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

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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/mm³ 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/mm³, ALT>200 U/L, AST>200 U/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).³

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. 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. 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/mm² had 6.97 times higher likelihood of death as compared to those with a platelet count of >20000 cells/mm² (OR=6.97 95%C.I 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).

We found that the relation between severe thrombocytopenia (<20,000 cells/mm³) 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). 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. 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 many researchers. 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). Importance of hepatitis in dengue has been highlighted in many other studies as well.14,15

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from hepatitis. Encephalitis may also be due to the neurotropic effect of the virus or to secondary bacterial infections.\textsuperscript{3,7}

In a study done by Karunakaran et al., in Kerala, India, impaired consciousness was found in 60% of dengue deaths.\textsuperscript{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.\textsuperscript{26} This was similar to the results published by Jog et al. in 2015.\textsuperscript{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/mm\(^3\))** | | | | | |
| <20000            | 10(10.41)            | 86 (98.6)               | 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 to 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.

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