Clinical Manifestation and Laboratory Findings as Predictive Factors for Dengue Mortality in Kota Bharu

by

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LIST OF ABBREVIATIONS

ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
CRT	Capillary refilling time
CPG	Clinical practice guideline
CT	Computer tomography
DBP	Diastolic blood pressure
ELISA	Enzyme-linked immunosorbent assay
FBC	Full blood count
Hb	Haemoglobin
HCT	Haematocrit
HREC	Human Research Committee
HRPZ II	Hospital Raja Perempuan Zainab II
HUSM	Hospital Universiti Sains Malaysia
IgM	Immunoglobulin M
IgG	Immunoglobulin G
JKNK	Jabatan Kesihatan Negeri Kelantan
MOH	Ministry of Health

NS	Non-structural
RNA	Ribonucleic acid
SBP	Systolic blood pressure
SOB	Shortness of breath
TWC	Total white count
UMMC	Universiti Malaya Medical Centre
WHO	World Health Organization

TABLE OF CONTENTS

CLINICAL MANIFESTATION AND LABORATORY FINDINGS AS PREDICTIVE FACTORS FOR DENGUE MORTALITY IN KOTA BHARU

ABSTRACT

Background: Dengue fever is an endemic disease in Malaysia. Changing of time made the classical clinical manifestation of dengue fever become vary and present a challenge in diagnosing and managing the patients. Warning signs and laboratory changes as describes in the WHO dengue guidelines 2009 are not usually present in every patient. We aim to identify the clinical manifestation and laboratory findings among the confirmed adults dengue-associated mortality patients in Kota Bharu Kelantan Malaysia.

Methods: We conducted a case control study in all confirmed dengue death patients in Kota Bharu from January of 2005 till December 2015. All adult death patients were included and control was by computer-generated randomization. Four controls were chosen for every dengue-associated death case. Data were analysed by simple and multiple logistic regression.

Results: Of 25 deaths, median age was 42 (SD ±14.5) years old. Male gender comprised of 56% and comorbidities existed in 60% of the cases. Majority of patients sought treatment at the average of day 5 of fever. The warning sign that most patients had were nausea/ vomiting while the least was mucosal bleed. Laboratory abnormalities on admission included leucopenia (40%), leucocytosis (16%), raised urea (28%) and creatinine (36%). 80% of the dengue-associated mortality had thrombocytopenia during presentation with mean of 74.2 x 10^3(SD ±62.61). Multiple logistic regression analysis showed two clinical manifestations were negatively associated with dengue-associated mortality – vomiting/nausea (adj. OR 0.13, 95% CI 0.02-0.76) and headache (adj.OR

0.15, 95% CI 0.03-0.86). Laboratory findings that were associated with dengue-associated mortality were first TWC (adj. OR 1.82, 95% CI 1.08-3.05), second TWC (adj. OR 1.54, 95% CI 1.15-2.07), second platelet (adj. OR 0.97, 95% CI 0.95-0.99), urea (adj. OR 2.35, 95% CI 1.43-3.85) and creatinine (adj. OR 0.98, 95% CI 0.97-1.00).

Conclusions: Dengue patients with vomiting/nausea and headache were the clinical manifestations of lower chance of having dengue-associated mortality. Laboratory findings of increasing in total white count and urea, reducing in platelet and creatinine were more likely to associate with dengue-associated mortality. Early detection of clinical deterioration and prompt treatment is the main key of prevention of death.

ABSTRAK

Pengenalan: Deman denggi adalah penyakit endemic di Malaysia. Perubahan masa menyebabkan pertunjukkan klinikal deman denggi yang klasik menjadi berbeza dan menjadikannya sebagai satu cabaran dalam mendiagnosa dan merawat. Tanda-tanda amaran seperti yang digambarkan dalam garis panduan deman denggi WHO 2009 adalah jarang ditunjukkan dalam setiap pesakit. Matlamat kami adalah untuk mengenal pasti pertunjukkan klinikal dan keputusan makmal di antara pesakit kematian demam denggi di kawasan Kota Bharu Kelantan Malaysia.

Kaedah: Kami menjalankan satu kajian case control di antara semua pesakit yang telah disahkan kematian demam denggi di Kota Bharu daripada Januari 2005 hingga Disember 2015. Semua pesakit yang kematian denggi dimasukan dalam kajian dan kes kawalan dipilih secara rawak oleh komputer. Empat kes kawalan dipilih untuk setiap satu kes kematian. Data dianalisis dengan simple dan multiple logistic regression.

Keputusan: Daripada 25 pesakit, median untuk umur ialah 42 tahun (SD ±14.5). Lelaki terdiri daripadda 56% dan yang mempunyai comorbid wujud dalam 60%. Majoriti pesakit mendapatkan rawatan dalam purata masa hari ke-lima demam. Tanda amaran yang ditunjukkan oleh kebanyakan pesakit adalah loya/muntah manakala yang paling sikit ialah pendarahan mukosa. Keputusan makmal yang tidak normal semasa kemasukan ke hospital termasuk leucopenia (40%), leukositosis (16%), kenaikan urea (28%) dan kreatinin (36%). 80% pesakit yang kematian denggi mempunyai thrombocytopenia semasa pertunjukkan dengan mean 74.2 x 10^3(SD ±62.61). multiple logistic regression analisis menunjukkan dua pertunjukkan klinikal berkaitan dengan kematian demam denggi-loya/muntah ((adj. OR 0.13, 95% CI 0.02-0.76) dan sakit kepala (adj.OR 0.15, 95% CI 0.03-0.86). keputusan makmal yang berkaitan dengan

kematian denggi ialah TWC pertama (adj. OR 1.82, 95% CI 1.08-3.05), TWC kedua (adj. OR 1.54, 95% CI 1.15-2.07), platelet kedua (adj. OR 0.97, 95% CI 0.95-0.99), urea (adj. OR 2.35, 95% CI 1.43-3.85) and kreatinin (adj. OR 0.98, 95% CI 0.97-1.00). **Kesimpulan**: Pesakit yang menunjukan kemutahan dan sakit kepala mempunyai kemungkinan kematian yang rendah manakala peningkatan dalam bilangan sel darah putih dan urea, penurunan dalam platelet dan kreatinin menjadikan kemungkinan kematian meningkat. Pengesanan kemerosotan klinikal dan pemberian rawatan yang segera adalah kunci utama untuk mengelakan kematian.

1. INTRODUCTION

Dengue viruses are mosquito-borne enveloped RNA viruses belonging to the family Flaviviridae in the genus Flavivirus. The new WHO classification for dengue severity is divided into dengue without warning sign, dengue with warning sign and severe dengue. According to WHO Western Pacific Region (WPRO), until 12 August 2014, cumulative number of reported cases in Malaysia is 53,246 and cumulative number of deaths reported is 147. Latest update from WPRO, for the week from 17 April to 23 April in 2016, the number of dengue cases was 1,607, a decrease from 1,854 cases reported in the previous week. The number of cases was higher than that reported during the same period in 2015. Within the same period there were two dengue-related deaths reported, bringing the total number of deaths for 2016 to 94, compared to a total of 120 deaths during the same reporting period in 2015. Refer to Centers for Disease Control and Prevention (CDC), dengue is endemic in more than 110 countries and it is a leading cause of illness and death in the tropics and subtropics. It only emerged as a global issue since 1950s.

Dengue virus (DENV) infection is a global disease which was affecting at least 3.6 billion people living in more than 125 countries in the tropics and subtropics (Gubler 2012, Sam, Omar et al. 2013). In Malaysia, cases of dengue had increased from 15.2 per 100,000 in 1973 to 361.0 per 100,000 populations by the year 2014. At the same time, the mortality cases also went up from 0.16% to 0.62% between 2000 to 2013 (Kadir, Mohamed et al. 2015). Kota Bharu area contributed almost 70% of the dengue fever cases in Kelantan (Hussin, Jaafar et al. 2005).

Dengue viruses are mosquito-borne enveloped RNA viruses belonging to the family Flaviviridae in the genus Flavivirus. Dengue virus is an envelope positive-sense RNA virus. It composed of 3 structural protein genes that encode the nucleocapsid or core protein (C), a membrane associated protein (M), an envelope protein (E) and seven non-structural (NS) protein genes (NS 1, NS 2A, NS 2B, NS 3, NS 4A, NS 4B, NS 5). Among that, NS 1 is an essential for the virus viability.

The new WHO classification for dengue severity is divided into dengue without warning sign, dengue with warning sign and severe dengue (Michael B. Nathan 2009). As Malaysia is one of the endemic countries for dengue, diagnostic investigation is a must. There are a few diagnostic tests that are available, include antibody detection (serology), virus isolation, detection of virus genetic materials (polymerase chain reaction -PCR) and detection of dengue virus protein (NS1 antigen). A study in UMMC showed that the dengue deaths were seen primarily in adult females and were associated with secondary dengue infection (Sam, Omar et al. 2013). Changes in the climate, urbanization, rapid industrialization and economic growth and poor environmental cleanliness were the factors that cause rapid increase in the dengue cases (Mudin 2015).

There were a number of reports reviewing the clinical manifestations and risk factors associated with the dengue fever and dengue-related deaths during the first two decades following the 1973 epidemic (Paramaesvaran 1965, George, Kassim et al. 1974, Wallace, Lim et al. 1980, Sam, Omar et al. 2013). In order to provide early and accurate management of the dengue patients and early public health notification and outbreaks control of dengue infection outbreaks, it is important to establish a diagnosis of acute dengue virus infection during the first

few days after manifestation of clinical symptoms. MOH Malaysia has come out with a method- Communication for Behavioural Impact (COMBI), it is an approach that can be utilized to mobilize communities for disease prevention. This approach is used to empower the people in dengue prone areas via mobilizing their community and resources in planning and implementing activities aimed at the prevention and control of dengue outbreaks in their area (Maimunah Bt A Hamid 2011).

Currently, there is neither a vaccine to prevent the disease nor an antiviral treatment. However, secondary prevention to reduce mortality through improved clinical case management has substantially lowered the mortality rate for severe dengue over the past two decades from 10—20% to <1% (Sumarmo, Jahja et al. 1983, Tran, Thanh Hung et al. 1998). Early clinical feature of dengue fever is influenza-like fever. This makes clinical diagnosis a challenge. The usual symptom associated with fever was nausea and vomiting, followed by abdominal pain, rash, body aches, diarrhea, cough, hematemesis, bleeding gums, malena, altered mental status and jaundice (Almas, Parkash et al. 2010). Risk factors for fatality in patients with dengue infection have been identified in studies in the Americas (Guzmán, Kouri et al. 2002, Guzmán, Kourí et al. 2002, García-Rivera and Rigau-Pérez 2003, Rigau-Pérez and Laufer 2006, Cavalcanti, Coelho et al. 2010), Africa (Adam, Jumaa et al. 2010), Australia (McBride 2005), Pacific islands (Barnes and Rosen 1974), South Asia (Raheel, Faheem et al. 2010, Juneja, Nasa et al. 2011) and Southeast Asia(Sumarmo, Jahja et al. 1983, Magpusao, Monteclar et al. 2003, Anders, Nguyet et al. 2011, Lee, Liu et al. 2012). Even though, there were no definite symptoms and signs that could predict the outcome of the disease. Different area had different factors that

contributed to the mortality. In order to better understand and able to recognize the risk factors for mortality and the epidemiology of severe dengue cases in Hospital Universiti Sains Malaysia (HUSM) and Hospital Raja Perempuan Zainab II (HRPZ II) population, we conducted a case-control study of all dengue associated deaths within our institution and HRPZ II

2. OBJECTIVE

The general objective of this study was to determine the associated factors between clinical features and laboratory findings in dengue mortality patients.

The specific objectives were:

1. To describe the demographic data of dengue mortality cases in Kelantan
2. To determine the association of clinical features in dengue-associated mortality patients
3. To determine the association of laboratory results in dengue-associated mortality patients
4. To determine the percentage of platelet reduction between first sample and second sample (at least 6 hour apart) in dengue-associated mortality patients.

3. MANUSCRIPT

The prepared manuscript is included in the following pages. The manuscript was prepared following MJMS journal format as attached at the end of the manuscript.

TITTLE: Clinical Manifestation and Laboratory Findings as Predictive Factors for Dengue Mortality in Kota Bharu

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ABSTRACT

Background: Dengue fever is an endemic disease in Malaysia. Changing of time made the classical clinical manifestation of dengue fever become vary and present a challenge in diagnosing and managing the patients. Warning signs and laboratory changes as described in the WHO dengue guidelines 2009 are not usually present in every patient. We aim to identify the clinical manifestation and laboratory findings among the confirmed adults dengue-associated mortality patients in Kota Bharu Kelantan Malaysia.

Methods: We conducted a case control study in all confirmed dengue death patients in Kota Bharu from January of 2005 till December 2015. All adult death patients were included and control was by computer-generated randomization. Four controls were chosen for every dengue-associated death case. Data were analysed by simple and multiple logistic regression.

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sought treatment at the average of day 5 of fever. The warning sign that most patients had were nausea/ vomiting while the least was mucosal bleed. Laboratory abnormalities on admission included leucopenia (40%), leucocytosis (16%), raised urea (28%) and creatinine (36%). 80% of the dengue-associated mortality had thrombocytopenia during presentation with mean of 74.2 x 10^3(SD ±62.61). Multiple logistic regression analysis showed two clinical manifestations were negatively associated with dengue-associated mortality – vomiting/nausea (adj. OR 0.13, 95% CI 0.02-0.76) and headache (adj.OR 0.15, 95% CI 0.03-0.86). Laboratory findings that were associated with dengue-associated mortality were first TWC (adj. OR 1.82, 95% CI 1.08-3.05), second TWC (adj. OR 1.54, 95% CI 1.15-2.07), second platelet (adj. OR 0.97, 95% CI 0.95-0.99), urea (adj. OR 2.35, 95% CI 1.43-3.85) and creatinine (adj. OR 0.98, 95% CI 0.97-1.00).

Conclusions: Dengue patients with vomiting/nausea and headache were the clinical manifestations of lower chance of having dengue-associated mortality. Laboratory findings of increasing in total white count and urea, reducing in platelet and creatinine were more likely to associate with dengue-associated mortality. Early detection of clinical deterioration and prompt treatment is the main key of prevention of death.

Key words: *clinical manifestation, laboratory findings, dengue fever, mortality, Kota Bharu*

Background

Dengue virus (DENV) infection is a global disease which was affecting at least 3.6 billion people living in more than 125 countries in the tropics and subtropics (1). In Malaysia, cases of dengue had increased from 15.2 per 100,000 in 1973 to 361.0 per 100,000 populations by the year 2014. At the same time, the mortality cases also went up from 0.16% to 0.62% between 2000 to 2013 (2). Total 1701 dengue cases in whole Malaysia were reported from 25 September till 1 October 2016. Throughout January 2016 till October 2016, 83224 cases were recorded compare with 91822 cases in year 2015. Kelantan is among the highest number of dengue cases, which was after Selangor, Johor and Kuala Lumpur (3).

Changes in the climate, urbanization, rapid industrialization and economic growth and poor environmental cleanliness were the factors that causing rapid increasing of the dengue cases (4). Study showed that dengue-related death is about 0.002% since 2001 (5). There were reports reviewing the clinical manifestations and risk factors associated with dengue fever and dengue-related deaths during the first two decades following the 1973 epidemic (6). A study in Universiti Malaya Medical Centre showed that the dengue deaths were seen primarily in adult females and were associated with secondary dengue infection (7).

In order to provide early and accurate management of the dengue patients and early public health notification and control of dengue infection outbreaks, it is important to prevent the dengue cases in the community and establish a diagnosis of acute dengue virus infection in healthcare facilities. MOH Malaysia has come out with a method - Communication for Behavioural Impact (COMBI), it is an approach that can be utilized to mobilize communities for disease prevention. This approach is used to empower the

people in dengue prone areas via mobilizing their community and resources in planning and implementing activities aimed at the prevention and control of dengue outbreaks in their area (8). Currently, there is neither a vaccine to prevent the disease nor an antiviral treatment. However, secondary prevention to reduce mortality through improved clinical case management has substantially lowered the mortality rate for severe dengue over the past two decades from 10—20% to <1% (9). The usual symptom associated with fever was nausea and vomiting, followed by abdominal pain, rash, body aches, diarrhea, cough, hematemesis, bleeding gums, malena, altered mental status and jaundice (10). Risk factors for fatality in patients with dengue infection have been identified in studies in the Americas (11), Africa (12), Australia (13), Pacific islands (14), and South Asia (15). Even though, there were no definite symptoms and signs that could predict the outcome of the disease. Different area had different factors that contributed to the mortality. In order to better understand and able to recognise the risk factors for mortality and the epidemiology of severe dengue cases in Hospital Universiti Sains Malaysia (HUSM) and Hospital Raja Perempuan Zainab II (HRPZ II) population, we conducted a case-control study of all dengue associated mortality within our institution and HRPZ II.

Materials and methods

A case-control study was performed. All cases of dengue-associated mortality in HUSM and HRPZ II for the period year 2005 to 2015 were identified through Jabatan Kesihatan Negeri Kelantan (JKNK) included those cases referred from other state and died at HRPZ II or HUSM. Paediatric patients and who were diagnosed dengue fever but cause of death was secondary to non-dengue fever were excluded from this study. Not all the cases from the year 2005 to 2015 were selected because of missing files and some were destroyed during the largest recorded flood in Kelantan history where HRPZ II was badly affected and had to close the hospital (16). This study was approved by Human Research Committee USM (HREC) and Medical Research and Ethics Committee Ministry of Health Malaysia. HUSM is a-783 bed tertiary care centre while HRPZ II is a-920 bed tertiary centre.

All cases of dengue were defined as: (i) a compatible clinical illness with (ii) positive serology (IgM and/or IgG by immunocromatographic test (2014 onward) or ELISA (before 2014) or iii) NS 1 antigen. Dengue- associated mortality was defined as deaths resulting from, and as a direct consequence of acute dengue infection. Patients admitted with dengue virus infection from year 2005 to 2015 were selected from the HUSM and HRPZ II patient database as controls. Four controls were chosen for every dengue-associated mortality case. The medical records of all cases identified were reviewed. Final disease categorization into dengue fever without warning signs, dengue with warning signs and severe dengue, based on the World Health Organization's recommended system of classification (WHO 2009). Duration of illness (day 1 of illness was counted as the day of fever onset), demographic, clinical, and laboratory data were collected on standardized data-collection forms. Petechiae, epistaxis and gingival bleeding were classified as minor bleeding complications. First full blood

count (TWC, platelet, haematocrit and haemoglobin) was taken upon arrival to the emergency department (ED) HUSM or HRPZ II. Second platelet was selected based on timing of subsequent full blood count taken which was at least 6 hours apart from the first full blood count.

Data were entered into SPSS version 22 software. The descriptive results for categorical variables were displayed by frequency and percentage. For continuous variables, mean and standard deviation were used. Certain variables were excluded from the univariate analysis such as lethargic, chest pain, convulsion, full blood count before treatment at ED, creatine kinase, coagulation profile, bicarbonate level, serum lactate, capillary blood sugar and the difference of platelet count between platelet before arrival referral to ED and arrival in the ED due to large number of missing values. There were 25 readily available biodata, clinical parameters and laboratory results (age, duration of illness, vomiting/nausea, abdominal pain, mucosal bleed, headache, myalgia, arthralgia, hepatomegaly, cold periphery, dehydration, rashes, pulse volume, systolic blood pressure, diastolic blood pressure, first TWC, second TWC, first platelet count, second platelet count, first haematocrit, second haematocrit, urea, creatinine, different between first and second platelet and percentage of reduction between first and second platelet) with $p<0.25$ and clinically significant from univariate analysis were put into the multivariate model. Level of significant set at 2 tailed p-value of <0.25.

Results

Table 1: Demographic of dengue mortality and uncomplicated cases

Variable		Mortality-associated group (n=25) n (%)	Uncomplicated DF (n = 100) n (%)
Age (years)*		42.4 (14.5)	32.6 (15.0)
Ethnicity	Malay	22 (88.0)	96 (96.0)
	Chinese	3 (12.0)	-
	Indian	-	1 (1.0)
	Others	-	3 (3.0)
Sex	Male	14 (56.0)	49 (49.0)
	Female	11 (44.0)	51 (51.0)
Location	Kota Bharu	17 (68.0)	71 (71.0)
	Pasir Puteh	1 (4.0)	2 (2.0)
	Bachok	1 (4.0)	18 (18.0)
	Machang	1 (4.0)	-
	Kuala Krai	2 (8.0)	-
	Pasir Mas	2 (8.0)	4 (4.0)
	Tumpat	1 (4.0)	5 (5.0)
Medical illness	DM	4 (16.0)	4 (4.0)
	HPT	7 (28.0)	10 (10.0)
	BA	2 (8.0)	3 (3.0)
	COAD	1 (4.0)	1 (1.0)
	IHD	2 (8.0)	1 (1.0)
	Others	5 (20.0)	5 (5.0)
Fever		24 (96)	100 (100)
Duration of fever (day)	1	0 (0.0)	3 (3.0)
	2	3 (12.0)	12 (12.0)
	3	5 (20.0)	13 (13.0)
	4	5 (20.0)	23 (23.0)
	5	9 (36.0)	19 (19.0)
	≥6	2 (8.0)	28 (28.0)

*Mean (SD)

Table 2: Presenting symptoms of dengue mortality and uncomplicated cases

Variable	Mortality-associated Group (n=25) n (%)	Uncomplicated DF (n = 100) n (%)
Vomit/nausea	12 (48)	70 (70)
Abdominal pain	6 (24)	42 (42)
Mucosal bleed	2 (8)	10 (10)
SOB	4 (16)	4(4)
Diarrhea	7 (28)	31 (31)
Cough	6 (24)	12 (12)
Running nose	2 (8)	3 (3)
Sore throat	2 (8)	4 (4)
Headache	13 (52)	73 (73)
Myalgia	19 (76)	86 (86)
Arthralgia	16 (64)	79 (79)
Retro-orbital pain	12 (48)	38 (38)
Hepatomegaly	9 (36)	7 (7)
Cold periphery	11 (44)	11 (11)
Dehydration	16 (64)	47 (47)
Rashes	3 (12)	22 (22)
Poor Pulse volume	5 (20)	1 (1)
Prolonged CRT	4 (16)	3 (3)

Table 3: Presenting signs and laboratory results of dengue mortality and uncomplicated cases

Variable	Mortality-associated group (n=25)		Uncomplicated DF (n = 100)	
	Mean (SD)	Range	Mean (SD)	Range
Duration of illness	7.6 (2.47)	3-13	7.9 (1.93)	3-14
Heart rate	102.6 (23.32)	61-137	89.5 (18.17)	45-135
Respiratory rate	23.0 (4.82)	17-36	19.8 (2.51)	12-32
SBP	112.6 (24.29)	52-164	117.6 (16.59)	88-180
DBP	68.1 (12.13)	32-95	72.6 (12.36)	40-100
Pulse pressure	44.0 (15.76)	18-72	44.6 (12.87)	16-102
Temperature	37.9 (1.05)	36.8-41.1	37.9 (0.89)	36.2-40.0
First TWC	5.9 x 10^9 (3.81)	1.6-16.7 x 10^9	3.6 x 10^9(1.64)	1.4-10.3 x 10^9
Second TWC	7.3 x 10^9 (5.91)	1.3-24.7 x 10^9	3.5 x 10^9(1.56)	1.3-9.0 x 10^9
First platelet	74.2 x10^3(62.61)	0-205 x 10^3	103.7 x 10^3 (59.49)	1-294 x 10^3
Second platelet	57.8 x 10^3 (54.21)	1-177 x 10^3	89.2 x 10^3 (55.80)	7-266 x 10^3
First HCT	41.4 (8.57)	20.1-54.2	41.0 (4.82)	24.0-53.7
Second HCT	39.7 (6.89)	23.4-50.7	39.6 (4.41)	24.9-49.5
First Hb	14.1 (3.13)	6.9-19.8	14.0 (1.96)	4.2-18.6
Second Hb	13.5 (2.62)	7.6-18	13.5 (1.69)	8.4-17.9
Urea	8.0 (6.07)	2.5-25.9	4.3 (3.33)	1.3-31.5
Creatinine	150.7 (154.09)	53-804	93.6 (106.14)	3-1109
Albumin	32.4 (11.60)	14-75	37.9 (5.90)	4-52
AST	421.4 (727.17)	5-3497	141.2 (165.04)	18-933
ALT	481.7 (1076.49)	12-4500	91.9 (97.52)	7-538
ALP	160.1 (123.51)	18-519	94.0 (53.72)	314-287
Different platelet	16.4 (28.47)	-46-89	14.9 (22.27)	-35-105
% different platelet	15.0 (39.21)	-88.8-76.0	13.9 (24.39)	-92.8-82.0

Table 4: Crude OR, 95% CI and p-value for univariate unadjusted binary logistic regression and multivariate adjusted binary logistic regression.

Variable	Univariate analysis		Multivariate analysis	
	Crude OR (95% CI)	p-value	Adjusted OR (95% Cl)	P-value
Age	1.04 (1.01,1.08)	0.005		
Sex	0.76 (0.31,1.82)	0.532		
Duration of illness	0.94 (0.38,1.17)	0.553		
Vomiting/nausea	0.40 (0.16,0.97)	0.420	0.13 (0.02,0.76)	0.023
Abdominal pain	0.44 (0.16,1.19)	0.104		
Mucosal bleed	0.78 (0.16,3.82)	0.762		
SOB	4.00 (0.92,17.33)	0.640		
Diarrhea	0.82 (0.31,2.16)	0.681		
Cough	2.11 (0.70,6.33)	0.185		
Running nose	2.52 (0.40,15.99)	0.326		
Sore throat	1.83 (0.32,10.60)	0.502		
Headache	0.31 (0.12,0.78)	0.013	0.15 (0.03,0.86)	0.033
Myalgia	0.48 (0.16,1.42)	0.184	0.25 (0.03,2.23)	0.215
Arthalgia	0.43 (0.16,1.11)	0.082		
Retro-orbital pain	1.05 (0.43,2.56)	0.924		
Hepatomegaly	7.31 (2.38,22.45)	<0.001		
Cold periphery	6.36 (2.32,17.42)	<0.001		
Dehydration	2.01 (0.81,4.96)	0.132		
Rashes	0.48 (0.13,1.77)	0.272		
CRT	6.16 (1.28,29.59)	0.023		
Heart rate	1.03 (1.01,1.06)	0.004		
Respiratory rate	1.32 (1.13,1.55)	<0.001		
SBP	0.99 (0.96,1.01)	0.226	0.92 (0.85,1.01)	0.068
DBP	0.97 (0.94,1.01)	0.109	1.01 (0.91,1.12)	0.883
Pulse pressure	0.99 (0.96,1.03)	0.841		
Temperature	0.97 (0.60,1.56)	0.887		
First TWC	1.45 (1.18,1.77)	<0.001	1.82 (1.08,3.05)	0.024
Second TWC	1.54 (1.23,1.94)	<0.001	1.54 (1.15,2.07)	0.004
First platelet	0.99 (0.98,0.99)	0.034		
Second platelet	0.99 (0.98,0.10)	0.018	0.97 (0.95,0.99)	0.005
First HCT	1.01 (0.94,1.10)	0.764		
Second HCT	0.99 (0.96,1.03)	0.704		
First Hb	1.01 (0.83,1.24)	0.893		
Second Hb	1.00 (0.98,1.03)	0.930		
Urea	1.21 (1.06,1.39)	0.005	2.35 (1.43,3.85)	0.001
Creatinine	1.00 (0.99,1.01)	0.097	0.98 (0.97,1.00)	0.008
Albumin	0.90 (0.85,0.97)	0.003		
AST	1.00 (1.00,1.00)	0.006		
ALT	1.01 (1.00,1.01)	0.008		
ALP	1.01 (1.00,1.02)	<0.001		
Different 1^{st} and 2^{nd} platelet	1.00 (0.98,1.02)	0.770		
% different 1^{st} and 2^{nd}	0.99 (0.98,1.01)	0.695		

From table 1, of the dengue-associated mortality cases, 14 (56.0%) were male with a mean age of 42.44, with the youngest was 17 and the oldest was 60, 11 were female (44.0%) with the mean age of 32.55, youngest age 23 while oldest age 64; 22 (88%) patients were Malay while Chinese comprised of 3 (12%) patients. Majority of them were originated from Kota Bharu which were 17 (68%) patients. 21 (84%) patients had comorbidity such as diabetes mellitus, hypertension, bronchial asthma, chronic obstructive pulmonary disease, ischemic heart disease and other illnesses. There was one afebrile dengue-associated mortality patient who presented to hospital with convulsion and low platelet. CT brain was done and was found to have intracranial haemorrhage and dengue confirmation was done by dengue serology which showed IgM positive. For the patients presented with fever, only 2 persons sought for treatment after 6 days of fever.

The criteria for admission of the dengue-associated mortality cases were compared to controls and shown in table 2 and 3. All controls were categorized as having uncomplicated dengue fever. Among the alarming signs, nausea/vomiting were the most presenting symptoms among the mortality patients, which was 48%. Followed by hepatomegaly, diarrhoea, abdominal pain and mucosal bleed which were 36%, 28%, 24% and 8% respectively. . Signs of shock manifested by dehydration, cold periphery, poor pulse volume and prolonged CRT which were 64%, 44%, 20% and 16% respectively. The mean duration of illness till death was 7.6 day, ranging from 3-13 days. Mean SBP was 112.56 mmHg (SD ±24.29) and mean DBP was 68.08 (SD ±12.13). Only 3 patients were in hypotensive state during the presentation. More than 50% of the patients had tachypnoeic (RR >20) with the mean respiratory rate was 22.96 (SD ±4.82). During presentation, 11 patients (SD ±23.32) were tachycardia and more than half (60%) of them sought for treatment during the time of defervescence (Michael

B. Nathan 2009). Laboratory abnormalities on admission included leucopenia (40%), leucocytosis (16%), raised urea (28%) and creatinine (36%). 80% of the dengue-associated mortality had thrombocytopenia during presentation with mean of 74.2 x 10^3(SD ±62.61). Mean of different first platelet and second platelet count was 16.4 (SD ±28.47). Based on univariate analysis, age, abdominal pain, cough, headache, myalgia, arthalgia, hepatomegaly, cold periphery, dehydration, abnormal CRT, heart rate, respiratory rate, systolic and diastolic blood pressure, first and second total white count, first and second platelet were statistically more frequent in mortality-associated cases. However multiple logistic regression analysis shows two clinical manifestations were negatively associated with dengue-associated mortality – vomiting/nausea (adj. OR 0.13, 95% CI 0.02-0.76) and headache (adj.OR 0.15, 95% CI 0.03-0.86). Laboratory findings that were associated with dengue-associated mortality were first TWC (adj. OR 1.82, 95% CI 1.08-3.05), second TWC (adj. OR 1.54, 95% CI 1.15-2.07), second platelet (adj. OR 0.97, 95% CI 0.95-0.99), urea (adj. OR 2.35, 95% CI 1.43-3.85) and creatinine (adj. OR 0.98, 95% CI 0.97-1.00).

Discussion

Dengue-associated mortality is about 2 to 3 in a thousand cases (5). Malaysia is not exceptional with the mortality of 336 cases in year 2015 from 28 persons in year 2005 (17). Early diagnosis is crucial to control or minimize the mortality rate especially for those working as the first-line healthcare provider like emergency room doctors. Identifying the warning clinical manifestation and laboratory findings of dengue patients are also important to improve the diagnosis and hasten the treatment (18).

Male gender comprised the majority in the mortality group, which is 14 (56%) cases compare with female 11 (44%) cases. Age among the mortality cases was 42.4 (SD ±14.5). Although in our study it did not showed significant, but it was consistent with a study in Singapore (19). While another study in Singapore also, dengue mortality is also predominatly male but the mean age is older, 59 years old (21).

Among the clinical manifestation of dengue-associated mortality patients, headache and vomiting/nausea during admission to the ED have lower risk of mortality (85% vs 87%). Another study in Malaysia also showed that vomiting is a risk factor of mortality (4). A case control study from the Kerala India found that altered sensorium ($p = 0.002$) and hypertension ($p = 0.03$) were associated with dengue mortality (20). While another study at Karachi, Pakistan, SGPT >300 mg/dl ($p=0.008$), bleeding ($p<0.001$), altered mental status ($p<0.001$) and shock ($p<0.001$) were significantly associated dengue death (10). A Singapore case-control study showed that early vomiting and hematocrit changed >20% concurrent with low platelet on admission should raised the doctor suspicion for dengue death (21). In our study, patients with vomiting/nausea during presentation to ED will have lesser risk of death, where this can be because of early seeking for treatment among those having nausea, vomiting and headache.

From our study, the laboratory findings of first and second total white count, second platelet count, urea and creatinine on admission were found to be independently associated with dengue mortality. Total white count normally will be normal until the disease progress and it become leucopenia (22). Increase in total white count during presentation secondary to bacterial infection has been proposed as a predictor of death in dengue infection (23). Our results were comparable with the previous study. In our study, two samples of full blood count were taken. Both results showed that increase in total white count would increase the risk of mortality. In context with dengue mortality

cases, leucocytosis and platelet count between first presentation and prior to succumb were shown to be significant (24). Lymphocyte and monocyte counts for 24 hours prior to intensive care unit admission had shown significance higher compared to lymphocyte and monocyte counts at first presentation only (25). However there is no guideline stated the usage of antibiotic in dengue infection because it was difficult to differentiate between sepsis in dengue shock and dengue with severe organ dysfunction although delayed in initiate antibiotic will increase the risk of mortality in coinfected patients (26).

Laboratory findings of thrombocytopenia has been shown to have higher risk of mortality (18). Our study showed risk of mortality increases by three percent in every 1,000/ul reduction in platelet count, which is consistent with the study in the Kerala India. Thrombocytopenia reduces the ability of clot formation and can lead to intracranial haemorrhage but it does not cause by thrombocytopenia per se. Deranged prothrombin time, disseminated intravascular coagulation, and hepatic dysfunction can contribute to the intracranial hemorrhage (27). Two samples of FBC were taken and only second FBC result of platelet count showed significant findings based on multivariate analysis. It may be due to dynamic process of the disease as the immune responses such as cytokine overproduction and generation of autoantibody acting against platelets (28). However, there was no significant different of the percentage of platelet reduction between the first sample and second sample with the mean platelet different was 16.4 X 10^3.

Higher level of urea level may be a predictor of mortality (20). Bleeding and dehydration can be a cause of raise urea level (25). However, the urea level can be varied among the patient with underlying chronic kidney disease. Our study showed the urea mean was higher in dengue-associated mortality patients compared to

uncomplicated dengue fever patient which was 8.0 (SD ±6.07) and 4.3 (SD ±3.33) respectively. Multivariate analysis showed that every 1 mmol/l of increment of urea, the risk of mortality increases by 2.3 folds. This result is comparable with the other study which showed that risk of morality increase by three percent (25). This is possible due to increase complement-fixation of dengue antigen in high urea environment (29). However, our study comes to a different view about the creatinine. Previous study had identified acute renal failure in about 80% of elderly dengue-associated mortality patient (30). Our study showed that 10 umol/l increased in creatinine decreased the odd of mortality by 16%. Early detection of renal failure and subsequently early intervention such as haemodialysis can be accomplished before deterioration. Anyway, further study is needed especially patient admitted to intensive care unit to determine the renal function and fluid therapy among the dengue patients.

Early recognition of hypoperfusion and organ failure by the identifying the warning sign is crutial to prevent mortality (26). Thus more attention should be put on these patients. Expedient and effective crystalloid replacement of fluid loss is essential in determining the progress and favourable outcome of the disease (31). We also found that in this study, the percentage of platelet reduction between first and second platelet count was not significant. It may carry a meaning that platelet count and platelet reduction rate were not an indicator of mortality in view of only eight percent of patient presented with mucosal ffbleed and coagulation profile showed insignificant results. Anyway, we belief that these finding need more evaluation and more study need to be

One of the strengths of our study was that all dengue infections were confirmed by NS1 and/or dengue serology. In contrast, previous reports on dengue mortality often depend on serology alone only. Some limitations of this study should be emphasized,

especially those related to retrospective study such as small sample size, incomplete documentation and missing data.

Conclusion

Our study demonstrates that clinical manifestation of vomiting/nausea and headache have lower risk of mortality whereas laboratory findings of the first and second total white count, second platelet count, urea and creatinine were found to be independently associated with dengue mortality. Not all the dengue patients will present with the classical warning signs and not all the patients with warning sign will have a poor outcome. Unusual clinical presentation of dengue most likely is a reflection of a change in the demographic pattern of the population being infected with dengue. Early detection of clinical deterioration and prompt treatment are still the main key of prevention of death.

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