Original Research Article

Predictors of mortality in adult patients with dengue: a study from South India

Vasudeva Acharya[1], Mohammed Fahad Khan[1]*, Srinivas Kosuru[1], Sneha Mallya[2]

[1]Department of Medicine, [2]Department of Community Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India

*Correspondence:
Dr. Mohammed Fahad Khan,
E-mail: mohammedfahadkhan92@gmail.com

ABSTRACT

Background: Dengue is one of the important causes of acute febrile illnesses in India. Dengue can be a fatal disease, however there are no reliable markers which can predict mortality among these patients.
Methods: A prospective cross sectional study was done in patients who were admitted to a tertiary care hospital with features of dengue fever. A total of 364 patients with IgM dengue serology positive were included in the study. Relevant clinical and laboratory parameters were collected from all patients. Association between clinico-laboratory parameters with mortality was studied using appropriate statistical methods.
Results: Among the 364 patients recruited in this study, 14 (3.85%) patients died. Mortality among patients with age group 18-40 years was 2.04%, in patients aged above 40 years was 7.56%. Mortality among patients with hypotension was 42.42% (14 out of 33), bleeding manifestations was 15.38% (8/52), platelets $<20,000/mm^3$ was 10.41% (10/96), ALT >200 was 13.04% (6/46), AST>200 was 12.34% (10/81), prolonged prothrombin time was 60%(12/20), renal failure was 28%(14/50), encephalopathy was 31.57% (6/19), multi organ dysfunction syndrome(MODS) was 43.33% (13/30), acute respiratory distress syndrome (ARDS) was 45.45% (5/11), pleural effusion was 7.5% (6/80).
Conclusions: The overall mortality in the present study was 3.85%. Following variables were associated with increased risk of death among the dengue patients: Age >40 years, presence of hypotension, platelets <20000 cells/mm^3, ALT>200U/L, AST>200U/L, prolonged prothrombin time, presence of renal failure, encephalopathy, MODS, ARDS and bleeding tendency (p value <0.05). Early identification of factors associated with mortality can help to make appropriate decision on care required.

Keywords: Dengue fever, Mortality predictors, Thrombocytopenia

INTRODUCTION

Dengue is the most widely distributed mosquito borne infection of humans.[1] Dengue, a flavivirus infection is transmitted by the Aedes mosquito.[2] There are four antigenically distinct dengue virus serotypes (DENV1, DENV2, DENV3, DENV4).[1]

The incidence of infection has been on a rise over the years with approximately 100 million people being affected each year.[1,3] Dengue is generally a self-limiting infection in adults. In cases of reinfection with different serotype, there is increased risk of severe disease. In 2009, WHO has revised the classification of dengue, which is easier to apply on a public health perspective. Large outbreaks of dengue are happening in many parts of India including national capital Delhi since past few years. According to National Vector Borne Disease Control Programme (NVBDCP) of Ministry of Health and Family Welfare, Government of India, 129,166 cases of dengue with 245 deaths have been reported during the year 2016 in the country.[4]

Dengue fever presents like any other viral infection with fever, headache, myalgia etc. Thrombocytopenia and elevated haematocrit are the two most common manifestations of dengue fever, however complications may happen in any organ system of the body. The WHO has clearly identified the warning signals for severe dengue. In the literature, various studies have mentioned different clinical and laboratory parameters as predictors of mortality in patients with dengue fever. Case fatality rate due to dengue reported from most countries is less than 5% but in absence of early recognition and proper management it may go high.[5-9] Early identification of the risk factors associated with mortality, would help clinicians prioritise the management of high-risk patients to reduce morbidity and mortality.

In the present study we aimed to identify the important clinical and laboratory parameters which predict the mortality in patients with dengue.

METHODS

A prospective study was done in a tertiary care hospital. The patients above 18 years of age who were admitted to the hospital with symptoms suggestive of dengue fever and positive for IgM dengue serology were recruited in this study. Informed consents were obtained from the patients and Institutional Ethical Committee Approval was obtained. IgM Panbio kit was used for dengue which has a sensitivity of 95% and specificity of 94%. A total of 364 patients with dengue were recruited in the study and their detailed clinical and laboratory parameters were noted. The other common causes of fever were ruled out by appropriate investigations. The least value of platelets and the highest values of alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time (PT), blood urea and serum creatinine during hospital stay was considered for analysis. Univariate analysis was done to assess the association between clinico-laboratory parameters and mortality and the risk of death was expressed as Relative Risk (RR) with 95% Confidence Intervals (CI). A p value of <0.05 was considered to be statistically significant. Multivariable analysis could not be performed due to small proportion of deaths in the study population.

RESULTS

A total of 364 patients fulfilling the inclusion criteria were included in the study. As shown in Table 1 males constituted 74% total patients. The disease was more commonly observed in younger population with adults up to the age 40 years contributing to 67.3% of total study population.

All patients had history of fever and the duration of fever ranged from 2 days to 18 days. Myalgia was the second most common symptom. Bleeding manifestations were observed in only 52 patients, skin bleeding being the commonest site. None had intracranial bleeding.

Table 1: Background characteristics and clinical features of the study participants (n=364).

Variables	Number	Percentage
Gender		
Male	269	74.00
Female	95	26.00
Age (years)		
18-40	245	67.30
>40	119	32.70
Clinical features		
Fever		
≤ 5 days	195	53.57
> 5 days	169	46.43
Myalgia	331	90.93
Headache	276	75.82
Abdominal pain	143	39.28
Skin rash	108	29.67
Bleeding (any site)	52	14.28
Hypotension	33	9.06

Laboratory parameters

As shown in Table 2, Thrombocytopenia was the commonest abnormality which was seen in all patients. Only 36 (9%) patients had their least platelet count above 1,00,000 cells/cumm^3. Elevated AST and ALT was observed in 245 (67.4%) and 173 (47.6%) of patients respectively. Renal failure was seen in 50 (13.8%) patients. Most of these patients had only mild hike in blood urea and/or serum creatinine and none required haemodialysis. Nineteen (5.21%) patients had features of encephalopathy manifested by altered sensorium. Multi-organ dysfunction was noted in 30 (8.24%) patients.

As shown in Table 3, the risk of death was 3.70 (95% CI 1.27-10.81, p=0.017) times higher among individuals aged >40 years as compared to those between the age of 18-40 years and the difference was statistically significant. There was no difference in the risk of death between males and females (OR=1.02, 95% CI 0.96-1.07 p=0.534). Dengue patients with hypotension had higher likelihood of death as compared to those without hypotension. Patients with a platelet count of <20000 cells/mm^3 had 6.97 times higher likelihood of death as compared to those with a platelet count of >20000 cells/mm^3 (OR=6.97 95%CI 2.24-21.73 p<0.001). Patients with elevated ALT (40-199 U/L) and AST (40-199 U/L and >200 U/L) were found to have higher risk of death as compared to patients with normal levels (p<0.05).

The risk of death was 0.6 times higher among those patients with a prolonged prothrombin time. Among the dengue patients, those without renal failure were 0.28 times less likely to die as compared to those who developed renal failure. The risk of death was 13.61 times higher in the presence of encephalopathy among dengue patients (OR=13.61 95% CI 5.25-35.29 p<0.001).

Dengue patients without MODS were 0.56 times less likely to die as compared to those who developed MODS (OR=0.56 95% CI 0.41-0.77 p<0.001). Presence of ARDS and bleeding tendency at any site were also significantly associated with higher risk of death (OR=17.82 and OR=8.0 respectively).

Table 2: Laboratory parameters of study participants (n=364).

Variable		Number	%
Hematocrit (%)	≤ 50	195	53.6
	>50	169	46.4
Leukocyte count (cells/mm^3)	<4000	62	17
	4001-11,000	255	70
	>11,000	47	13
Platelets (cells/mm^3)	<10000	23	6.3
	10,000-19,999	73	20.5
	20,000-49,999	108	29.6
	50,000-99,999	124	34.6
	≥1,00,000	36	9
AST (U/mL)	<40	119	32.6
	40-199	164	45
	≥200	81	22.4
ALT (U/mL)	<40	191	52.4
	40-199	127	34.8
	≥200	46	12.8
Renal failure	Present	50	13.8
	Absent	314	86.2
Chest X ray	Normal	261	71.7
	Pneumonia	12	3.3
	ARDS	11	3
	Pleural effusion	80	22

DISCUSSION

In our study, a total of 364 patients who were admitted to the hospital fitting the selection criteria were included. Of the 364 cases, 14 patients died giving a mortality rate of 3.85% which is comparable with studies done in other parts of world.[1-3,5]

A study from Malaysia reported 1.1% mortality among 667 patients studied.[6] Pinto RC from Brazil reported 62 deaths (0.06%) among 105,459 cases diagnosed with dengue between 2001 and 2013, however the mortality among severe dengue cases was 3.8% (61 out of 1605).[5] A recent report from Kerala state of South India reported 1.76% mortality among 1308 cases of dengue.[10]

From our review of literature, we have found that there are several predictors of mortality in patients with Dengue. We have excluded the common and non-specific manifestations like fever, headache, arthralgia, myalgia and abdominal pain from our analysis. There is evidence from available literature showing an association between mortality and various clinical, biochemical and haematological parameters like haematocrit, prothrombin

time, activated partial thromboplastin time, lactate levels, acute kidney injury and ARDS.[6-9] In our study, there was no relation of mortality with gender of the patients. Males constituted 64% of the 14 deaths (p value = 0.534). Patients aged >40 years had 3.7 times higher risk of death when compared adults aged ≤40 years. Pinto RC et al, from Brazil reported age >55 years was significantly associated with death (OR=4.98) in their cohort.[5]Karunakaran A et al, from Kerala state of India reported 9.3 times (95% CI;1.9-44.4) higher mortality in dengue patients above 40 years.[3]

We found that the relation between severe thrombocytopenia (<20,000cells/mm^3) and mortality was statistically significant (RR 6.97, p value =<0.001). This was similar to the results reported by Krishnamoorthy et al (p value = 0.015).[10] Thrombocytopenia is a marker of clinical severity as per WHO guidelines.[11,12]

It was found that markedly elevated transaminases (>200U/L) showed a significant association with mortality. The p value calculated was 0.070 and <0.001 for ALT and AST respectively. This was similar to the results found in the study by Parkash et al, where a statistical association between elevated transaminases and mortality (p value = 0.004).[13] Importance of hepatitis in dengue has been highlighted in many other studies as well.[14,15]

In this study, presence of bleeding tendencies like gastrointestinal bleeding and haematuria were identified as the clinical markers of risk of death due to dengue with p value of 0.001. This was similar to results reported by Pinto et al in a Brazilian study.[5] Severe dengue cases presenting with bleeding and prolonged APTT had a five times greater risk of death than the other cases.

The association between clinical signs related to bleeding has been found to be plausible and already accepted by many researchers.[16-22] Acute kidney injury(AKI) defined as a serum creatinine of more than 1.2mg/dl was seen in 50 patients. It is also interesting to note that all 14 patients who succumbed to dengue had AKI. The relationship was significant with a p value of 0.001. AKI resulted from hypoxia and hypoperfusion as a consequence of shock. Similar results were observed by Khalil et al, in their study conducted in Pakistan and other studies.[8,23,24]

The presence of altered sensorium and abnormal reflexes is indicative of CNS involvement in the form of encephalopathy. As evidenced in this study and suggested in several other studies, brain involvement is associated with a higher incidence of mortality in dengue patients (p value <0.001).

Presence of altered sensorium was associated with higher mortality (unadjusted OR =5.8) among patients with dengue shock syndrome according to a study from North India.[25] Encephalopathy may be due to acute liver failure

from hepatitis. Encephalitis may also be due to the neurotropic effect of the virus or to secondary bacterial infections.[3,7]

In a study done by Karunakaran et al, in Kerala, India, impaired consciousness was found in 60% of dengue deaths.[3] ARDS was seen in 45% of the dengue deaths in our study and was a strong predictor of mortality (p value <0.001). The mechanism of ARDS is attributed to the capillary leak syndrome.[26] This was similar to the results published by Jog et al in 2015.[27] It was also concluded that patients with Multiple Organ dysfunction (MODS) had a higher mortality compared to those who didn't (p value <0.001).

Table 3: Predictors of mortality in patients with dengue.

Variable	Outcome-death n (%)	Outcome-survived n (%)	Relative risk	95% CI	P value
Age (years)					
18-40	5 (2.04)	240 (97.95)	Ref		
>40	9 (7.56)	110 (92.43)	3.70	1.27-10.81	0.017*
Gender					
Male	9 (3.34)	260 (96.65)	1.02	0.96-1.07	0.534
Female	5 (5.26)	90 (94.73)	Ref		
Hypotension					
Present	14(42.42)	19 (57.57)	Ref		
Absent	00 (0)	331(100)	0.57	0.43-0.77	<0.001*
Platelets (cells/mm³)					
<20000	10(10.41)	86 (89.6)	6.97	2.24-21.73	<0.001*
>20000	4 (1.49)	264 (98.5)	Ref		
ALT (u/l)					
<40	3 (1.57)	188 (98.42)	Ref		
40-199	5 (3.93)	122 (96.06)	8.30	2.15-31.96	0.002*
>200	6 (13.04)	40 (86.95)	3.31	1.06-10.33	0.070
AST (u/l)					
< 40	1 (0.84)	118 (99.15)	Ref		
40-199	3 (1.82)	161 (98.17)	14.69	1.91-12.55	0.001*
>200	10(12.34)	71 (87.65)	10.93	3.13-38.19	<0.001*
Prothrombin time					
Prolonged	12 (60.0)	8 (40.00)	Ref		
Normal	2 (0.58)	342 (99.41)	0.402	0.23-0.68	<0.001*
Renal failure					
Present	14 (28.0)	36 (72.0)	0.720	0.60-0.85	<0.001*
Absent	0 (0)	314 (100)	Ref		
Encephalopathy					
Present	6 (31.57)	13 (68.42)	13.61	5.25-35.29	<0.001*
Absent	8 (2.31)	337 (97.68)	Ref		
MODS					
Present	13(43.33)	17 (56.66)	Ref		
Absent	1 (0.29)	333 (99.70)	0.568	0.41-0.77	<0.001*
ARDS					
Present	5 (45.45)	6 (54.54)	17.82	7.14-44.45	<0.001*
Absent	9 (2.54)	344 (97.45)	Ref		
Bleeding tendency					
Present	8 (15.38)	44 (84.61)	8.00	2.89-22.11	<0.001*
Absent	6 (1.92)	306 (98.07)	Ref		
Pleural effusion					
Present	6 (7.50)	74 (92.5)	2.66	0.95-7.45	0.091
Absent	8 (2.81)	276 (97.18)	Ref		

Hence, even though the serious complications are not very common in dengue, when present are strongly associated with increased risk of death.

CONCLUSION

In this study on patients with dengue fever, we noticed 3.85% mortality which is comparable with studies done in other parts of world. Age >40 years, presence of hypotension, bleeding tendency, severe thrombocytopenia, elevated AST/ALT above 200U/mL, prolonged PT, features of encephalopathy, presence of AKI, ARDS and MODS were independently found be significantly associated with mortality in our cohort of patients. Hence it is recommended to identify the patients with these features for intense monitoring and appropriate interventions to prevent deaths.

REFERENCES

1. Mandal SK, Ganguly J, Sil K, Chatterjee S, Chatterjee K. Clinical profiles of dengue fever in a teaching hospital of Eastern India. Natl J Med Res. 2013;3(2):173-176.
2. Thein TL, Leo YS, Fisher DA. Risk factors for fatality among confirmed adult dengue inpatients in Singapore: a matched case-control study. PLoS One. 2013;8:e81060.
3. Karunakaran A, Ilyas WM, Sheen SF, Jose NK, Nujum ZT. Risk factors of mortality among dengue patients admitted to a tertiary care setting in Kerala,India. J Infect Public Health. 2014;7(2):114-20.
4. National Vector Borne Disease Control Programme, Directorate General of Health Services, Ministry of Health and Family Welfare. Available at: http://www.nvbdcp.gov.in/den-cd.html.
5. Pinto RC, Castro DB, Albuquerque BC, Sampaio Vde S, Passos RA, Costa CF, Sadahiro M, Braga JU. Mortality Predictors in Patients with Severe Dengue in the State of Amazonas, Brazil. PLoS ONE. 2016;11(8):e0161884.
6. Mallhi TH, Khan AH, Sarriff A, Adnan AS, Khan YH. Determinants of mortality and prolonged hospital stay among dengue patients attending tertiary care hospital: a cross- sectional retrospective analysis. BMJ Open. 2017;7:e016805.
7. Thanachartwet V, Oer-Areemitr N, Chamnanchanunt S. Identification of clinical factors associated with severe dengue among Thai adults: a prospective study. BMC Infect Dis. 2015;14:420.
8. Khalil MA, Tan J, Khalil MA. Predictors of hospital stay and mortality in dengue virus infection experience from Aga Khan University Hospital Pakistan. BMC Res Notes. 2014;7:473.
9. Ejaz K, Khursheed M and Raza A. Pleural effusion dengue. Karachi perspective. Saudi Med J. 2011;32:46-49.
10. Krishnamoorthy S, Bhatt AN, Mathew CT, Ittyachen AM. Hepatitis and thrombocytopenia: markers of dengue mortality. Tropical Doctor. 2017;47(2):136-141.
11. Funahara Y, Sumarmo and Wirawan R. Features of DIC in dengue hemorrhagic fever. Bibl Haematol. 1983;49:201-11.
12. Lee IK, Liu JW and Yang KD. Fatal dengue hemorrhagic fever in adults: emphasizing the evolutionary pre-fatal clinical and laboratory manifestations. PLoS Negl Trop Dis. 2012;6:e1532.
13. Parkash O, Almas A, Jafri S. Severity of acutehepatitis and its outcome in patients with dengue fever in a tertiary care hospital Karachi, Pakistan (South Asia). BMC Gastroenterol. 2010;10:43.
14. Alvarez ME and Ramirez-Ronda CH. Dengue and hepatic failure. Am J Med. 1985;79:670-4.
15. Lum LC, Lam SK, George R. Fulminant hepatitis in dengue infection. Southeast Asian J Trop Med Public Health. 1993;24: 467-71.
16. Mathew A and Rothman AL. Understanding the contribution of cellular immunity to dengue disease pathogenesis. Immunol Rev. 2008;225:300-13.
17. Halstead SB. Dengue. Lancet. 2007;370:1644-52.
18. Rondina MT, Weyrich AS. Dengue virus pirates human platelets. Blood. 2016;126(3):2015-7.
19. Ramos M, Trugilho DO, Hottz ED, Villa G, Carvalho PC, Salazar GA, et al. Platelet proteome reveals novel pathways of platelet activation and platelet-mediated immunoregulation in dengue. PLoS Pathog. 2017;1-27.
20. Martina BEE, Koraka P, Osterhaus ADME. Dengue Virus Pathogenesis : an Integrated View. Clinical Microbiology Review. 2009;22(4):564-81.
21. Edelman R, Nimmannitya S, Colman RW. Evaluation of the plasma kinin system in dengue hemorrhagic fever. J Lab Clin Med. 1975;86:410-21.
22. Hottz ED, Oliveira MF, Nunes PC. Dengue induces platelet activation, mitochondrial dysfunction and cell death through mechanisms that involve DC-SIGN and caspases. J Thromb Haemost. 2013;11:951-62.
23. Oliveira JFP, Burdmann EA. Dengue-associated acute kidney injury. Clinical Kidney J. 2015;8(6):681-5.
24. World Health Organization. Comprehensive guidelines for prevention and control of Dengue fever and dengue haemorrhagic fever-revised and expanded edition. Geneva: WHO;2011.
25. Jain S, Mittal A, Sharma SK, Upadhyay AD, Pandey RM, Sinha S, et al. Predictors of dengue-related mortality and disease severity in a tertiary care center in North India. Open Forum Infectious Diseases. 2017;4(2):ofx 056.

26. Lum LC, Thong MK, Cheah YK, Lam SK. Dengue-associated adult respiratory distress syndrome. Annals of tropical paediatrics. 1995;15(4):335-9.
27. Jog S, Prayag S, Rajhans P. Dengue infection with multiorgan dysfunction: SOFA score, arterial lactate and serum albumin levels are predictors of outcome. Intensive Care Med. 2015;41(11):2029-30.