AN OBSERVATIONAL STUDY OF FACTORS ASSOCIATED WITH DENGUE OUTCOMES IN INTENSIVE CARE UNIT

SEE CHANG SENG

FACULTY OF MEDICINE
UNIVERSITY OF MALAYA
KUALA LUMPUR

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UNIVERSITY OF MALAYA

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Name of Candidate: See Chang Seng

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ABSTRACT

In Malaysia, dengue fever is one of the major public health problem which has had significant impact on socio-economic and health resources especially when involving intensive care unit (ICU) stay. This study aimed to determine the factors associated with outcomes in those dengue patients who admitted to ICU. This was a retrospective observational study of patients in a tertiary level state hospital in Malaysia, between Jan 1 and Dec 31 2017. Patients with confirmed dengue diagnosis were stratified into 2 groups based on ICU stay (≤ 3 days or > 3 days) and mortality (fatal and non-fatal cases). Socio-demographic, clinico-laboratory data and therapeutic parameters between these groups were compared by using appropriate statistical analysis method. Total 140 patients were included in this study with mean length of ICU stay 3.79+2.47 days. Mortality rate among these patients was 7.8% and prolonged stay was seen in 36.4% studied patients. Factors including age > 50 years old, pre-existing diabetes mellitus and hypertension, higher number of co-morbidities, prolonged prothrombin time and activated partial thromboplastin time, thrombocytopenia, hypoalbuminemia, increased creatinine, alanine aminotransferase and aspartate aminotransferase level, and dialysis support were common seen in non-survivors. However, multiple logistic regression analysis showed only number of co-morbidities (OR 2.6, 95% CI 1.26 to 5.38, p-value 0.009) and aspartate aminotransferase (AST) level (OR 1.0, 95% CI 1.0-1.01, p-value 0.001) were found independently significant factors associated with dengue mortality. Meanwhile, patients having severe dengue, pre-existing blood disorder, increased number of co-morbidities, renal impairment, mild thrombocytopenia, required intubation or inotropic support were significantly associated with prolonged ICU stay. However, only female gender (OR 0.36, 95% CI 0.14 to 0.90, p-value 0.029) and elevation of activated partial thrombin time

2 times above normal value (OR 0.11, 95% CI 0.02 to 0.66, p-value 0.015) were found to be independently significant related to ICU stay duration. In conclusion, early recognition of risk factors associated with prolonged ICU stay and mortality among dengue fever patients can help in early decision making for ICU admission. Hence early aggressive care and organ support from ICU on higher risk patients can help in decreasing dengue morbidity and mortality.

Keywords: dengue fever, ICU, length of stay, mortality, dengue outcome

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LIST OF SYMBOLS AND ABBREVIATIONS

AKI	Acute kidney injury
AKIN	Acute kidney injury network
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CFR	Case fatality rate
CPG	Clinical practice guideline
CRRT	Continuous renal replacement therapy
CVA	Cerebral vascular accident
DF	Dengue fever
DM	Diabetes mellitus
GCS	Glasgow coma scale
HD	Hemodialysis
HTJ	Hospital Tuanku Jaafar
HTN	Hypertension
ICB	Intracranial bleed
ICU	Intensive care unit
LGIB	Lower gastrointestinal bleed
PT	Prothrombin time
SLED	Sustained low efficiency dialysis
UGIB	Upper gastrointestinal bleed

LIST OF APPENDICES

CHAPTER 1: INTRODUCTION

Dengue is the most rapidly spreading arthropod-borne disease in the world. According to World Health Organization (WHO)[1], there are more than 70% of population at risk for dengue live in South-East Asia Region & Western Pacific Region. Bhatt et al[2] estimate there to be 390 million of dengue infections per year, which is more than 3 times the dengue burden estimated by WHO.

In Malaysia, dengue fever is one of the major public health problem with high mortality and morbidity. In year 2017, Malaysia[3] had reported 83849 dengue cases nationwide with 177 deaths (CFR 0.21%). According to Malaysian Registry of Intensive Care (MRIC) report[4], dengue is the most common diagnosis leading to ICU admission for year 2014 & 2015, 3rd most common for year 2016. In year 2016[5], there were total 2760 dengue fever patients admitted to ICU which contributed to in-hospital mortality rate of 8.5%.

There are few studies[6-12] done in oversea to determine the factors associated with outcome among dengue patients who admitted to ICU. Those factors are including old age, acute kidney injury, acute respiratory failure, hepatitis, altered mental status, bleeding and coagulopathy. However, we are lack of similar study in Malaysia. Hence this study aims to determine the factors associated with dengue-related outcomes in those patients who admitted to ICU.

CHAPTER 2: LITERATURE REVIEW

In Malaysia, according to study done by Mallhi TH et al[13] showed prolong PT & aPTT, multiple organs dysfunction and diagnosis of dengue hemorrhagic fever associated with prolonged length of hospital stay. Meanwhile, there are another 9 factors associated with dengue mortality, included age >40 years, secondary infection, co-morbidities, acute kidney injury, prolonged PT, multiple organs dysfunction, hematocrit > 20%, rhabdomyolysis and respiratory failure in above study. However, this study included all dengue fever patients that admitted to hospital and not merely focus on those admitted to ICU. Next, WHO 1997 dengue classification was used in above study and not according to the latest 2009 WHO dengue classification.

Another study done by Pang, J et al[14] showed age >60 years, diabetes mellitus, cardiac disorder, asthma and having 2 or more pre-existing co-morbidities were independent factors of severe organ involvement in dengue patients. Meanwhile Deven J et al[6] showed the most common organ failure in ICU dengue patients was coagulation followed by respiratory failure which is similar to 2015 MRIC report[4].

As there was a dengue outbreak in Taiwan at year 2015 hence many studies were done to determine the predictor factors for dengue fever outcome. Hsieh C-C et al[8] showed that prolonged aPTT and organ failure (included cardiac and renal failure) were independent factors for in-hospital mortality. It was further supported by Yeh C-Y et al[10] which showed increasing age, respiratory distress, altered consciousness and thrombocytopenia at the time of admission were associated with dengue mortality. Another similar study by

Chen C-M et al[11] showed that ICU dengue mortality was significantly associated with low GCS, low platelet count before discharge and increased number of organs failure.

Generally, there is well known that low albumin level on admission will increase mortality rate if not corrected before discharge home. Amancio FF et al[7] showed that dengue fatality cases were not only associated with lower serum albumin concentration but also elder age and higher serum creatinine level. However, according to Lee LK et al[15] although liver enzymes elevated in conjunction with dengue severity but AST and ALT value did not discriminate between severe dengue and non-severe dengue.

In conclusion, early recognition of risk factors associated with prolonged ICU stay and mortality can help in early decision for requirement of ICU admission. Early aggressive care and organ support from ICU on higher risk patients can decrease the dengue morbidity and mortality.

CHAPTER 3: METHODOLOGY

3.1 Ethical Concern

This study adhered to the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline and was approved by the Medical Research & Ethics Committee (MREC), Ministry of Health (NMRR number-18-1053-41637). All data were analysed retrospectively and, hence, informed consent was not required.

3.2 Study Location and Population

This study was conducted in Hospital Tuanku Jaafar (HTJ), a tertiary-level teaching hospital with 1070 beds that serves population of state Negeri Sembilan, Malaysia. It is a referral centre for all district hospitals, community clinics & private hospitals in the state. Total 8 ICU beds available in HTJ during the study was conducted.

The medical records of all patients with dengue fever who admitted to ICU HTJ from 1 Jan 2017 until 31 Dec 2017 were reviewed. Data of the cases were retrieved and specific numeral codes were given to each case before data analysis. Identity of all patients was not disclosed in this study.

The diagnosis of dengue was confirmed either by Dengue Immunoglobulin M Enzyme-Linked Immunosorbent Assay (IgM ELISA) or ELISA Dengue specific Non-Structural protein 1 (NS1) Antigen test. Serologically confirmed dengue patients were classified into Dengue Fever (DF) without warning signs, DF with warning signs and Severe Dengue, according to 2009 WHO classification[1].

Usually severe dengue patients have hospital stay between 3 and 4 days[6,8], therefore >3 days is used as cut-off point for prolonged ICU stayed. Patients having ICU stayed less or equal to 3 days were compared with those staying > 3 days in order to determine possible risk factors of increased duration of hospitalization. Similarly, all patients were divided into fatal & non-fatal cases and their socio-demographic, clinic-laboratory data and therapeutic parameters were compared.

3.3 Definitions

Terms used in this study were defined as follows.

Prolonged ICU stayed (> 3 days); Actual body weight (in kg); Type of co-morbidities (DM, HTN, cardiac disease, lung disease, liver disease, renal and blood disorder); Dengue classification (DF with warning signs and severe dengue based on 2009 WHO classification[1]); Cardiac impairment (included acute coronary syndrome, myocarditis, cardiac arrhythmia and inotropic support); Lung impairment (included pleural effusion, pneumonia and non-invasive or invasive ventilation support); Liver impairment (elevated liver enzymes); Renal impairment (elevated creatinine level or dialysis support); Bleeding (included UGIB, LGIB, unprovoked gum bleeding, epistaxis and coagulopathy); Neurology impairment (included CVA, ICB and encephalopathy); Metabolic acidosis was defined as a pH 7.30 or a base deficit $\geqslant$5.0 mEq/L; Oxygen support (room air, nasal prong, face mask, non-invasive & invasive ventilation support); Platelet count on admission (severe thrombocytopenia <20, moderate thrombocytopenia 20-69, mild thrombocytopenia 70-150, normal>150 x 10^9 cells); Albumin level on admission (normal 35-45 g/L, mild hypoalbuminemia 25-34 g/L, marked

hypoalbuminemia < 25 g/L); Prolonged prothrombin time (PT> 14.3 sec); Prolonged activated partial thromboplastin time (normal 30.4-43.7, 1x above normal 43.9-87.4, 2x above normal 87.5-131.1, 3x above normal > 131.1 sec); Creatinine level on admission (based on AKIN classification- normal < 114 µmol/L, AKIN I 114-228 µmol/L, AKIN II 229-342 µmol/L, AKIN III > 342 µmol/L); Highest AST level throughout admission (normal <45 u/L, mild 45-225 u/L, moderate 226-450 u/L, severe > 450 u/L); Highest ALT level throughout admission (normal < 49 u/L, mild 49-245 u/L, moderate 246-490 u/L, severe > 490 u/L); Dialysis support (HD, SLED, CRRT)

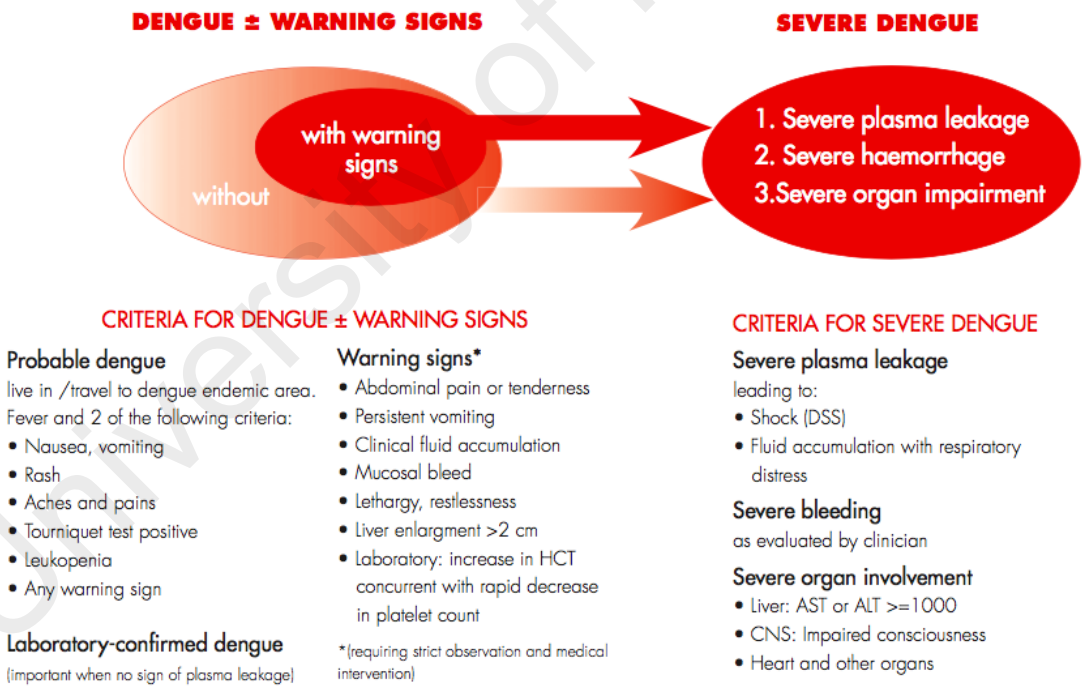

Figure 3.1 2009 WHO Dengue Classification and Level of Severity

3.4 Statistical Analysis

Data obtained from this study was analysed using a statistical package for social sciences, SPSS version 25.0 to make inference and draw robust conclusions. In brief, descriptive statistics of the socio-demographic characteristics were initially done to evaluate the distribution, normality and homogeneity of the data. Frequency and percentage was reported for distribution of categorical variables and Chi Square Test was used to determine homogeneity of the data. Continuous variables were reported as Mean ± Standard Deviation (SD) and Independent t Test was used to determine homogeneity of the data.

Both Simple Logistic Regression Analysis (univariable analysis) and Multiple Logistic Regression Analysis (multivariable analysis) were performed to identify the associated factors that contribute to the prolonged ICU stay and dengue mortality in HTJ. The simple Logistic Regression analysis is a univariable analysis that gives a preliminary idea which variables were identified as the potential significant associated factor. These potential factors were chosen on the basic of statistical significance. The strength of association was evaluated using an OR and a 95% CI. The variables with univariate p value < 0.25 included in Multiple Logistic Regression analysis. The advantage of using univariate p value < 0.25 enable to include more variables in multivariable analysis while traditional levels of p value such as 0.05 fail in identifying variable known to be important. The two-sided statistical significance level, p value, was set at 0.05 for all inferential analyses in this study.

CHAPTER 4: RESULTS

4.1 Descriptive

140 patients with mean age 38.1+17.6 years were included in this study during 1 year duration. Males accounted for 57.1% of the patients (Table 4.3).

The most common co-morbidities included hypertension (25%), diabetes mellitus (18.6%) followed by cardiac and renal disease 5% respectively. There were also total 9 pregnant women admitted to ICU HTJ due to dengue fever. Twenty-five (17.9%) patients were classified as having dengue fever with warning signs, and another 115 (82.1%) classified as severe dengue at ICU admission according to the 2009 WHO dengue classification[1].

In this study, 104 (74.2%) had liver impairment with 54 (24.3%) and 37 (28.5%) patients had marked elevated AST and ALT level more than 10-folds normal value respectively. Sixteen (11.4%) patients had marked hypoalbuminemia (serum albumin < 25 g/L) on admission. Ninety-nine (70.7%) patients developed lung impairment during ICU admission which had included pleural effusion and pneumonia. Approximately 58% patients required ventilator support (65 patients for non-invasive ventilator support, and another 17 patients were intubated). Metabolic acidosis occurred at 85 (60.7%) patients during ICU admission.

There are 34 (24.3%) patients had cardiac impairment included myocarditis, acute coronary syndrome and cardiac arrhythmia. One-fifth (28, 20%) patients required inotropic support during stay. Twenty-one (15%) patients suffered from renal impairment where among these 12 patients required dialysis support. Renal impairment was classified

based on serum creatinine level on admission by referring to AKIN classification. 3 types of dialysis support were offered to those patients which had included HD, SLED and CRRT.

Similarly, there were 21 (15%) patients developed bleeding during ICU admission, included UGIB, LGIB, unprovoked gum bleeding and epistaxis. Approximately three quarter (103, 73.5%) patients developed moderate to severe thrombocytopenia when first presented to ICU. There was only 32 (22.9%) patients had prolonged PT but more than three quarter (196, 75.7%) had prolonged aPTT 1-2-folds above normal value. There were total 7 (5%) patients had neurological impairment in this study, included cerebral vascular accident, intracranial bleed or encephalopathy.

The mean length of ICU stay was 3.79+2.47 days. Prolonged ICU stay (>3 days) was seen in 36.4% (n=51/140) studied patients (Table 4.2). Mortality rate among ICU dengue fever patients in this study was 7.9% (n=11/140) (Table 4.1).

Table 4.1: Distribution of the patients based on the dengue mortality

Outcome	**Frequency (%)**
Alive	129 (92.1)
Dead	11 (7.9)

Table 4.2: Distribution of the patients based on the length of ICU stay

Outcome	**Frequency (%)**
≤ 3 days	89 (63.6)
> 3 days	51 (36.4)

Table 4.3: Comparison of variables associated with dengue mortality

Variables	Total Cohort (n=140)	Alive (n=129)	Dead (n=11)	p-value
Age, Mean±SD	38.11±17.59	36.7±17.1	54.8±15.5	0.001
10-29	51 (36.4%)	50 (38.8%)	1 (9.1%)	
30-39	29 (20.7%)	28 (21.7%)	1 (9.1%)	0.001
40-49	22 (15.7%)	22 (17.1%)	0 (0.0%)	
50-59	20 (14.3%)	15 (11.6%)	5 (45.5%)	
>60	18 (12.9%)	14 (10.8%)	4 (36.3%)	
Gender				
Male	80 (57.1%)	74 (57.4%)	6 (54.5%)	>0.999
Female	60 (42.9%)	55 (42.6%)	5 (45.5%)	
Weight, Mean±SD	69.98 ± 20.76	69.9±21.5	71.5±9.8	0.807
No. of Co-morbidities				
0	86 (61.4%)	84 (65.1%)	2 (18.2%)	
1	20 (14.3%)	18 (14.0%)	2 (18.2%)	
2	21 (15.0%)	16 (12.4%)	5 (45.5%)	0.005
3	8 (5.7%)	7 (5.4%)	1 (9.1%)	
4	5 (3.6%)	4 (3.1%)	1 (9.1%)	
Diabetes Mellitus	26 (18.6%)	21 (16.3%)	5 (45.5%)	0.032
Hypertension	35 (25.0%)	27 (20.9%)	8 (72.7%)	0.001
Cardiac Disease	7 (5.0%)	6 (4.7%)	1 (9.1%)	0.443
Lung Disease	5 (3.6%)	5 (3.9%)	0 (0.0%)	>0.999
Liver Disease	5 (3.6%)	4 (3.1%)	1 (9.1%)	0.340
Renal Disease	7 (5.0%)	6 (4.7%)	1 (9.1%)	0.443
Blood Disorder	6 (4.3%)	6 (4.7%)	0 (0.0%)	>0.999
Pregnancy	9 (6.4%)	9 (7.0%)	0 (0.0%)	>0.999
Dengue Classification				
DF with Warning Signs	25 (17.9%)	25 (19.4%)	0 (0.0%)	0.213
Severe Dengue	115 (82.1%)	104 (80.6%)	11 (100%)	
Cardiac Impairment	35 (25.0%)	24 (18.6%)	11 (100%)	<0.001
Lung Impairment	99 (70.7%)	91 (70.5%)	8 (72.7%)	>0.999

Table 4.3, continue

Variables	Total Cohort (n=140)	Alive (n=129)	Dead (n=11)	p-value
Liver Impairment	104 (74.3%)	93 (72.1%)	11(100%)	0.066
Renal Impairment	21 (15.0%)	13 (10.1%)	8 (72.7%)	<0.001
Bleeding	21 (15.0%)	16 (12.4%)	5 (45.5%)	0.012
Neurology Impairment	7 (5.0%)	5 (3.9%)	2 (18.2%)	0.095
Metabolic Acidosis	85 (60.7%)	76 (58.9%)	9 (81.8%)	0.201
Platlet Count on Admission >150 x 10^9 cells (normal) 70-150 x 10^9 cells (mild) 20-69 x 10^9 cells (moderate) < 20 x 10^9 cells (severe)	 9 (6.4%) 28 (20.0%) 59 (42.1%) 44 (31.4%)	 6 (4.7%) 27 (20.9%) 56 (43.4%) 40 (31.0%)	 3 (27.3%) 1 (9.1%) 3 (27.3%) 4 (36.3%)	0.053
Albumin level on Admission 35-45 g/L (normal) 25-34 g/L (mild) < 25 g/L (marked)	 37 (27.0%) 84 (61.3%) 16 (11.7%)	 36 (28.6%) 76 (60.3%) 14 (11.1%)	 1 (9.1%) 8 (72.7%) 2 (18.2%)	0.290
Prothrombin Time <14.3 sec (normal) >14.3 sec (prolonged)	 104 (76.5%) 32 (23.5%)	 101 (80.8%) 24 (19.2%)	 3 (27.3%) 8 (72.7%)	<0.001
aPTT Normal: 30.4-43.7 sec 1x above normal: 43.8-87.4 sec 2x above normal: 87.5 – 131.1 sec 3x above normal: > 131.1 sec	 27 (19.9%) 91 (66.9%) 15 (11.0%) 3 (2.2%)	 26 (20.8%) 84 (67.2%) 13 (10.4%) 2 (1.6%)	 1 (9.1%) 7 (63.6%) 2 (18.2%) 1 (9.1%)	0.130
Creatinine level on Admission Normal = < 114 μmol/L Stage 1 = 114 – 228 μmol/L Stage 2 = 229 – 342 μmol/L Stage 3 = > 342 μmol/L	 117 (84.8%) 14 (10.2%) 1 (0.7%) 6 (4.3%)	 115 (90.6%) 6 (4.7%) 1 (0.8%) 5 (3.9%)	 2 (18.2%) 8 (72.7%) 0 (0.0%) 1 (9.1%)	<0.001
AST level Normal: <45 u/L Mild: 45-225 u/L Moderate: 226-450 u/L Severe: >450 u/L	 4 (3.0%) 52 (38.2%) 26 (19.1%) 54 (39.7%)	 4 (3.2%) 52 (41.3%) 26 (20.6%) 44 (34.9%)	 0 (0.0%) 0 (0.0%) 0 (0.0%) 10(100%)	0.001

Table 4.3, continue

Variables	Total Cohort (n=140)	Alive (n=129)	Dead (n=11)	p-value
ALT level Normal: < 49 u/L Mild: 49 – 245 u/L Moderate: 246 – 490 u/L Severe: > 490 u/L	 27 (19.7%) 55 (40.2%) 18 (13.1%) 37 (27.0%)	 27 (21.4%) 55 (43.7%) 15 (11.9%) 29 (23.0%)	 0 (0.0%) 0 (0.0%) 3 (37.3%) 8 (72.7%)	 <0.001
Oxygen Support Non invasive ventilator Face mask Nasal prong Intubated Room air	 65 (46.4%) 5 (3.6%) 26 (18.6%) 17 (12.1%) 27 (19.3%)	 65 (50.4%) 5 (3.9%) 26 (20.1%) 6 (4.7%) 27 (20.9%)	 0 (0.0%) 0 (0.0%) 0 (0.0%) 11 (100%) 0 (0.0)	 <0.001
Dialysis Support	12 (8.6%)	5 (3.9%)	7 (63.6%)	<0.001
Inotropic Support	28 (20.0%)	17 (13.2%)	11 (100%)	<0.001

4.2 Factors associated with dengue mortality

Overall there were 11 dengue-related deaths in this study, 6 (55%) were male (Table 4.3). The mean age was 54.8±15.5 years but most of mortality cases (n=9, 82%) were age > 50 years old. Non-survivors were more frequently reported hypertension and diabetes mellitus. Seven (63.7%) patients were having at least 2 pre-existing co-morbidities condition. However, patients classified as having severe dengue upon ICU admission were not associated with death when compared to those classified as having DF with warning signs.

Among the clinical presentations, cardiac impairment, renal impairment and bleeding were more common in non-survivors. Other organs (lung, liver and neurological) impairment and metabolic acidosis were not associated with dengue mortality. All 11 dengue death cases developed cardiac impairment and severe transaminitis (AST level more than 10 folds normal value[1]) during ICU stay.

Regarding laboratory results, non-survivors were found to have higher creatinine levels, prolonged PT, higher ALT and AST levels compared to non-survivors. Seven non-survivors (63.6%) had moderate to severe thrombocytopenia during ICU admission. About three quarters (72.7%) patients had stage 1 AKI, mild hypoalbuminemia, prolonged PT, and elevation of ALT > 10 folds normal.

As for treatment and interventions, intubation, dialysis and inotropic or support were found more common in non-survivors. Seven non-survivors (63.6%) required more than 2 inotropic support while similar number of patients required CRRT during ICU stay. Five non-survivors (45.5%) died in ICU within 3 days after admission.

A series of logistic regression analyses were done to determine the factors independently associated with dengue mortality. From Simple Logistic Regression analysis, 10 variables were found to have significant value less than 0.25 (Table 4.4). The potential significant variables were age, number of co-morbidities, platelet count on admission, albumin level on admission, PT, aPTT, creatinine level on admission, AST level, ALT level and dialysis support. All of these variables were included in Multiple Logistic Regression analysis and any variables with $p<0.05$ would be considered significant factors associated with dengue mortality. However, only two variables were found to be independently significant which were number of comorbidities (OR 2.6, 95% CI 1.26 to 5.38, p-value 0.009) and AST level (OR 1.0, 95% CI 1.0-1.01, p-value 0.001). It concluded that by increasing one number of co-morbids, the chance of patients to die from dengue was increased by 2.6 times.

Table 4.4 Univariable analysis to evaluate risk factors of dengue mortality

	Univariable Analysis		
Variables	**OR**	**95% CI**	**p-value**
Age	1.1	1.02 to 1.09	0.003
Age 50-59	16.7	1.80 to 153.9	0.013
Age > 60	14.3	1.47 to 138.2	0.022
Numbers of co-morbidities	1.9	1.20 to 2.99	0.006
Mild thrombocytopenia	0.07	0.01 to 0.84	0.036
Moderate thrombocytopenia	0.1	0.02 to 0.65	0.015
Albumin level	0.9	0.77 to 0.99	0.030
PT level	1.4	1.09 to 1.77	0.007
PT > 14.3 sec	11.2	2.77 to 45.49	0.001
aPTT level	1.0	1.10 to 1.04	0.014
Creatinine level	1.0	1.0 to 1.01	0.003
Stage 1 AKI	76.7	13.28 to 442.71	< 0.001
AST level	1.0	1.0 to 1.01	< 0.001
ALT level	1.0	1.0 to 1.01	< 0.001
Dialysis support	0.02	0.01 to 0.11	< 0.001

4.3 Factors associated with prolonged ICU stay

Prolonged ICU stay (>3 days) was seen in 51 (36.4%) studied participants. Variables of patient with and without prolonged ICU stay were compared (Table 4.5)

Patients having severe dengue, pre-existing blood disorder, increased number of co-morbidities, renal impairment, elevated creatinine level, and required intubation or inotropic support were significantly associated with prolonged ICU stay. However, in this study surprisingly normal and mild thrombocytopenia upon ICU admission were associated with prolonged stay as well.

Although other factors such as pre-exisiting diabetes mellitus, hypertension, cardiac disease, renal disease and pregnancy were more common among patients with prolonged ICU stay but their statistical association were not significant (p-value > 0.05). Meanwhile, among patients with prolonged ICU stay, lung impairment, bleeding, mild hypoalbuminemia, PT > 14.3 sec, elevation of ALT and AST> 10 folds above normal value and dialysis support were more common but still statistically insignificant. It was also interestingly to note that female gender was more likely to stay <=3 days in this study.

A series of logistic regression analyses was done to determine the factors independently associated with prolonged ICU stay. From Simple Logistic Regression analysis, 12 variables were found to have significant value less than 0.25 (Table 4.6). The potential significant variables were gender, number of comorbidities, pregnant, severe dengue, platelet count on admission, PT, aPTT, creatinine level on admssion, ALT level, dialysis, inotropic and oxygen support. All of these variables were included in Multiple Logistic

Regression analysis and any variables with p<0.05 would be considered significant factors associated with length of stay. However, only two variables were found to be independently significant which were female gender (OR 0.36, 95% CI 0.14 to 0.90, p-value 0.029) and elevation of aPTT 2x above normal value (OR 0.11, 95% CI 0.02 to 0.66, p-value 0.015). It concluded that the chance for female to has longer length of stay was 64% lesser compared to male patient and the chance for patient with aPTT between 87.5-131.1 to has longer length of stay was 89% lesser compared to patient with normal aPTT level.

Table 4.5: Comparison of variables associated with length of ICU stay

Variables	Total cohort (n=140)	<=3 days (n=89)	>3 days (n=51)	p-value
Age				
10-29	51 (36.4%)	33 (37.1%)	18 (35.3%)	
30-39	29 (20.7%)	18 (20.2%)	11 (21.6%)	
40-49	22 (15.7%)	16 (18.0%)	6 (11.8%)	0.680
50-59	20 (14.3%)	13 (14.6%)	7 (13.7%)	
>60	18 (12.9%)	9 (10.1%)	9 (17.6%)	
Gender				
Male	80 (57.1%)	47 (52.8%)	33 (64.7%)	0.171
Female	60 (42.9%)	42 (47.2%)	18 (35.3%)	
No. of Comorbidities				
0	86 (61.4%)	60 (67.4%)	26 (51.0%)	
1	20 (14.3%)	12 (13.5%)	8 (15.7%)	
2	21 (15.0%)	10 (11.2%)	11 (21.6%)	0.018
3	8 (5.7%)	2 (2.2%)	6 (11.8%)	
4	5 (3.6%)	5 (5.6%)	0 (0%)	
DM	26 (18.6%)	14 (15.7%)	12 (23.5%)	0.253
Hypertension	35 (25.0%)	18 (20.2%)	17 (33.3%)	0.085
Cardiac Disease	7 (5.0%)	4 (4.5%)	3 (5.9%)	0.705
Lung Disease	5 (3.6%)	3 (3.4%)	2 (3.9%)	>0.999

Table 4.5, continue

Variables	Total cohort (n=140)	<=3 days (n=89)	>3 days (n=51)	p-value
Liver Disease	5 (3.6%)	4 (4.5%)	1 (2.0%)	0.653
Renal Disease	7 (5.0%)	4 (4.5%)	3 (5.9%)	0.717
Blood Disorder	6 (4.3%)	1 (1.1%)	5 (9.8%)	0.024
Pregnancy	9 (6.4%)	4 (4.5%)	5 (9.8%)	0.286
Dengue Classification DF with Warning Signs Severe Dengue	 25 (17.9%) 115 (82.1%)	 20 (22.5%) 69 (77.5%)	 5 (9.8%) 46 (90.2%)	0.060
Cardiac Impairment	34 (24.3%)	18 (52.9%)	16 (47.1%)	0.139
Lung Impairment	99 (70.7%)	59 (66.3%)	40 (78.4%)	0.129
Liver Impairment	104 (74.3%)	67 (75.3%)	37 (72.5%)	0.722
Renal Impairment	21 (15.0%)	9 (10.1%)	12 (23.5%)	0.032
Bleeding	21 (15.0%)	10 (11.2%)	11 (21.6%)	0.099
Neurology Impairment	7 (5.0%)	5 (5.6%)	2 (3.9%)	>0.999
Metabolic Acidosis	85 (60.7%)	54 (60.7%)	31 (60.8%)	>0.999
Platlet Count on Admission >150 x 10^9 cells (normal) 70-150 x 10^9 cells (mild) 20-69 x 10^9 cells (moderate) < 20 x 10^9 cells (severe)	 9 (6.4%) 28 (20.0%) 59 (42.1%) 44 (31.4%)	 2 (2.2%) 13 (14.6%) 42 (47.2%) 32 (36.0%)	 7 (13.7%) 15 (29.4%) 17 (33.3%) 12 (23.5%)	0.004
Albumin level on Admission 35-45 g/L (normal) 25-34 g/L (mild) < 25 g/L (marked)	 37 (27.0%) 84 (61.3%) 16 (11.7%)	 26 (29.5%) 50 (56.8%) 12 (13.6%)	 11 (22.4%) 34 (69.4%) 4 (8.2%)	0.332
Prothrombin Time <14.3 sec (normal) >14.3 sec (prolonged)	 104 (76.5%) 32 (23.5%)	 70 (81.4%) 16 (18.6%)	 34 (68.0%) 16 (32.0%)	0.076

Table 4.5, continue

Variables	Total cohort (n=140)	<=3 days (n=89)	>3 days (n=51)	p-value
aPTT				
Normal: 30.4-43.7 sec	27 (19.9%)	12 (14.0%)	15 (30.0%)	
1x above normal: 43.8-87.4 sec	91 (66.9%)	60 (69.8%)	31 (62.0%)	
2x above normal: 87.5 – 131.1 sec	15 (11.0%)	11 (12.8%)	4 (8.0%)	0.091
3x above normal: > 131.1 sec	3 (2.2%)	3 (3.5%)	0 (0.0%)	
Creatinine level on Admission				
Normal = < 114 μmol/L	117 (84.8%)	80 (90.9%)	37 (74.0%)	
Stage 1 = 114 – 228 μmol/L	14 (10.2%)	5 (5.7%)	9 (18.0%)	0.025
Stage 2 = 229 – 342 μmol/L	1 (0.7%)	0 (0.0%)	1 (2.0%)	
Stage 3 = > 342 μmol/L	6 (4.3%)	3 (3.4%)	3 (6.0%)	
AST level				
Normal: <45 u/L	4 (3.0%)	2 (2.3%)	2 (4.0%)	
Mild: 45-225 u/L	52 (38.2%)	34 (39.5%)	18 (36.0%)	0.740
Moderate: 226-450 u/L	26 (19.1%)	18 (20.9%)	8 (16.0%)	
Severe: >450 u/L	54 (39.7%)	32 (37.2%)	22 (44.0%)	
ALT level				
Normal: < 49 u/L	27 (19.7%)	15 (17.2%)	12 (24.0%)	
Mild: 49 – 245 u/L	55 (40.2%)	41 (47.1%)	14 (28.0%)	0.165
Moderate: 246 – 490 u/L	18 (13.1%)	11 (12.6%)	7 (14.0%)	
Severe: > 490 u/L	37 (27.0%)	20 (23.0%)	17 (34.0%)	
Oxygen Support				
Nasal invasive ventilator	65 (46.4%)	40 (44.9%)	25 (49.0%)	
Face mask	5 (3.6%)	4 (4.5%)	1 (2.0%)	
Nasal prong	26 (18.6%)	18 (20.2%)	8 (15.7%)	0.01
Intubated	17 (12.1%)	5 (5.6%)	12 (23.5%)	
Room air	27 (19.3%)	22 (24.7%)	5 (9.8%)	
Dialysis Support	12 (8.6%)	5 (5.6%)	7 (13.7%)	0.122
Inotrope Support	28 (20.0%)	13 (14.6%)	15 (29.4%)	0.035

Table 4.6 Univariable analysis to evaluate risk factors of prolonged ICU stay

	Univariable analysis		
Variables	**OR**	**95% CI**	**p-value**
Female gender	0.61	0.30 to 1.24	0.173
Number of co-morbidities	1.25	0.93 to 1.69	0.145
Pregnancy	2.31	0.50 to 9.03	0.229
Severe dengue	2.67	0.93 to 7.61	0.067
Intubation	3.84	1.31 to 12.21	0.023
Mild thrombocytopenia	0.33	0.06 to 1.88	0.211
Moderate thrombocytopenia	0.12	0.02 to 0.61	0.011
Severe thrombocytopenia	0.11	0.02 to 0.59	0.010
PT > 14.3 sec	2.06	0.92 to 4.61	0.079
aPTT 1x above normal value	0.41	0.17 to 0.99	0.048
aPTT 2x above normal value	0.29	0.07 to 1.15	0.078
Stage 1 AKI	3.89	1.22 to 12.42	0.022
Mild elevation of ALT	0.43	0.16 to 1.13	0.086
Dialysis support	2.67	0.80 to 8.91	0.110
Inotropic support	2.44	1.05 to 5.65	0.038

CHAPTER 5: DISCUSSION

This study is one of few to focus on factors that affect the outcome of dengue patients admitted to ICU and the first of these studies[6, 11,13,16] to be conducted in Malaysia. Although Mallhi TH et al[13] published similar study in year 2017 but it was not focus on ICU dengue patients.

Mean age of this study population was 38.1+17.6 years which showed no different to Rajender A et al[17] study. In this study non-survivors were older, exhibited multiple co-morbidities especially hypertension and diabetes mellitus. Age group more than 60 years old was observed to has 14 times higher risk for dengue mortality than those aged 10-29 years. As elderly usually had increased risk of developing multiple co-morbidities hence many studies[7, 8, 10, 13, 14, 16, 18] reported that older age was an independent risk factor for severe dengue. Our study adds to this evidence. Elderly patients also predispose to impaired functional reserve for various organs. Another study by CY Chen et al[19] showed that dengue patients with diabetes mellitus tended to develop more severe thrombocytopenia and severe dengue which is similar to our study.

Meanwhile, this study showed that by increasing one number of co-morbid, the chance of patients to die from dengue increased by 2.3 times. It is further supported by few studies[7, 8, 9, 14] that reported number of co-morbidities is an independent factor of dengue mortality. As fluid management is crucial in treating dengue patients, therefore excessive fluid therapy in patients with pre-existing co-morbidities such as heart disease or renal disease will increase risk of death[20].

Cardiac impairment, respiratory impairment and renal impairment have been reported to be predictive factors for dengue mortality[6, 11, 13, 14]. In our study cardiac impairment, renal impairment, bleeding and transaminitis were more common in non-survivors. In this study, acute kidney injury was staged according to Acute Kidney Injury Network (AKIN) as there was study[21] showed that AKIN criteria was superior than conventional definition with regard to early diagnosis and sensitivity among patients with dengue.

Hypoalbuminemia had been proven to increase ICU mortality rate in many studies[7, 11, 19, 22, 23] and this factor also showed its significance by using univariate analysis in our study (OR 0.9, 95% CI 0.77 to 0.99, p-value 0.03). In addition, both D. Junej[6] and Amâncio FF[7] studies showed that need for vasopressor, renal and mechanical ventilator support were found to be associated with increased risk of dengue death which was similar to our study too.

In this study, elevation of AST had been seen in 97% of patients while elevation of ALT levels in 80.3%. This result was similar to what had been reported in Malaysia dengue infection CPG[20]. However, in our study more than 10-fold rise of AST and ALT had been seen in 39% and 27% of ICU dengue patients respectively. This number was much higher compare to Malaysia CPG[20] (3-15%) and W. Shahin et al[24] (8-14%) study. It may be due to both these studies calculated based on general dengue population but our study only enrolled those who admitted to ICU which were usually more ill and suffered from more severe transaminitis. Interestingly, in our study 53% of patients had AST level 2 times higher than ALT level. AST is usually expressed in the liver, heart, red blood cells, skeletal muscle, kidneys and brain while ALT is secreted mainly by the liver[25, 26]. Hence, raised aminotransferase levels may not solely due to severe liver involvement.

This study also showed that female gender was independently associated with lesser chance of prolonged ICU stay which contrary to Mallthi TH et al[13] study. In fact, many studies have conflicting statement on the association of gender with dengue severity. Malaysia[16], Taiwan[8] and India[12] showed female has higher mortality rate but a study in France[27] showed male gender associated with severe dengue manifestation.

Patients having blood disorder, increased number of co-morbids, severe dengue, renal impairment, mild thrombocytopenia, elevated creatinine level and required intubation or inotropic support were associated with prolonged ICU stay in this study. However none of these was considered significant independent factor associated with prolonged ICU stay after multivariate analysis. It means prolonged stay is multifactorial and not due to single factor alone. Interestingly the chance for patient with aPTT between 87.5-131.1 on admission to has longer length of stay was 89% lesser compared to patient with normal aPTT level. It can be explained with most of patients having normal aPTT level on admission were on early phase of dengue fever hence tend to have longer ICU stay.

There are few limitations in this study. Firstly, as it is a single-center study, the number of cases is limited and hence may not be generalised to other population. Next, as a retrospective study, data extracted from medical records may be inadequate or misclassified. Additionally, the small number of dengue mortality cases in this study may not giving high statistical power for identification of factors associated with dengue death and this is the reason of wide confidence intervals. Lastly, there are few studies[6, 22, 28] using Acute Physiology and Chronic Health Evaluation (APACHE) and Sequential Organ Failure Assessment (SOFA) score to predict dengue mortality which is not included in this study.

CHAPTER 6: CONCLUSION

In conclusion, factors including older age, co-morbidities, prolonged PT and aPTT, thrombocytopenia, hypoalbuminemia, increased creatinine, ALT, AST level and dialysis support were found to be associated with dengue mortality. However, only number of co-morbidities and AST level were considered independent predictor factors for dengue death. Meanwhile, patients with dengue fever who have underlying blood disorder, multiple co-morbidities, renal impairment, thrombocytopenia, required intubation or inotropic support have a higher risk of prolonged ICU stay. However, only female gender and elevation of activated partial thrombin time 2 times above normal value were found to be independently significant related to ICU stay duration. Early recognition of dengue patients with these factors may lead to early ICU admission and hence can provide early advanced physiological monitoring and organ support for these group of patients. Time and resources can be focused on those at higher risk if health care provider can identify above factors earlier and hence can decrease the dengue morbidity and mortality.

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