES

1. Pang, Ee Leen & Loh, Sandy Hwei-San. (2016). Current perspectives on dengue episode in Malaysia. Asian Pacific Journal of Tropical Medicine. 9. 10.1016/j.apjtm.2016.03.004
2. Cheah, Wee-Kooi & Ng, Zicheng & Marzilawati, AR & Lum, Lucy. (2014). A review of dengue research in Malaysia. The Medical journal of Malaysia. 69 Suppl A. 59-67.
3. Guha-Sapir D. & Schimmer B. Dengue fever: new paradigms for a changing epidemiology. *Emerg Themes Epidemiol*. 2005;2(1):1. Published 2005 Mar 2. doi:10.1186/1742-7622-2-1
4. Guzman MG, Halstead SB, Artsob H, Buchy P, Farrar J, Gubler DJ, Hunsperger E, Kroeger A, Margolis HS, Martínez E, Nathan MB, Pelegrino JL, Simmons C,Yoksan S, Peeling RW.Dengue: a continuing global threat. Nat Rev Microbiol. 2010 Dec;8(12 Suppl):S7-16. doi: 10.1038/nrmicro2460. PMID: 21079655; PMCID: PMC4333201.
5. Nor, D.A.T.M., et al., CPG Management of Dengue Infection In Adults Clinical Practice Guideline MOH/P/PAK/302.15(GU), 2015. **Third edition**(2015): p. 82.
6. WHO (2017). Dengue and severe dengue (Fact sheet Updated April 2017) https://apps.who.int/mediacentre/factsheets/fs117/en/index.html (accessed 26 October 2020)

7. Mohd Hanief Ahmad, M.I.I., Zeehaida Mohamed, Nabilah Ismail, Muhammad Amiruddin Abdullah, Rafidah Hanim Shueb, Mohd Nazri Shafei, The Sensitivity, Specificity and Accuracy of Warning Signs in Predicting Severe Dengue, the Severe Dengue Prevalence and Its Associated Factors. international journal of enviromental resarch and public health, 2018. **15**(9).

8. S Fadilah SAW, Sahrir S, Mazlam MZ, Raymond AA (2000) A com-parison of the pattern of liver involvement in dengue hemorrhagic fever with classic dengue fever. Southeast Asian J Trop Med Public Health 31: 259–263

9. Rajapakse S, Rodrigo C, Rajapakse A. Treatment of dengue fever. *Infect Drug Resist*. 2012;5:103-112. doi:10.2147/IDR.S22613

10. Hasan S, Jamdar SF, Alalowi M, Al Ageel Al Beaiji SM.2016. Dengue virus: A global human threat: Review of literature. *J Int Soc Prev Community Dent*. 2016;6(1):1-6. doi:10.4103/2231-0762.175416

11. WHO (2020). Dengue and severe dengue (Fact sheet Updated 23 June 2020).https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue (accessed 26 October 2020)

12. MOH, 2020. Malaysian Health at a glance 2018. Ministry of Health Malaysia 2019

13 Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emerg Med J. 2003 Jan;20(1):54-60. doi: 10.1136/emj.20.1.54. PMID: 12533370; PMCID: PMC1726024.

14. Setia MS. (2016). Methodology series module 3: Cross-sectional studies. Indian J Dermatol. 2016. 61:261–264.doi: 10.4103/0019-5154.182410: 10.4103/0019-5154.182410PMCID: PMC4885177PMID: 27293245

15. MOH (2015). Ministry of Health Malaysia clinical practice guidelines MOH/P/PPK/302.15(GU): Management of Dengue Infections in Adults (3rd Ed.). Ministry of Health Malaysia & Academy of Medicine Malaysia. 70pp.

16 WHO. Dengue Guidelines for Diagnosis, Treatment, Prevention and Control; WHO: Geneva, Switzerland, 2009. pp148o

17. Huy, N.T., et al., Factors associated with dengue shock syndrome: a systematic review and meta-analysis. PLoS Negl Trop Dis, 2013. **7**(9): p. e2412.

18. H. Zhang, Y. P. Zhou, H. J. Peng, X. H. Zhang, F. Y. Zhou, Z. H. Liu, X. G. Chen "Predictive Symptoms and Signs of Severe Dengue Disease for Patients with Dengue Fever: A Meta-Analysis" *BioMed Research international,* Vol. 2014, Article ID 359308, 10 pages, 2014. https://doi.org/10.1155/2014/359308

19. Jayasundara B, Perera L, Ajith de Silva, Dengue fever may mislead the surgeons when it presents as an acute abdomen, Asian Pacific Journal of Tropical Medicine,
Volume 10, Issue 1 (2017) Pages 15-19,ISSN 1995-7645,
https://doi.org/10.1016/j.apjtm.2016.12.010.

20. Ibrahim, Jamaiah & Rohela, M & Nissapatorn, Veeranoot & Maizatulhikma, M & Norazlinda, R & Syaheerah, H & Tan, H. (2005). Prevalence of dengue fever and dengue hemorrhagic fever in Hospital Tengku Ampuan Rahimah, Klang, Selangor, Malaysia. The Southeast Asian journal of tropical medicine and public health. 36 Suppl 4. 196-201.

21. Soo KM, Khalid B, Ching SM, Chee HY. Meta-Analysis of Dengue Severity during Infection by Different Dengue Virus Serotypes in Primary and Secondary Infections. PLoS One. 2016 May 23;11(5):e0154760. doi: 10.1371/journal.pone.0154760. PMID: 27213782; PMCID: PMC4877104

22. Suppiah J, Ching S-M, Amin-Nordin S, Mat-Nor L-A, Ahmad-Najimudin N-A, Low GK-K, et al. (2018) Clinical manifestations of dengue in relation to dengue serotype and genotype in Malaysia: A retrospective observational study. PLoS Negl Trop Dis 12(9): e0006817. https://doi.org/10.1371/journal.pntd.0006817

23. Mia, M.S., et al., Trends of dengue infections in Malaysia, 2000-2010. Asian Pacific Journal of Tropical Medicine, 2013. **6**(6): p. 462-466

24. Vuong NL, Manh DH, Mai NT, et al. Criteria of "persistent vomiting" in the WHO 2009 warning signs for dengue case classification. *Trop Med Health*. 2016;44:14. Published 2016 May 16. doi:10.1186/s41182-016-0014-9

25. Thomas, Laurent & Brouste, Yannick & Najioullah, Fatiha & Hochedez, Patrick & Hatchuel, Yves & Moravie, Victor & Kaidomar, Stéphane & Besnier, François & Abel, Sylvie & Rosine, Jacques & Quénel, Philippe & Cesaire, Raymond & Cabié, André. (2010). Predictors of severe manifestations in a cohort of adult dengue patients. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 48. 96-9. 10.1016/j.jcv.2010.03.008.

26. Karunakaran, A., et al., Risk factors of mortality among dengue patients admitted to a tertiary care setting in Kerala, India. J Infect Public Health, 2014. **7**(2): p. 114-20.

27. Thein T-L, Gan VC, Lye DC, Yung C-F, Leo Y-S (2013) Utilities and Limitations of the World Health Organization 2009 Warning Signs for Adult Dengue Severity. PLoS Negl Trop Dis 7(1): e2023. https://doi.org/10.1371/journal.pntd.0002023

28. Samanta J, Sharma V. Dengue and its effects on liver. *World J Clin Cases*. 2015;3(2):125-131. doi:10.12998/wjcc.v3.i2.125

29. Rowe, Emily & Leo, Yee & Wong, Joshua & Thein, Tun Linn & Gan, Victor & Lee, Linda & Lye, David. (2014). Challenges in Dengue Fever in the Elderly:

Atypical Presentation and Risk of Severe Dengue and Hospital-Acquired Infection. PLoS neglected tropical diseases. 8. e2777. 10.1371/journal.pntd.0002777.

30. Tee, H.P., et al., Risk factors associated with development of dengue haemorrhagic fever or dengue shock syndrome in adults in Hospital Tengku Ampuan Afzan Kuantan. Medical Journal of Malaysia, 2009. **64**(4): p. 263-267

31. Anders, K.L., et al., Epidemiological factors associated with dengue shock syndrome and mortality in hospitalized dengue patients in Ho Chi Minh City, Vietnam. Am J Trop Med Hyg, 2011. **84**(1): p. 127-34.

32. Wharton-Smith, A., Green, J., Loh, E.C. *et al.* Using clinical practice guidelines to manage dengue: a qualitative study in a Malaysian hospital. *BMC Infect Dis* **19,** 45 (2019). https://doi.org/10.1186/s12879-019-3680-5

TABLES

Table 1 : Sociodemographic characteristic, clinical presentation, investigations and treatment of patient with dengue infection

Variables	Category	Dengue fever ± warning sign, n (%)* n=261	Severe dengue, n (%)* n=66	Total n (%)* N=327
Age (years), mean (SD)		32.77 (15.42)	30.33 (14.94)	32.28 (15.34)
Weight (kg), mean (SD)		61.87 (14.33)	55.79 (14.10)	60.64 (14.47)

Gender	Female	124 (47.5)	36 (54.5)	160 (48.9)
	Male	137 (52.5)	30 (45.5)	167 (51.1)
Race	Malay	255 (97.7)	65 (98.5)	320 (97.9)
	Non-Malay	6 (2.3)	1 (1.5)	7 (2.1)
Symptoms at presentation				
Epigastric pain		89 (34.1)	18 (27.3)	107 (32.7)
Shortness of breath		4 (1.53)	5 (7.57)	9 (2.8)
Nausea		79 (30.3)	18 (27.3)	97 (29.8)
Vomiting		149 (57.1)	33 (50.0)	182 (55.7)
Diarrhoea		113 (43.3)	18 (27.3)	131 (40.1)
Petechial rash		33 (12.6)	7 (10.6)	40 (12.2)
Loss of appetite		195 (74.7)	51 (77.3)	246 (75.2)
Signs at presentation				
Hypotension		0 (0.0)	15 (22.7)	15 (4.6)
Tachycardia		70 (26.8)	32 (48.5)	102 (31.2)
Tachypnoeic		5 (1.92)	4 (6.1)	9 (2.8)
Fever		172 (65.9)	43 (65.2)	215 (65.7)
Prolonged capillary refill time		4 (1.5)	11 (16.7)	15 (4.6)
Reduced pulse volume		3 (1.1)	7 (10.6)	10 (3.1)
Cold peripheries		8 (3.1)	8 (12.1)	16 (4.9)
Hepatomegaly		25 (9.6)	12 (18.2)	37 (11.3)
Pleural effusion		1 (0.4)	0 (0.0)	1 (0.3)
Ascites		1 (0.4)	0 (0.0)	1 (0.3)
Investigations on admission				
IgG antibodies	Positive	38 (14.6)	8 (12.1)	46 (14.1)
	Negative	223 (85.4)	58 (87.9)	281 (85.9)
Platelet	<35,000	21 (8.0)	5 (7.6)	26 (8.0)
	≥35,000	240 (92.0)	61 (92.4)	301 (92.0)
HCT	Normal	193 (73.9)	55 (83.3)	248 (75.8)
	Raised	68 (26.1)	11 (16.7)	79 (24.2)
AST	Normal	54 (20.7)	24 (36.4)	78 (23.9)
	Raised	207 (79.3)	42 (63.6)	249 (76.1)
ALT	Normal	119 (45.6)	37 (56.1)	156 (47.4)
	Raised	142 (54.4)	29 (43.9)	171 (52.3)

Treatment			
Blood product transfusion	1 (0.4)	2 (3.0)	3 (0.9)
Colloid infusion	1 (0.4)	1 (1.5)	2 (0.6)

* n (%) for categorical variables, mean (SD) for numerical variables.
Abbreviation: SD = Standard Deviation, AST = Aspartate Transferase, ALT = Alanine Transferase, CNS = Central nervous system, HCT = Haematocrit, IgG = Immunoglobulin G, kg = kilogram

Table 2: Complications of severe dengue infection

Variables	Category	**N = 327**
Prevalence of severe complications of dengue infection		66 (20.2%)
Type of complication	Dengue shock syndrome	60 (18.3%)
	Respiratory distress	4 (1.2%)
	Severe bleeding	1 (0.3%)
	Liver AST or ALT > or 1000	2 (0.6%)
	Dengue encephalitis	3 (0.9%)
	Cardiac complication	3 (0.9%)
	Death	0 (0.0%)

Abbreviations: AST = Aspartate Transferase, ALT = Alanine Transferase, CNS = Central nervous system

Table 3: Simple logistic regression for factors associated with severe dengue

Variables	Regression coefficient, b	Wald (df)	Crude OR (95% CI)	p-value
Age	-0.006	0.382 (1)	1.00 (0.98- 1.01)	0.248
Gender				
Male	0	1		
Female	-0.282	1.040 (1)	0.75 (0.44 – 1.30)	0.308

Race				
Non-Malay	0	1		
Malay	0.425	0.152 (1)	1.53 (0.18 – 12.92)	0.696
Symptoms at presentation				
Epigastric pain	-0.322	1.109 (1)	0.73 (0.40 – 1.32)	0.292
Shortness of breath	1.661	5.869 (1)	5.27 (1.37 – 20.20)	0.015
Nausea	-0.125	0.165 (1)	0.88 (0.48 – 1.61)	0.685
Vomiting	-0.248	0.793 (1)	0.78 (0.45 – 1.38)	0.373
Diarrhoea	-0.696	5.248 (1)	0.50 (0.28 – 0.90)	0.022
Petechial rash	-0.199	0.203 (1)	0.82 (0.35 – 1.95)	0.652
Loss of appetite	-0.280	0.657 (1)	0.76 (0.39 - 1.49)	0.418
Signs at presentation				
Tachycardia	1.124	11.704 (1)	3.08 (1.62 - 5.86)	0.001
Tachypnoea	0.043	0.012 (1)	1.04 (0.49 – 2.21)	0.911
Fever	0.143	0.983 (1)	1.15 (0.87 - 1.53)	0.321
Hepatomegaly	0.741	3.757 (1)	2.10 (0.99 – 4.44)	0.053
IgG antibodies positive	-0.053	0.017 (1)	0.95 (0.43 - 2.09)	0.896
Platelet <150,000	0.593	4.223 (1)	1.81 (1.03 – 3.18)	0.040
HCT raised	-0.097	8.544 (1)	0.38 (0.20 – 0.73)	0.003
AST raised	-0.774	5.830 (1)	0.46 (0.25 – 0.86)	0.016
ALT raised	0.001	0.894 (1)	1.00 (0.99 - 1.00)	0.344

Abbreviations: AST = Aspartate Transferase, ALT = Alanine Transferase, CNS = Central nervous system, OR = Odd Ratio, HCT = Haematocrit, IgG = Immunoglobulin G,

Table 4: Multiple logistic regression for factors predictive of severe dengue

Variables	Regression coefficient (b)	Adjusted odd ratio (95% CI)	p-value
Shortness of breath			
No	0	1	
Yes	1.762	5.82 (1.37-24.69)	0.017
Diarrhoea			
No	0	1	
Yes	-0.712	0.49 (0.27-0.91)	0.023
Tachycardia			
No	0	1	
Yes	1.049	2.85 (1.59-5.10)	0.001
Hepatomegaly			
No	0	1	
Yes	1.016	2.76 (1.24 – 6.18)	0.013

Abbreviation: AOR Adjusted Odd Ratio; CI Confidence Interval.

Constant = -1.733

Forward and Backward LR method was applied

No multicollinearity and no interaction

Hosmer Lemeshow test, p-value=0.988

Classification table 80.7% correctly classified

Area under Receiver Operating Characteristic (ROC) curve was 80.7%

3.14 JOURNAL FORMAT

HONG KONG JOURNAL OF EMERGENCY MEDICINE

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APPENDICES

Appendix A: Data Collection Proforma

1. Study ID		
2. Age		
3. Gender	Male ☐	Female ☐
4. Race	Malay ☐ Chinese ☐ Indian ☐ Others:_____	
5. BMI	Height:_____ Weight: _____	BMI: _____ Obese / Non-obese
6. Comorbidity Yes ☐ No ☐	Hypertension ☐ Diabetes mellitus ☐ Heart failure ☐	Liver failure ☐ Renal failure ☐ Anemia ☐
7. Day of fever on presentation	Day of fever on 1st presentation to healthcare: _____ Day of fever on presentation to HUSM: _____	
8. Symptoms on presentation (Yes/No/Not stated)	Epigastric pain Y / N / NS	Nausea Y / N / NS
	Vomiting Y / N / NS	Diarrhea Y / N / NS
	Petechial rash Y / N / NS	Shortness of breath Y / N / NS

	Headache Y / N / NS	URTI Y / N / NS	
	Lethargy Y / N / NS	LOA Y / N / NS	
	If atypical: lethargy / Syncope / Others:		
9. Clinical features and examinations (Yes/No/Not stated)	Blood pressure	Poor pulse volume Y / N / NS	
	Pulse rate	Cold peripheries Y / N / NS	
	Respiratory rate	Hepatomegaly Y / N / NS	
	Temperature	Pleural effusion Y / N / NS	
	Prolonged CRT Y / N / NS	Ascites Y / N / NS	
10. Investigation *taken on day of presentation	NS1 Positive/Neg	IgM Ab Positive/Neg	IgG Ab Positive/Neg
	Platelet	Hb	Hct
	Hct: Raised / Normal / Low	Hct fluctuation>20% Y / N	
	AST	ALT	
	IVC collapsibility index:		
11. Stay in ED more than 6 hours? Yes / No			
12. Treatment	IV Fluid given in ED: Yes / No -First 3 hours _____ crystalloid/_____colloid -First 6 hours _____ crystalloid/_____colloid		
	Colloid given (any time): Yes / No		
	Blood product given: Yes / No		

	PC	FFP	Others
	Intubation: Yes / No		
13. Admission Yes ☐ No ☐ *admission include admission to Observation ward ED	Length of stay i. ICU/HDW (day) ii. General ward (day) iii. Observation ward ED (hours) iv. Total		
14. Complication Yes ☐ No ☐	☐ Shock (DSS) ☐ Fluid accumulation with respiratory distress ☐ Ascites ☐ Severe bleeding: specify _____ ☐ Severe organ involvement Liver AST or ALT > or 1000 AST level _____/ ALT level _____ CNS impaired consciousness Heart:_____ Other organs:_____ ☐ Death (Day of illness at death:_____) ☐ Others, specify: _____		
	Day of illness at first occurance of severe dengue:		

Appendix B: Raw Data in SPSS Format (CD)