ASSOCIATED FACTORS OF PROLONGED HOSPITAL STAY AMONG ADULT DENGUE FEVER PATIENTS IN HOSPITAL RAJA PEREMPUAN ZAINAB II

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By

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LIST OF ABBREVIATION

Adj. OR	Adjusted odds ratio
CI	Confidence interval
MOH	Ministry of Health Malaysia
OR	Odds ratio
ROC	Receiver Operating Characteristic
SD	Standard deviation
SPSS	Statistical Package for the Social Science
WHO	World Health Organization
HRPZ II	Hospital Raja Perempuan Zainab II

LIST OF SYMBOLS

>	More than
<	Less than
=	Equal to
≥	More than and equal to
≤	Less than and equal to
β	Beta
%	Percentage
Δ	Precision / Delta

FAKTOR PENYUMBANG KEPADA KEMASUKKAN WAD BERPANJANGAN DI KALANGAN PESAKIT DEWASA DEMAM DENGGI DI HOSPITAL RAJA PEREMPUAN ZAINAB II

ABSTRAK

Latar belakang: Deman Denggi merupakan penyakit bawaan vektor yang mempunyai kes yang tinggi di Malaysia. Di Kelantan, kebanyakan kes demam denggi adalah dilaporkan dari daerah Kota Bharu. Walaupun banyak kajian berkaitan deman denggi yang telah dilakukan di Malaysia, namun kajian mengenai prevalens kemasukkan wad yang berpanjangan dan faktor-faktor berkaitan dengannya di kalangan pesakit demam denggi masih kurang.

Objektif: Objektif kajian ini adalah untuk menentukan prevalens kemasukkan wad yang berpanjangan dan faktor-faktor berkaitan kemasukkan wad yang berpanjangan dalam kalangan pesakit denggi.

Metodologi: Kajian keratan rentas ini melibatkan 302 pesakit denggi yang mendapat rawatan di Hospital Raja Perempuan Zainab II pada tahun 2015-2016. Data telah dikumpul pada Januari 2017. Alat kajian yang digunakan dalam proses pengumpulan data adalah ‘proforma’ yang telah dibentuk. Data telah dianalisa menggunakan perisian SPSS versi 23.0. Regresi logistik berganda telah digunakan untuk menentukan faktor-faktor yang berkaitan dengan kemasukkan wad yang berpanjangan dikalangan pesakit denggi.

Keputusan: Nilai min (sisihan piawai) umur pesakit demam denggi adalah 33.46(8.32). Sebanyak 29.1% daripada pesakit mengalami kemasukkan wad

berpanjangan di wad (kemasukkan selama 72 jam atau lebih). Nilai min (sisihan piawai) untuk durasi kemasukkan hospital adalah 64.47 (31.26) jam. Daripada regresi logistik berganda, faktor-faktor yang menyumbang kepada kadar kemasukan berpanjangan di dalam wad adalah gejala keletihan/kecelaruan, kebocoran plasma yang teruk/ sindrom renjatan denggi dan penglibatan organ yang teruk.

Kesimpulan: Prevalens untuk kemasukkan berpanjangan dalam ward di kalangan pesakit denggi dewasa adalah agak tinggi. Pesakit yang mengalami gejala keletihan/kecelaruan, kebocoran plasma teruk/sindrom renjatan denggi dan penglibatan organ yang teruk adalah faktor-faktor penyumbang kepada kemasukkan berpanjangan di hospital. Pesakit yang mengalami gejala-gejala ini harus diberikan lebih perhatian dalam rawatan supaya tidak mengalami kemasukkan berpanjangan yang berpanjangan disebabkan deman denggi.

Kata Kunci: Demam Denggi, Kota Bharu, Kemasukkan Wad Yang Berpanjangan

ASSOCIATED FACTORS OF PROLONGED HOSPITAL STAY AMONG ADULT DENGUE FEVER PATIENTS IN HRPZ II

ABSTRACT

Background: Dengue fever is regarded as one of the most common vector-borne related diseases in Malaysia. In Kelantan, most of dengue cases is reported from Kota Bharu district. Although dengue research is done extensively in Malaysia, very few studies done to determine the prevalence of prolonged hospital stay and its associated factors.

Objective: The objectives of this study were to determine the prevalence of prolonged hospital stay among adult dengue patients in Hospital Raja Perempuan Zainab II in 2015-2016 and its associated factors.

Methodology: This was a cross sectional study involving 302 adult patients who were admitted in 2015-2016 for dengue fever in Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan. Data was collected in January 2017. The research tool that was used for data collection was a designed proforma. Data were analysed using SPSS version 23.0. Multiple logistic regression analysis was performed to determine the associated factors for prolonged hospital stay.

Results: The mean (SD) age of adult dengue patient in this study was 33.46 (8.32) years old. Out of 302 patients, 29.1% of them have prolonged hospital stay. The mean length for hospital stay is 64.47 ± 31.26 hours. . The study also noted that factors associated with longer hospital stay among dengue patient were

lethargy/restlessness, severe plasma leakage/ dengue shock syndrome and severe organ involvement.

Conclusion: Prevalence for prolonged hospital stay among adult dengue patient is high. Patients with lethargy/restlessness, severe plasma leakage/dengue shock syndrome and severe organ involvement should be given more importance in term of management to avoid longer hospital stay among dengue fever patient.

Keyword: Dengue fever, Kota Bharu, Prolonged Hospital Stay

Chapter 1

INTRODUCTION

1.1 Overview of Dengue Worldwide

Dengue is an infectious disease that is caused by dengue virus and is transmitted by Aedes mosquito. It is estimated that 50 million of new dengue cases happened every year (WHO, 2016). Dengue fever is caused by dengue virus. The dengue virus (DEN) comprises of four different serotypes (DEN-1, DEN-2, DEN-3 and DEN-4) which belong to the genus Flavivirus. Different genotypes have been identified within each serotype, which mean that the virus have extensive genetic variability of the dengue serotypes. For example, “Asian” genotypes of DEN-2 and DEN-3 is common in Asian region, and are frequently associated with severe disease especially during the secondary dengue infections (WHO, 2009).

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. The incidence of dengue has grown dramatically around the world in recent decades. The actual numbers of dengue cases are underreported and many cases are misclassified. Estimation done by WHO indicates there are around 390 million dengue infections per year (95% credible interval 284–528 million), of which 96 million (67–136 million) manifest clinically (with any severity of disease). Another study, of the prevalence of dengue, estimates that 3.9 billion people, in 128 countries, are at risk of infection with dengue viruses (WHO, 2009). Before year 1970, only

nine countries had experienced severe dengue epidemics. Unfortunately, the disease is now endemic in more than 100 countries in the WHO regions of Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific. The America, South-East Asia and Western Pacific regions are the most seriously affected.

According to WHO report, all the four serotypes of dengue virus present simultaneously in Malaysia, making Malaysia 'hyperendemic' for dengue (WHO, 2012). The commonest serotype for dengue virus in Malaysia is DEN-1 and DEN-2. There are many reasons that contributes to increase of dengue incidence in Malaysia mainly urbanization process, poor solid waste management system and rise in international movement in form of migration (Sunyoto et al., 2013)

1.2 Overview of dengue in Malaysia, Kelantan and Kota Bharu

In Malaysia, *Aedes Aegyptie* is the principal vector of dengue and *Aedes Albopictus* is the secondary vector (Mohd-Zaki et al., 2014). Both species are common in tropical and subtropical countries. The viruses are transferred on to humans through the bites of an infective female *Aedes* mosquito which mainly acquires the virus while feeding on the blood of an infected person. There is also trans-ovarian infection in which the infection is transferred from generation to generation(WHO, 2012). In the mosquito, the virus infects the mosquito mid-gut and subsequently spreads to the salivary glands over a period of 8-12 days. After this incubation period, the virus can be transmitted to humans during subsequent probing or feeding. The immature stages are found in water-filled habitats, mostly in artificial containers closely associated with human dwellings and often indoors.

Dengue is one of the most important vector-borne viral diseases in term of public health problem in Malaysia (WHO). Although a lot of efforts has been done to combat dengue like strengthening national capacities for surveillance, clinical management, early detection, preparedness, control of outbreaks and vector control, the number of dengue cases is still increasing in trend in Malaysia. The incidence of dengue in Malaysia is increasing from 32 cases per 100 000 population in 2000 to 361 cases per 100 000 population in 2014 (CPG, 2015). Although the mortality rate of dengue in Malaysia is low and still below the national indicator of 0.2%, high prevalence of dengue has associated with reduced productivity and financial burden at country and household level (MOH Malaysia, 2015).

Kelantan is among the states in Malaysia which has high number of dengue cases in Malaysia alongside Selangor, Johor and Putrajaya. In 2014, Kelantan recorded highest case of dengue with more than 10 000 confirmed dengue cases (MOH Malaysia, 2016). In Kota Bharu, the number of registered dengue cases was 1480 in 2015 and 3838 Dengue cases from Kota Bharu accountable for 76% of total dengue cases in Kelantan state (MOH Malaysia, 2016) .From Hospital Raja Perempuan Zainab II record office, the number of admission to Hospital Raja Perempuan Zainab II due to dengue fever was 322 in 2015 and 531 in 2016 (HRPZ II, 2014).

1.3 Overview of Kota Bharu and Hospital Raja Perempuan Zainab II

Kota Bharu is the capital city of Kelantan. Its covers the area of 115.4 km2 and was founded during the late of 19th century around year 1844. It is situated in the northeast part of Peninsular Malaysia close to Thailand border. Literally, it can be

loosely translated as new fort/city in Malay. Currently, it functions as administration, trade and education hub for Kelantan (Kelantan Archive, 2000).

Kota Bharu has the population of 539 601 with 97% of the population is Malay. Other ethnicity includes Chinese, Indian and Siamese (Department of Statistic Malaysia, 2015). In term of health services, it has 12 government clinics, 86 private clinic, and 2 government tertiary hospitals. The two tertiary hospitals are Hospital Raja Perempuan Zainab II and Hospital Universiti Sains Malaysia.

Hospital Raja Perempuan Zainab II (HRPZ II) was previously known as Kota Bharu General Hospital and began operations in the 1920s. Initially, it was established to provide medical services to European who lived in Kelantan. Later, it offered health services to the local population. In the earlier years, the hospital building consists of only two buildings which were known as the "European Ward" and a different building was built in 1930s for the people local of Kelantan. There were three main services that were offered during that time which were medical, surgical and maternity services. To cater the expanding need of the population, two new blocks were built and completed in 1938 (HRPZ II, 2014).

Currently, HRPZ II has 35 wards with 16 clinical departments and nine clinical support departments. It can accommodate 920 patients in maximum load. It has three medical wards but in case of severe outbreak and increases of dengue cases in Kota Bharu or Kelantan as a whole, two additional wards will be opened to cater dengue patients exclusively (HRPZ II, 2014).

1.4 Classification of Dengue Cases in Malaysia

Dengue has a wide spectrum of clinical presentations and outcomes. It can be divided into probable dengue, dengue with no warning sign, dengue with warning signs and severe dengue. According to CPG Management of Dengue in Adult (MOH, 2015), dengue cases can be classified into:

1. Probable Dengue which is defined as patient who live/travel into dengue endemic area, has fever and two of the following criteria

a) Nausea, vomiting

b) Rash

c) Aches and pains

d) Tourniquet test positive

e) Leukopenia

f) Any Warning sign

2. Dengue with warning signs which is defined as confirmed case with signs of

a. Abdominal pain/tenderness

b. Persistent vomiting

c. Clinical fluid accumulation

d. Mucosal bleed

e. Lethargy, restlessness

f. Liver enlargement more than 2 cm

g. Laboratory diagnosis: increase in haematocrit concurrent with decrease in platelet count

3. Severe dengue which is defined as severe plasma leakage that leads to shock (dengue shock syndrome), fluid accumulation with respiratory distress, severe bleeding or severe organ involvement (liver, central nervous system and heart involvement).

Regarding management of dengue cases, World Health Organization (WHO) has introduced Guideline for Diagnosis, Treatment, Prevention and Control Manual in 2007, which was further reviewed in 2009. There are some advantages of using 2009 WHO guideline which emphasis more on warning sign and re-defining severe dengue criteria compared to 2007 version. A study done in Singapore revealed that 78.6 % of cases is identified by using 2009 WHO guideline compared to only 32.1% if using WHO 2007 Guideline. It is also noted that previous WHO guideline only fulfilled 35.7% of hospital admission criteria compared to 2009 version, most notably due to lack of clinical bleeding which is reviewed in 2009 (Carrasco et al., 2014).

Ministry of Health Malaysia had introduced Clinical Practice Guideline on Dengue in 2010 based on the WHO Dengue Guidelines for Diagnosis, Treatment, Prevention and Control (2009) and was further reviewed up to latest update in 2015.. Although adherence to this guideline may not necessarily guaranteed the best outcome for every cases, it has the best available evidence at the time of the development. In Malaysia, a lot of courses and trainings based on Malaysia Dengue CPG have been given to health care providers especially the medical practitioners so that the diagnosis and management of dengue patient to provide better care for dengue patient. This is the reason why all selected independent variables in this study is based on Malaysia Clinical Practice Guideline on Dengue Management as it is used widely in Malaysia in term of its diagnosis and management.

1.5 Study Rationale

Dengue fever is a major and never ending problem in Malaysia including Kelantan. Dengue is also affects almost all of states in Malaysia especially urban area. Although a lot of effort already spent in combating dengue, the increased prevalence of dengue cases from year to year has caused adverse effects to domestic and national level.

Although dengue infection is common in Malaysia, currently, there are limited publication on duration of hospital stay and its associated factors in adult dengue patients. Most studies are more likely to find the association between severity of dengue fever or outcome of treatment (especially in term of mortality) and its associated factors. By knowing the factors that is associated with prolonged hospital stay among dengue patients, necessary actions and intervention can be done

during their hospital stay so that unnecessary stay will not be required. This is very important especially during the current Malaysian economic status, where resources are very limited in term of financial, man power and they need to be managed optimally.

Objective of the study

General Objective

1. To study the proportion of prolonged hospital stay and its associated factors among dengue patient admitted into HRPZ II in year 2015 and 2016

Specific Objective

1. To determine the proportion of prolonged hospital stay among dengue patients admitted into HRPZ II in 2015 and 2016

2. To determine the associated factors of prolonged hospital stay among dengue patients who were admitted into HRPZ II in 2015 and 2016

Research Hypothesis

1. There are significant association between the sociodemographic factors, pre-existing medical condition and clinical manifestations with prolong hospital stay among dengue patients who were admitted into HRPZ II in 2015-2016

Chapter 2

LITERATURE REVIEW

2.1 Hospital Admission and Stay among Adult Dengue Patient

In Malaysia, the decision for admission for dengue patient is not based on single clinical parameter but on total assessment of the patient. Warning signs, manifestation of severe dengue, special situation of the patient (comorbidity, age, pregnancy status) are assessed properly before decision of hospital admission is made. It is estimated that one in seven dengue patients is hospitalized worldwide (WHO, 2013). In Hospital Raja Perempuan Zainab II from 2015-2016, the proportion of admitted case among dengue patient is 15.6 %, which is 853 out of 5319 of total notified confirmed dengue cases form Kota Bharu district.

Not only criteria for admitting the patient, criteria for discharging the patient is also outlined properly in Guideline of Dengue Infection in Adult. Generally in Malaysia, the main considerations that are taken into consideration before discharging a dengue patient includes improved general wellbeing, afebrile for 24-28 hours, rising white cell count followed by the platelet count, resolution/recovery of organ dysfunction and stable haematocrit (MOH Malaysia, 2015)

Due to broad spectrum of the disease, currently there are no optimum duration have been suggested on how many days hospital stay is required for dengue fever. However, it is known that some of the hospital stay is unnecessary and longer than optimum duration. According to research done in Saudi Arabia, most of patient

have prolonged hospital stay while waiting for improvement in platelet count although patient is already asymptomatic and passed the critical period (Khan et al., 2008). This might be contributed by practice of defensive medicine among health care provider which might lead to unnecessary diagnostic test and treatment, thus prolonging the duration of hospital stay (Sekhar and Vynas, 2013).

It is generally known that unnecessary hospital stay especially for infectious disease can lead to many adverse effect. According to study done in Australia, an average hospital stay carries a 5.5% of an adverse drug reaction, 17.6% risk of nosocomial infection and 3.1% risk of ulcer with an increased risk for additional night of stay (Hauck et al., 2011). Other study done in India also revealed common for hospital stay where 34% of patients experienced home sickness, 20% boredom, 18% an effect on households responsibility and 17% effect on education (Subramaniam, 2008).

High prevalence of dengue cases also incurs additional cost in treating the patient especially inpatient dengue patient. According to studies done by Oxford Business group in 2010 in Malaysia, the number of working days lost because of dengue fever is estimated at 940 000 a year. The report also report monetary cost of treatment stands at USD 718 per person. Not only that, the cost for vector control for dengue is also substantial at USD 73.5 million in 2010 (Oxford Business Group, 2010).

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2.1 Proportion of Prolonged Hospital Stay among Dengue Patients

Regarding the duration of hospital stay, a study from Pakistan revealed that 27% of the patients have prolonged hospital stay of more than seventy two hours. The mean of the stay was 3.46 (3.45) days (Khalil *et al.*, 2014). An unpublished study in Malaysia stated that the prevalence of prolonged hospital stay in Malaysia is 22.9% (Mallhi *et al.*, 2016b). This is consistent with study done in Saudi Arabia where 31% of the admitted dengue patients also have a prolonged hospital stay (Khan *et al.*, 2008).

Although it is not stated specifically on how many percentage of patient have prolonged admission more than 72 hours, a study in Singapore reported that 53% of the patients have hospital stay for seven days or more (Carrasco *et al.*, 2014). Lastly, one study done in Malaysia shows significant differences in mean (SD) of hospital stay (days) among patients who are admitted because of classical dengue fever compared to patient who develop severe form of dengue fever (2.52±1.92 vs. 4.64±1.99) (Mallhi *et al.*, 2015).

2.2 Demographic Characteristics of Hospitalized Dengue Patients

In Pakistan, 70.9% of dengue patients were male. One study in Philippines among hospitalized dengue cases showed that 52% of patients were male. This is also corresponded with a report from Laos which revealed that excess of males (>20 %) were found among reported dengue patient. Although the number of male that are infected with dengue is higher than women, women are at higher risk of developing

severe dengue and having prolonged hospital stay (OR 3.17 1.76-5.75 95% CI p value <0.001).

Regarding age, the mean age for study done in Pakistan is 35.2 (14.7) years with the range of 15 to 85 years. The other studies in Pakistan regarding comorbidities and death among dengue patients also shown that mean age is around 36 years old. In Philippines, 70% of the patient come from 15-64 years old while 29.5% of the remaining is made up from population aged 0-14 years old. This is similar to a study done in Laos that shows population between ages 16-40 has highest number of dengue fever notification rates compared to other age group in both males and females.

Duration between the onsets of illness to admission is also being studied in this study. In study done among confirmed dengue death in Singapore, patients were admitted to ward after median duration of four days after contracting illness (range 1-10 days). Study in Philippines indicates that more than 60% of patients were admitted between 3-5 days after illness. In one Malaysia study, patient were admitted on average on day four of illness (Mallhi *et al.,* 2015).This is comparable to study done in Cuba which shows late admission of dengue patients leads to severe dengue and prolonged hospital average interval between dengue illness and hospital admission is four days (Guzman *et al.,* 1999).

2.3 Factors Associated with Prolonged Hospital Stay

Increased age is also associated with increased hospital stay. In studies done in Pakistan, it is noted that patients that were older than 41 years old have odd of

1.03 of having longer hospital admission compared to their younger counterpart (Khalil et al., 2014). In research on dengue mortality in Malaysia, it has shown that increasing age has association with mortality (OR 1.03; 95% CI: 1.01-1.05; p= 0.004). Study in Singapore also reported that median age for dengue death was 59 years old. Meanwhile, study in Taiwan done in 2006 shows patient aged more than 65 years old have higher risk of developing severe form of dengue (OR 1.84; 95% CI: 1.11-3.08; p = 0.019). Study in India done in 2006 shows patient aged more than 40 years old also having higher risk of developing severe dengue (OR 9.30 ;95% CI: 1.80-39.4 p= 0.007).

Comorbidity is highly associated with severity of dengue. According to Saqib *et el*., patient with hypertension, diabetes or hepatitis is also having risk of severe dengue. Diabetes is associated with higher (OR 1.75; 95% CI: 1.08-2.84; p-value= 0.022) of developing severe dengue compared to non-diabetic in meta-analyses study (Htun *et al.,* 2015). This is correspondent to research done in India by Karunakaran et al that showed patient with diabetes was more likely to have severe presentation of dengue(OR 26.0 ;95% CI: 2.48-272.29 ;p= 0.020) . Study in Taiwan done in 2006 showed patient with history of diabetes mellitus have higher risk of developing severe form of dengue (OR 1.86 95% CI: 1.04-3.37 p-value=0.039) (Htun *et al.,* 2015).

Study in Taiwan done in 2006 shows patient with hypertension have more risk of developing severe form of dengue (OR 1.74; 95% CI: 1.11-3.08; p-value =0.021). This is parallel to research done in India (OR 44.0 95% CI: 6.2-315.5 p-value <0.000). Study done in Malaysia also showed significant association between

underlying hypertension and severity of dengue (OR 2.3 95%; 95% CI 1.9-3.3, p < 0.001)(Mallhi et al., 2015) .

There is no association between abdominal pain and severity of dengue (p 0.921) (Mallhi et al., 2016) .This is correspondent with other study done in Malaysia on abdominal pain and dengue mortality (p=0.77)(Liew *et al.*, 2016). Study done in Pakistan also revealed no association between presence of abdominal pain and prolonged hospital stay among dengue patient (Khalil *et al.*, 2014). However, as abdominal pain is considered as one of the commonest warning sign among dengue patient, it is considered an important variable among dengue patients study (Lye DC, 2008).

Persistent diarrhoea and vomiting has been found to lead to poor progression of dengue fever and prolonged hospital stay. In research done in Cuba, patient who develop vomiting had total illness duration of seven days, compared to patient who did not develop symptom of vomiting of who develop four day of illness(Guzman *et al.*, 1999).This is corresponding with the study done in Singapore (Lye DC, 2008).However, there was also study that showed no significant association between nausea and vomiting and severity of dengue illness and duration of hospital stay (OR 1.38; 95% CI 0.72-2.67; p-value= 0.327) (Liew et al., 2016). Other study that is done in Malaysia also found no association between diarrhoea and severity of dengue disease (Mallhi et al., 2015).

Mucosal bleed is also a common warning sign among dengue patient. Study from dengue mortality in Malaysia also suggested that patient with mucosal bleed has higher chance of dying compared to patient with no mucosal bleed (OR 5.84; CI: 2.17-15.70; p-value< 0.05).However, there is no association noted in other study

between mucosal bleed and prolonged hospital stay and severity of dengue (Leo *et al.*, 2011).

Lethargy and restlessness has been reported to have mixed association with severity of the dengue and prolonged hospital stay. In study done in Malaysia, patient with lethargy symptom is at higher risk of having dengue haemorrhagic fever (OR 3.1 95% CI 1.88-4.78 p-value= 0.005). However, other studies done in Malaysia found no association of lethargy and prolonged hospital stay (Mallhi *et al.*, 2016b). This is supported with study done by in Taiwan(Lee *et al.*, 2006) which found no association in term of lethargy/restlessness and prolonged hospital stay among dengue patient.

In latest guideline by WHO, any hepatomegaly is considered as warning sign, not necessarily only if the enlargement is more than 2 centimetre. In study done in Malaysia, no significant association between hepatomegaly and severity of dengue was found (p=0.740) (Mallhi et al., 2015). Study done in Singapore also revealed no association between hepatomegaly and severity of dengue among dengue patients (Leo *et al.*, 2011). This is further proofed by study among dengue mortality in Malaysia that showed hepatomegaly is not significant prognosis in dengue mortality (Liew *et al.*, 2016)

Regarding severe plasma leakage its effect on hospital stay, most studies showed significant association between them. A study from dengue mortality cases in Malaysia also suggested that patient with severe plasma leakage had significantly higher chance to develop prolonged hospital stay and chance of dying compared to patient with no plasma leakage (OR 66.68; 95% CI: 9.13-487.23; p-value < 0.001) (Liew et al., 2016). Another study in Malaysia also shows that increased in

hemocentration was also associated with severe dengue in Malaysia (Mallhi *et al.*, 2016a).

Coagulopathy in dengue patient is usually caused by three mechanism which are low platelets, deranged coagulation profile, deranged liver function test and hepatitis. Prolonged prothrombin time (OR 2.03; 95% CI: 1.07-3.84; p = 0.002) and activated partial thromboplastin time (OR 1.80 ;95% CI: 1.15-2.83; p = 0.001) were highly associated with prolonged admission among dengue patients. However, study in Taiwan done in 2006 showed patient with coagulopathy has no association of having severe dengue (OR 1.30 95% CI: 0.58-2.86 p-value= 0.019).

Regarding thrombocytopenia, most studies revealed there was no association between prolonged hospital stay and level of platelet among dengue patient. Study done in Trinidad and Tobago also showed there was no association between platelet level and hospital stay (p-value= 0.660). Other study that is done by Karunakaran et el also shows no significant association between platelet level and severity of dengue (OR 1.7; 95% CI: 1.20-2.40, p-value= 0.09). Research done also showed no association between platelet level and hospital stay among dengue patients in Pakistan (OR 0.23; 95% CI 0.04-1.13; p-value= 0.070) (Khalil et al., 2014).

Pertaining to severe dengue, severe organ involvement is also associated with severe dengue and mortality. Among organs that are commonly severely affected are brain, kidney, liver and heart. Patient with abnormal reflex and altered sensorium have higher risk of contracting severe dengue (OR 8.5 95% CI: 1.8-39.4, p-value= 0.007 and OR 156 95% CI: 12.6-193, p-value= <0.000 respectively)(Liew *et al.*, 2016). Study in Malaysia also showed that severe dengue fever is associated with longer hospital stay compared to normal dengue fever (4.64 days vs. 2.52 days, p-

value 0.006).Acute kidney injury is also a common organ involvement of severe dengue. According to Khalil et el, acute kidney injury is associated with prolonged hospital stay. Study in Taiwan done in 2006 shows patient with renal insufficiency have higher risk of developing severe form of dengue (OR 3.65; 95% CI: 1.14-16.26 ; p-value= 0.048) (Lee *et al.*, 2006). In Malaysia, high serum creatinine level was associated with dengue haemorrhagic fever (OR 2.3; 95% CI 1.9-2.6; p-value <0.001) (Mallhi et al., 2015).

Other severe form of severe dengue is severe plasma leakage which can lead to dengue shock syndrome (DSS). Dengue shock syndrome has been recognised as one of the associated factors that lead to prolonged hospital stay and or even death (WHO, 2009). This is shown in a study on factor associated with dengue mortality in Malaysia (OR 1457.879, 95% CI 125.44-25982.98 p-value< 0.001) (Liew *et al.*, 2016). Study done in Singapore also show prolonged hospital admission among people who develop Dengue Shock Syndrome(Leo *et al.*, 2011).

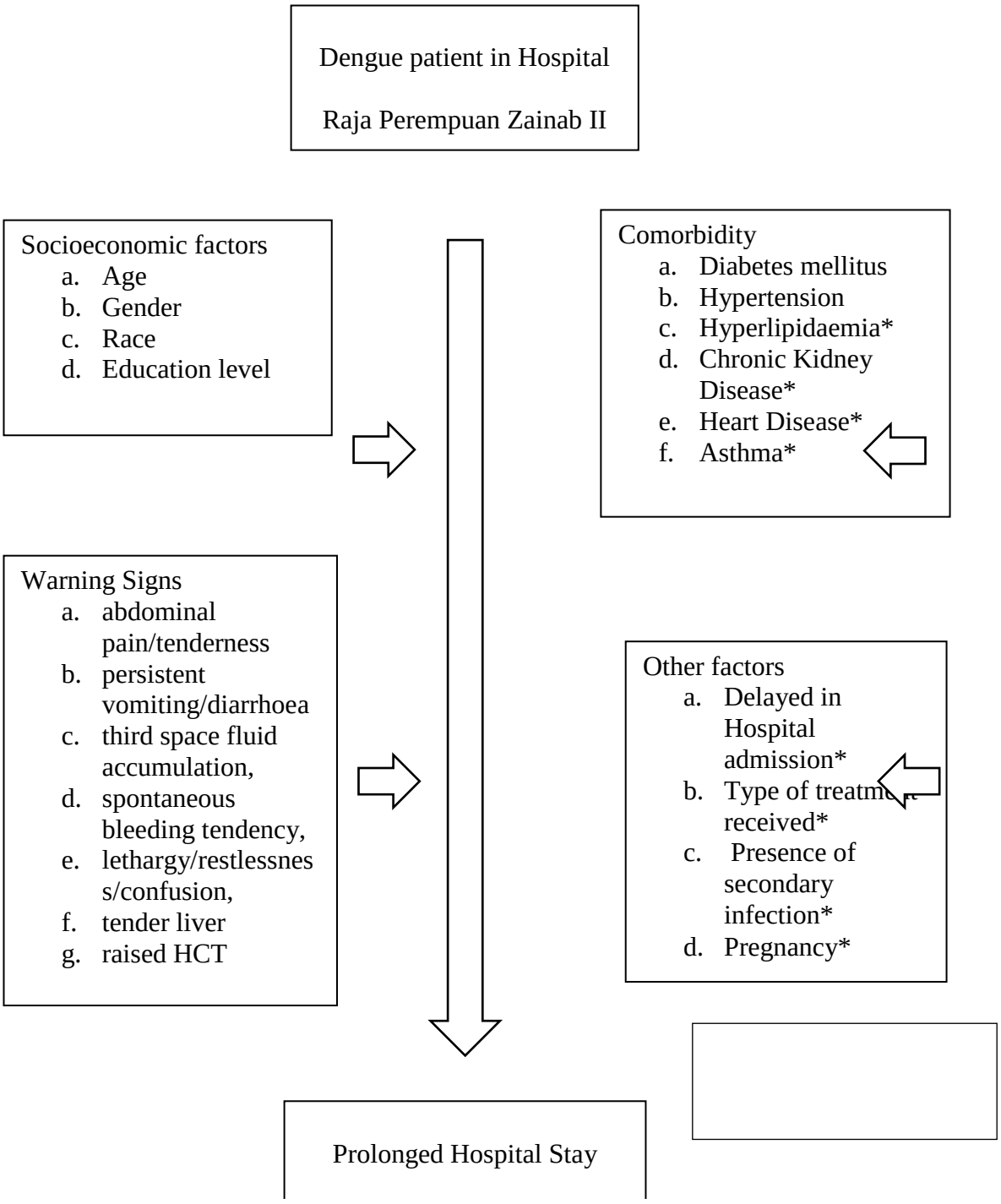

Figure 2.1: Conceptual Framework of Associated Factors of Prolonged Hospital Stay among Adult dengue Patient

Chapter 3

METHODOLOGY

3.1 Study design

This was a cross sectional study.

3.2 Study location

Data were collected from dengue patients' medical case record who were admitted into Hospital Raja Perempuan Zainab II in year 2015-2016.

3.3 Reference and Source population

All adult dengue fever patients who were admitted into Hospital Raja Perempuan Zainab II.

3.4 Sampling Frame

List of all adult dengue fever patients who were admitted to Hospital Raja Perempuan Zainab II in 2015-2016 who fulfilled the study criteria were obtained from the record office.

3.4.1 Study criteria

Inclusion criteria:

a. All adult patient (aged > 18 years old)who were being diagnosed as dengue fever patient based on hospital discharge. This is based on International Classification of Disease (ICD) 10 classification. All patient who are coded as A 90 (classical dengue) and A 91 (haemorrhagic dengue) were selected for this study.

b. Adult patient who were admitted to the Hospital Raja Perempuan Zainab II from 1st January 2015 until 31st December 2016.

Exclusion criteria:

a. Patients with more than 20% missing data in their records.

b. Patients who passed away within 72 hours of admission

c. Pregnant women

d. Patients who were transferred from other district hospitals

e. Patients who were transferred to other hospital for completion of treatment

f. Patients who acquire the dengue infection outside Kota Bharu district

3.5 Operational Definition

The operational definition that were used for this study were as below:

a) Prolonged hospital stay was defined as hospital stay of more than 72 hours (Khalil et al., 2014)

b) Patient is considered to have dengue fever infection based on the diagnosis on their hospital discharge. All patients with discharge criteria A 90 and A 91 was selected for this study. This is based on International Classification of Disease (ICD) 10 classification which code A 90 as classical dengue and A 91 as haemorrhagic dengue.

c) Presence of comorbidities (diabetes mellitus and hypertension) as diagnosed by clinician

d) Warning signs in dengue fever was characterized by the presence of the following clinical manifestations:

I. Abdominal pain or tenderness and/or
II. Persistent vomiting and/or diarrhoea (>3 times per day) and/or
III. Clinical fluid accumulation and/or
IV. Mucosal bleed and/or
V. Lethargy, confusion, restlessness and/or

VI. Tender liver (CPG on Management of Dengue Management in Adult)

e) Patients were considered as having raised haematocrit when they fulfilled the following criteria:

I. HCT for male less than 60 years is set at 46 %

II. HCT for male 60 years and above is set at 42 %

III. HCT for female in all age group) Is set at 40 %

(CPG on Management of Dengue Management in Adult)

f) Dengue patients were considered as having severe dengue when they fulfilled the following criteria:

I. Severe plasma leakage leading to dengue shock syndrome (DSS) and fluid accumulation with respiratory distress and/or

II. Severe bleeding (as evaluated by clinician) and/or

III. Severe organ involvement; liver AST or ALT >1000mmol/L, CNS: impaired consciousness, involvement of heart and other organ

(CPG on Management of Dengue Management in Adult)

3.6 Sample size estimation

Sample size was calculated for each objective of the study.

For objective 1 which is to describe the proportion of adult dengue fever patients with prolonged hospital stay in Hospital Raja Perempuan Zainab II in 2015 and 2016

Sample size estimation was calculated based on the single proportion formula:

$$n = (z\alpha/\Delta)2\ p(1-p)$$

Absolute precision, $\Delta = 5\%$ (0.05)

$z = 1.96$

Proportion of patients with prolonged hospital stay due to dengue fever:

p = 27.4 % or (0.27) (Khalil *et al.*, 2014)

$n = (1.96/0.05)^2\ (0.27 \times 0.73)$

= 302

For objective 2 which is determine the associated factors of prolonged hospital stay among dengue patient in HRPZ II from 2015 to 2016

$\alpha = 0.05$ power = 0.8

p0 = expected proportion of associated factors in normal hospital stay among dengue patient

p1 =proportion of associated factors in prolonged hospital stay among dengue patient (from literature review)

The sample size was calculated based on proportion of associated factors of prolonged hospital stay dengue patient among dengue patients. The largest sample size required was from prevalence of prolonged hospital stay among dengue patients, n=302. Therefore, to get a significant result with the power of study of 80%, sample size of 302 was needed.

3.7 Sampling method and subject recruitment

A list of dengue patients were generated based on notification of the cases from Kota Bharu district. This ensured that the patients were already investigated and contracted the disease in Kota Bharu district. The list was obtained from eDengue website. eDengue is an exclusive dengue surveillance notification system that was first introduced in 2012. It is an online system that incorporated all information regarding dengue cases, laboratory result, vector control activity, health education and other activities. The integration of the information can be shared and help in better surveillance and dengue management programs (MOH Malaysia, 2016). All adult dengue patients who fulfilled the study criteria were listed and randomly selected. A list of randomly selected patients using Microsoft Excel 2013 was sent to Hospital Raja Perempuan Zainab II record office and the patients' record were sought by the staff for data collection later.