CLINICAL FACTORS ASSOCIATED WITH MORTALITY IN DENGUE INFECTION AT A TERTIARY CARE CENTER

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Abstract. We conducted a cross-sectional study to investigate the clinical factors associated with mortality in patients with dengue viral infection at a tertiary care center over a 3 year period. Six hundred ninety-nine patients with a clinical diagnosis of dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) during the study period were included in the study. Data were collected with a predesigned form comprised of demographics, duration of fever**,** associated symptoms, diagnosis of DF, DHF and DSS, and laboratory parameters [complete blood count, coagulation tests, creatinine, serum glutamic pyruvic transaminase (SGPT)]; dengue IgM was checked in all patients by ELISA. Outcomes (survival/mortality) and complications were recorded. Mortality was the primary outcome measure. DF constituted 86.4% (604), DHF constituted 11.6% (81) and DSS constituted 2% (14) of patients. The mortality rate was 2.7% (19). The mean white blood cell count in those who died was 13.3, in those who survived was 5.3, the difference was significant (p=0.02). The mean BUN in those who died was 33.2, those who survived was 13.8, (p=0.007). The mean bicarbonate level in those who died was 17.1, those who survived was 18.5 (p <0.001). Mean activated partial thromboplastin time in those who died was 56.8, those who survived was 36.8 (p=0.01). The mean SGPT in those who died was 802, those who survived was 176 (p=0.01). Those who died were significantly (p <0.001) more likely to have severe hepatitis (63%) than those who survived (13.8%). On multivariate logistic regression analysis, having an SGPT > 300 mg/dl, bleeding, an altered mental status and shock at presentation were all significantly associated with mortality in patients with dengue virus infection (p=0.008, p<0.001, p<0.001, p<0.001, respectively).

Key words: dengue infection, mortality, associated factors

INTRODUCTION

Every year 50-100 million cases of dengue fever (DF) and 500,000 cases of dengue hemorrhagic fever (DHF), resulting in 24,000 deaths are reported worldwide with the numbers increasing annually (Barboza *et al*, 2008; Itrat *et al*, 2008). Epidemics of dengue virus infection are witnessed sporadically throughout the tropics and dengue is endemic in Southeast Asia and India. Recently it has become endemic in Pakistan, with cases seen in major hospitals all year round (Wasay *et al*, 2008).

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Dengue leads to a spectrum of symptoms in humans including a mild flu like illness, the colloquial "break-bone" fever, DHF and dengue shock syndrome (DSS). A recent study done in a tertiary care hospital in Pakistan showed cases of DHF and DSS are on the rise (Wasay *et al*, 2008). No specific treatment exists for dengue (Ahsan, 2008). Only supportive care can be provided to patients, this includes frequent monitoring of platelet levels and replacement as needed along with replacement of other blood products when necessary. Hematocrits, liver transaminases and electrolytes should also be monitored. Fever should be controlled with acetaminophen (paracetamol) and sponging, while NSAIDs should be avoided (Kabra *et al*, 1999).

Although inadequate supportive care may be an issue in some hospitals, which contributes to the morbidity and mortality in some patients with dengue fever, there are several risk factors that are associated with poor patient outcomes and mortality. Several predictors of mortality have been identified. In a study done in Taiwan the chances of mortality due to dengue infection are higher in the elderly (Lee *et al*, 2008). A study done in Singapore revealed the presence of any chronic disease is associated with poorer outcomes (Lahiri *et al*, 2008). These included renal disease (Kuo *et al*, 2008; Lee *et al*, 2008) and chronic obstructive pulmonary disease (Lee *et al*, 2008). The study done in Taiwan mentioned above found secondary bacteremia contributes to death as well (Lahiri *et al*, 2008). A study done in the Philippines revealed prolongation of PTT was associated with an increased likelihood of fatal bleeding (Chua *et al*, 1993). In recent years in Pakistan, dengue infection has taken the form of an epidemic and has been associated with poor outcomes; data is scarce regarding the factors associated with mortality in dengue infection. We therefore conducted this study to investigate the relationships between clinical factors associated with mortality in patients with dengue viral infection at a tertiary care center.

MATERIALS AND METHODS

We conducted a cross-sectional study, in patients with dengue viral infection admitted to our tertiary care center over a 3 year period from the emergency room or clinic to the medicine wards of Aga Khan University Hospital. Ethical clearance was obtained for the study from the Institutional Ethical Review Committee (ERC/06-11-07).

We included all patients admitted with a diagnosis of DF, DHF or DSS age greater than 14 years old and a positive ELISA test for dengue IgM. DF is characterized by sudden onset fever and a variety of nonspecific signs and symptoms, including frontal headache, retro-orbital pain, body aches, nausea and vomiting, joint pains, weakness, and rash. DHF is characterized by sudden onset fever, lasting 2 to 7 days, with signs of circulatory failure or hemorrhagic manifestations occuring from about 24 hours before to 24 hours after the temperature falls to normal or below normal. Common hemorrhagic manifestations include skin hemorrhages, such as petechiae, purpuric lesions, and ecchymoses. Epistaxis, bleeding gums, gastrointestinal hemorrhage and hematuria occur less frequently (Hayes and Gubler, 1992). DSS is characterized by a rapid, weak pulse with a narrowing pulse pressure of less than 20 mmHg, or profound hypotension (systolic blood pressure less than 90 mmHg among those five years of age or older) (Gibbons and

Vaughn, 2002). Those with dengue viral infection along with malaria or typhoid fever and who were transferred to another hospital due to unavailability of beds were excluded from the study.

Data were collected on a predesigned form consisted of demographics, duration of fever and associated symptoms (diarrhea, vomiting, cough, rash, bleeding gums, hematemasis, melena, hematochezia, abdominal pain, shortness of breath, generalized body aches, and red conjunctiva). Other data included diagnosis (*eg*, DF, DHF, DSS), laboratory results (complete blood count, coagulation tests, creatinine, and serum glutamic pyruvic transaminase (SGPT); dengue IgM (ELISA) was checked in all patients. Outcomes (survival/mortality) and complications during the inpatient stay were recorded.

A minimum sample size of 115 patients with dengue viral infection was required to predict factors for mortality with dengue infection. For testing beta coefficients the following was used: n=104+k, where k = number of independent variables (Tabachnick, 2005).

Statistical analysis

Mortality was the primary outcome measure. Demographics, clinical presentation, lab workup (complete blood count, SGPT, coagulation tests, and creatinine) were independent variables. Analysis was done using SPSS version 15. Means and standard deviations were calculated for quantitative variables and frequencies and percentages for qualitative variables. The chi-square test was used to see the association among qualitative variables, such as gender and fever with outcome variables. The Student's *t*- test was used to see the differences in quantitative variable, such as age and blood pressure with outcome variables.

Multiple logistic regression was used to predict a model of factors associated with mortality in patients with dengue fever. Univariate analysis was done of independent variables and outcome mortality (dichotomous). Only those variables were used for univariate analysis which had some biological plausibility with the outcome. Those variables with a p-value <0.05 on univariate logistic regression were run in the multivariable model. Those found insignificant were then checked for interaction and confounding and based on this were excluded from the model if they had no significant interactions and were not confounders. The model was checked for goodness of fit with the Hosmer-Lemeshow test.

RESULTS

A total of 699 patients were admitted with the clinical diagnosis of dengue viral infection. DF comprised 86.4% (604) of cases, DHF comprised 11.6% (81) and DSS comprised 2% (14). The mean age of the patients was 31.9 years. The mean duration of fever was 6.1 ± 3 days. Sixty percent were males. The most common associated symptom with fever was nausea and vomiting (48.6%, 340), followed by abdominal pain (18.2%, 127), rash (16.7%, 117), body aches (15.9%, 111), diarrhea (10.2%, 71), cough (9.4%, 66), hematemasis (5.7%, 40), bleeding gums (5.2%, 36), melena (4.3%, 30), altered mental status (3.7%, 29) and jaundice (3.1%, 22).

Primary outcome measure (mortality)

The mortality rate was 2.7% (19). When comparing the clinical presentation of those who survived and those who did not, the significant differences were duration of fever (4.31 and 6.14 days; p=0.004), jaundice (21.1% and 2.7%; p=0.002) and

Table 1
Comparision of mortality and survival groups in dengue viral infection.

Lab parameter *N*=699	Overall mean	± SD	Mortality *N*=19 ± SD	Survival *N*= 680 ± SD	*p*-value
Hb	13.71	2.37	12.17 4.05	13.75 2.30	0.10
Ht	39.59	7.80	34.94 10.41	39.72 7.68	0.06
WBC	5.53	5.50	13.30 13.61	5.31 4.93	0.02
Platelets	67.16	59.54	60.47 43.99	67.35 59.94	0.51
BUN	14.46	14.62	33.23 25.58	13.82 13.69	0.007
Creatinine	1.92	9.52	1.8 0.92	1.92 9.67	0.39
Bicarbonate	23.70	18.17	17.09 4.87	23.98 18.47	<0.001
Prothrombin time	13.02	4.62	27.18 23.13	15.72 55.12	0.06
Activated partial thrombin time	36.50	12.28	56.75 31.18	36.83 19.91	0.01
SGPT	194.87	351.93	802.78 976.72	176.85 299.01	0.012
SGPT Mild to moderate (23-299)	71% (496)		31.6% (6)	76% (490)	<0.001
Severe hepatitis (>300)	14.7% (103)		63.2% (12)	13.8% (91)	
Normal	8.3% (58)		5.3% (1)	9% (57)	
SGOT	436.76	987.47	2,569.11 3,555.81	372 711.55	0.022

Hb, hemoglobin; Ht, hematocrit

altered mental status (47.4% and 2.5%; $p<0.001$), respectively. The overall lab results and comparisons between those who survived and those who did not are shown in Table 1. The significant differences between those who died and those who survived included white blood cell counts (WBC) (13.30 and 5.31; $p=0.02$), BUN (33.23 and 13.82; $p=0.007$), bicarbonate (17.09 and 23.98; $p<0.001$), APTT (56.75 and 36.83; $p=0.01$), SGPT (802 and 176; $p=0.01$), and the presence of severe hepatitis (63% and 13.8%; $p<0.001$), respectively.

On univariate logistic regression analysis, hematocrit ($p=0.02$), APTT ($p=0.04$), severe hepatitis ($p=0.05$), bleeding ($p<0.001$), renal failure ($p<0.001$), altered mental status ($p<0.001$), and shock ($p<0.001$) were significantly associated with mortality. On multivariate logistic regression (Table 2), 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

Table 2
Factors associated with mortality in dengue viral infection.

Exp (β) coefficient: odds of mortality for each unit change in predictor

	Univariate		Multi variate		
	Exp(β) coefficient	Significance[b]	Exp(β) coefficient	Significance[b]	Hosmer-Lemeshow
Hematocrit	1.05	0.02			
APTT[a]	2.62	0.04			
SGPT group[a]		<0.001			
Dummy 1	0.09	0.74			
Dummy 2	0.69	0.05	0.122	0.008	
Platelets[c]	0.90	0.85			
Bleeding	0.007	<0.001	0.003	<0.001	*p*-value 0.23
Pulse pressure	0.99	0.9			
Altered mental status[d]	37.09	<0.001	131.2	<0.001	
Renal failure	0.011	<0.001			
Shock	0.02	<0.001	0.008	<0.001	
HCO_3[e]	1.40	0.53			

[a]APTT, <34 and >34; [b]SGPT, 23-300, >300, normal (<23); [c]Platelet, <100 and >100;
[d]Altered mental status, normal, abnormal (drowsy, confused , comatose); [e]HCO_3, <18, >18

with mortality in patients with dengue virus infection.

DISCUSSION

Severe hepatitis (SGPT > 300), history of bleeding, altered mental status on admission and shock were the best predictors of mortality in patients with dengue viral infection. We report the clinical factors associated with mortality in an evaluation of the largest number of cases of dengue infection from the Indo Asian region. Many studies have evaluated individual predictors of mortality, while we report these together in one model.

The presence of shock, coma on presentation and seizures were previously reported as important predictors of mortality in dengue infection (Wasay *et al*, 2008). On multivariate analysis in elderly patients, DSS (odds ratio = 77.33, p=0.001) was found to be an independent risk factor for mortality (Lee *et al*, 2008). Shock has been reported previously as an important factor for mortality with or without a history of associated blood loss. Vascular collapse (shock) was present in 12 (85.7%) cases, with or without the association of major bleeding, and was the most important cause of death (Montenegro *et al*, 2006). Shock in itself is an alarming presentation in patients with dengue virus infection and as an indicator of the severity of disease in a case series of 23 patients from Puerto Rico (Rigau-Perez and Laufer, 2006). Shock in those patients was related to bleeding diathesis in most cases.

Spontaneous bleeding is a fairly common complication in dengue patients and is associated with increased mortality (Diaz-Quijano, 2008). Several mechanisms

have been discussed to account for the bleeding in dengue infection. Thrombocytopenia, coagulopathies and hepatic alterations are associated with bleeding (Diaz-Quijano, 2008).The platelet counts may be predictors of mortality: the risk for death is 6 times greater in those with a platelet count <50,000/μl than in those with a platelet count >50,000/μl in the pediatric population (Chua *et al*, 1993).

We found a significant association between encephalopathy and hepatitis. Encephalopathy is significantly associated with mortality in dengue infection. Several factors may be responsible for the high percentage of encephalopathy cases in this study. Hepatitis may be a cause of encephalopathy in these patients. Acute hepatitis and hepatic encephalopathy have been reported as rare manifestations of DHF (Shah, 2008). Acute liver failure is the most common cause of encephalopathy in patients with dengue infection (Montenegro *et al*, 2006). In contrast to other viral infections which involve the liver, the AST (SGOT) levels were much higher than ALT (SGOT) levels as described by others (Kuo *et al*, 1997). This difference could be due to the release of AST (SGOT) from skeletal muscle and the myocardium as damage to muscle in dengue infections has been reported (Davis and Bourke, 2004). The reverse ratio could be hypothesised to contribute to the encephalopathy. It is unclear whether hepatitis alone can explain the encephalopathy observed. Hepatitis, with transaminase levels, occurred in the majority of patients, who were generally anicteric. The dengue virus itself may be responsible for encephalopathy. DHF causes a clinical spectrum that infrequently involves encephalitis due to a direct neurotropic effect of dengue virus (Cam *et al*, 2001). Secondary infection in patients with dengue infection may also contribute to encephalopathy in these patients.

In evaluating individual lab parameters, we found mortality due to dengue viral infection was significantly associated with a high white cell count, uremia, acidosis and deranged liver function. A high white cell count indicates an associated bacterial infection. Dengue infection usually causes leukopenia (Ahmed *et al*, 2008). Secondary bacterial infection on presentation has been postulated to be a predictor of death from dengue (Lahiri *et al*, 2008). We did not investigate the type of bacterial infection the patients had, these infections lead to hypothesis dengue infection makes patients more susceptible to bacterial infection. More studies are needed to evaluate this hypothesis and assess the role of antibiotics in high risk patients with dengue infection. Both acute and chronic renal failure are associated with mortality in dengue infection (Kuo *et al*, 2008). Acute renal failure has a worse prognosis in the elderly with dengue infection (Lee *et al*, 2008). Metabolic acidosis in these patients may be associated with renal failure and shock. Prolonged shock is associated with metabolic acidosis and DIC which may lead to hypoxia/ischemia and results in both hepatic and cerebral dysfunction (Nimmannitya *et al*, 1978). Metabolic acidosis is found significantly more often in patients with DSS than DHF (Kasim *et al*, 1991).

A strength of our study was that it was the largest dataset of patients with dengue infection reported from the Indo Asian region which identified the clinical factors associated with mortality at a tertiary care center in a multivariate model. Previously, only associations with individual factors were reported. All patients with serology proving dengue infection were included in the study. There were several limitations

to our study. It was a single center study and has limited external validity. We did not account for confounders, such as associated comorbidity or infections.

In summary, severe hepatitis (SGPT > 300), a history of bleeding, altered mental status on admission and shock were clinical factors associated with mortality on patients with dengue viral infection. We recommend patients with dengue infection with such predictors of mortality on presentation warrant management in high dependency units.

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