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A study on dengue and its predictors of mortality in ICU- a prospective study

[1]Dr. Srinivas Aditya S, Assistant professor, Department of General Medicine, Kamineni Institute of Medical Sciences, Narketpally, Nalgonda, Telangana.

[2]Dr. Sowjanya Reddy B, Assistant professor, Department of General Medicine, Kamineni Institute of Medical Sciences, Narketpally, Nalgonda, Telangana

Corresponding Author: Dr. Sowjanya Reddy B, Assistant professor, Department of General Medicine, Kamineni Institute of Medical Sciences, Narketpally, Nalgonda, Telangana

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Abstract

Health experts have known about dengue fever about for more than 2 centuries. As time progressed research added more literature to this infectious disease carried by mosquitoes and caused by four different types serotypes DENV1, DENV2, DENV3, DENV4. In 2009, WHO has revised the classification of dengue, which is easier to apply on a public health perspective. According to National Vector Borne Disease Control Programme (NVBDCP) of Ministry of Health and Family Welfare, Government of India, 136,422 cases of dengue with 132 deaths have been reported during the year 2019 in the country and raise of 36509 case 99913 from 2015. The current study aimed to identify the important clinical and laboratory parameters which can predict the mortality in critically ill patients with dengue in ICU. A prospective study was conducted in 2018 with the 50 patients above 18 years of age who were admitted to the tertiary hospital with symptoms suggestive of dengue fever after a positive IgM dengue serology, were enrolled for the study. The least value of platelets and the highest values of alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time (PT), Activated partial thromboplastin time (APTT) and serum creatinine during hospital stay were analysed. Univariate analysis was done to assess the association between clinico-laboratory parameters and mortality. The risk of death was expressed as Relative Risk (RR) with 95% Confidence Intervals (CI). $p<0.05$ was considered to be statistically significant. Current study on dengue patients we noticed 26% of mortality in ICU which was in compromise with previous studies, in other parts of the world. We demonstrated that presence of hypertension, bleeding tendency, severe thrombocytopenia, elevated AST/ALT above 200 IU/L, prolonged PT, APTT levels, presence of AKI, ARDS were independently found be significantly associated with mortality. We may recommend to identify the severity of dengue in patients with these biochemical and haematological parameters to make appropriate interventions to prevent deaths.

Keywords: Aedes mosquitos, APTT, AST, ALT, Dengue, ICU, PT.

Introduction

Dengue fever is an infectious disease carried by mosquitoes and caused by any of four related dengue viruses. There are four antigenically distinct dengue virus serotypes (DENV1, DENV2, DENV3, DENV4). Dengue, a flavivirus infection is transmitted by the Aedes mosquitos [1]. This disease used to be called "break-bone" fever because it sometimes causes severe joint and muscle pain that feels like bones are breaking. Health experts have known about dengue fever for more than 200 years. The incidence of infection has been on a rise over years with approximately 100 million people being affected each year [2,3]. Dengue is generally a self-limiting infection in adults. In cases of reinfection with 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, 136,422 cases of dengue with 132 deaths have been reported during the year 2019 in the country [4] and raise of 36509 case 99913 from 2015, number of infected cases in Andhra Pradesh was about 4647 and stand first among Indian states with no mortality. Dengue has emerged as a global health threat, while scientists still know little about how the virus infects cells and causes the disease. New research findings from National Institute of Allergy and Infectious Disease (NIAID) are shedding light on the mechanisms of dengue infection, such as how the virus enters the cells and how the human immune system responds to dengue infection and are identifying the human and viral factors that determine and contribute to the severity and transmissibility of this disease. NIAID-supported scientists are working to understand the pathology of dengue disease and to develop cost-effective, sensitive, and specific diagnostic tests for use in dengue-endemic countries. Researchers are developing an automated, portable, point-of-care machine for rapid dengue diagnosis, the goal of these tests is to provide early detection of the disease, distinguish between the different viral dengue, and predict which people are at highest risk of developing the more severe forms of the disease, dengue haemorrhagic fever and dengue shock syndrome. In other studies, researchers are generating and evaluating neutralizing monoclonal antibodies and small molecule drugs in animal models. Results from these animal trials may result in new treatment options for people with dengue. In one NIAID-funded research, researchers evaluated about 7,500 antiviral compounds *in vitro* to test their efficacy against dengue. So far, 49 have been identified for further evaluation. Dengue fever presents symptoms like any other viral infection with fever, myalgia and headache etc elevated haematocrit and thrombocytopenia are 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 previous studies have mentioned different clinical and laboratory parameters as predictors of mortality in patients with dengue fever. The fatality rate due to dengue reported from most of the countries worldwide is less than 5% but in absence of early recognition and proper management it might increase [5-9]. Early identification of the risk factors would help clinicians manage the high-risk patients to reduce morbidity and mortality. The current study aimed to identify the important clinical and laboratory

parameters which predict the mortality in patients with dengue.

Materials and Methods

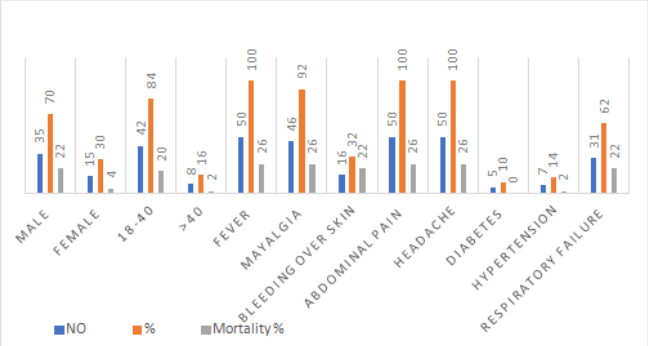
A prospective study was conducted in 2018 with 50 patients above 18 years of age who were admitted to the tertiary hospital ICU with symptoms suggestive of dengue fever after a positive IgM dengue serology were enrolled for the study. Institutional Ethical Clearance and Informed consents were obtained from patients enrolled for the study. IgM (DxSelect™ #EL1500M - CE, Focus diagnostics) rapid test kit was used for dengue which has a sensitivity of 96% and specificity of 97%. A total of 50 patients with dengue were enrolled for the study and their detailed clinical and laboratory parameters were investigated. The least value of platelets and the highest values of alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time (PT), APTT (activated partial prothrombin time) and serum creatinine during hospital stay were analysed. Univariate analysis was done to assess the association variables between clinico-laboratory parameters and mortality and the risk of death was expressed as Relative Risk (RR) with 95% Confidence Intervals (CI). $p<0.05$ was considered to be statistically significant.

Results

A total of 50 patients after satisfying the inclusion criteria were enrolled for the study. Males constituted 70% and female patients was 30% of total patients. Mortality among male was 22% and female was 4%. Younger population with adults upto 40 years of age contributing to 65% where commonly affected. All patients presented with the history of fever and the duration of fever was ranged from 4 days to 16 days. Myalgia was the second most common symptom observed among the enrolled patients 92%. 60% of patients have shown bleeding manifestations, skin bleeding being the commonest site. None of them identified with intracranial haemorrhage (Figure 1). Thrombocytopenia was the commonest abnormality which was seen in all patients. Only 54% patients had their least platelet count below 50,000, 50,000 to 100,000 was 28% and 100,000 to 150,00 cells/cumm of blood was 16%. Increased AST and ALT was observed in 46 (92%) and 37 (74%) of patients respectively, 21 (42%) have shown renal failure and most of these patients had increase of creatinine levels. The risk of mortality was 26% among the patients but was not significant (RR- 1.90, 95% CI 0.2816 -12.8832, p=0.50) with the age groups of 18-40 years and >40 years. But there was a slight increase of mortality in 18-40 years which can't be neglected. There was no significant difference in the risk of death between males and females (RR-2.35 95% CI 0.5931-9.3686, p=0.22). There was a significant difference of mortality among hypertensive and non-hypertensive dengue patients (RR-0.12, 95% CI-0.0200-0.7819, p=0.02). Patients with a platelet count of <50000 cells/cumm of blood have higher risk of mortality as compared to those with a platelet count of >50000 cells/cumm of blood (RR-1.18, 95% CI 1.0032-01.3923, p=0.04). Patients higher PT and APTT have higher risk of mortality (RR 0.69, 95% CI 0.5592-0.8625 p=0.001 and RR-0.72, 95% CI 0.5494-0.9622, p=0.02). Patients with elevated ALT >200 IU/L (RR-0.71, 95% CI 0.5984-0.8601, p=0.003) and AST >200 IU/L (RR-0.81, 95% CI 0.6939-0.9474, p=0.008) were found to have higher risk of mortality as compared to patients with normal levels. An increase in albumin levels were found in 86% of dengue patients and values are statistically significant with mortality (RR-0.72, 95% CI 0.5986-0.8683, p=0.006). 42% of enrolled patients have shown an increase of creatinine

levels which was statistically significant (RR- 0.66, 95% CI 0.4927-0.9021, P=0.008) with mortality due to renal failure. Presence of ARDS resulted in mortality of the dengue patients which was statically significant (RR- 0.64, 95% CI 0.4969-0, 8376, p=0.001). (Table1, 2)

Figure 1: Population variation and clinical feature in dengue patients



Data presented as no and % gender and mortality with clinical manifestations

Table 1: Haematological and Biochemical findings

Variable		Number	Percentage (%)	Mortality (%)
Haematological				
Haematocrit		12	24	6
Platelets	<50,000	28	56	56
	50,000 – 100,000	14	28	4
	100,000 - 150,000	8	16	4
PT	>15	36	72	22
APTT	>35	36	72	26
Biochemical				
AST (IU/mL)	>200	46	92	26
ALT (IU/mL	>200	37	74	14
Albumin	5.5gm/100mL	43	86	24
Creatinine	>1.8mg/100mL	21	42	14

Table 2: predictors of mortality in dengue patents.

Variable		Death	%	Survival	%	Relative Risk (CI -95%)	P-value
Gender	Male	11	22	24	48	2.35 (0.5931-9.3686)	=0.22
	Female	02	4	13	26		
Age (years)	18-40	10	20	32	64	1.90(0.2816-12.8832)	=0.50
	>40	01	2	07	14		
Platelets	<50000	28	56	0	0	1.18(1.0032-1.3923)	=0.04*
	>50000	22	44	04	8		
PT	>15	11	22	25	50	0.69(0.5592-0.8625)	=0.001*
APTT	>35	13	26	23	46	0.72(0.5494-0.9622)	=0.02*
AST	>200	13	26	33	66	0.71(0.5984-0.8601)	=0.003*
ALT	>200	07	14	30	60	0.81(0.6939-0.9474)	=0.008*
Albumin		12	24	31	62	0.72(0.5986-0.8683	=0.006*
Creatinine		07	14	14	28	0.66(0.4927-0.9021)	=0.008*
Respiratory failure		11	22	29	58	0.64(0.4969-0.8376	=0.001*

Data present as % and significance * - RR - Relative Risk with confidence interval (CI)

Discussion

Current study, a total of 50 patients who were admitted to the tertiary hospital ICU satisfying the inclusion criteria were included. Out of the 50 cases, 13 patients died giving a mortality rate of 26% and 37 patients survived with survival rate of 74% which is comparable with previous studies done in other parts of world [1-3,5]. In previous study 667 patients enrolled, the mortality rate was 1.1% in Malaysia [6]. In another study between 2001 to 2013 from brazil by Pinto RC reported 62 deaths among 105,459 cases studied with the mortality rate of 0.06%[5] a study from south Indian state of Kerala demonstrated 1.76% mortality in 1308 cases of dengue[10]. No sufficient studies have been done exclusively to predict mortality from dengue in ICU. From present study, we have found several predictors of mortality in patients with dengue. so we have excluded non-specific manifestations like fever, headache, myalgia and abdominal pain from our analysis. Previous literature high lights the evidence of an association between mortality and various haematological and biochemical parameters such as haematocrit, prothrombin time, activated partial thromboplastin time, acute kidney injury and respiratory failure due to ARDS[6-9]. In current study, there was no evidence of relation of mortality with gender (p=0.22) and age (p=0.50) of the patients with dengue. Males constituted 70% of 11 deaths we have found no significant relation with gender. Patients aged 18-40 years had 20% of mortality rate which was not significant with >40 year of age but mortality rate was little more in this group. Study by Pinto RC et al, from Brazil in their cohort reported that age >55 years was significantly associated with death (OR=4.98)[5] in another study from the state of Kerala in south India, reported 9.3 times higher mortality in dengue patients above 40 years[3], our study found to be contradictory to above studies may because of more patients in this group. As per WHO guidelines decreased platelet count (thrombocytopenia) is a haematological marker of dengue[11,12]. Our study demonstrated the relation of thrombocytopenia (<50,000 cells/Cumm of blood) with mortality was statistically significant with p=0.001 (RR- 0.69) previous study by Krishnamoorthy et al (p value = 0.015)[10] is in compromise with our study.

Our study found an increase of AST (p=0.003) and ALT (p=0.008) levels >200IU/L was statistically significant with mortality. Previous studies highlighted the importance of hepatitis in dengue [14,15]and its adverse effects on liver. Similar results also found by Prakash et al in their study, increase of AST and ALT transaminase to mortality [13]. Current study also suggests strong evidence of hepatitis in dengue. A raise of serum creatinine indicates the acute kidney injury, our study put a glance on raised levels of serum creatinine in 42% of patients and send signal towards kidney impaired function, which was statistically significant with mortality (p=0.008 RR 0.66). Similar results were demonstrated by the researcher Khalil et al in their studies on dengue in the year of 2013 and 14 [8]. The association of clinical signs related to respiratory failure was found to be plausible and accepted by many researchers who worked on dengue, in our study there was association of mortality with respiratory failure due to ARDS. In a previous study conducted by researcher Karunakaran et al, in Kerala, India, 60% of dengue deaths were associated with impaired consciousness[3]. In current study 62% of patients were with respiratory failure supported with mechanical ventilators, 11 of them were trapped to

death making mortality to 22%. ARDS was seen in 22% of the dengue deaths in our study and was a strong predictor of mortality (p value <0.001). The capillary leak syndrome may be the probable mechanism of ARDS in dengue patients. Researchers have reported MODS (Multi Organ Dysfunction) and abnormal reflexes in dengue patients [25] with the possible involvement of CNS and other organs. Hence, complications are very common in dengue and are strongly associated with increased risk of mortality.

Conclusion

In current study on dengue patients we noticed high mortality of 26% in ICU which is comparable to studies done in other parts of world. As per our studies presence of hypertension, bleeding tendency, severe thrombocytopenia, elevated AST/ALT above 200IU/L, prolonged PT, APTT levels, presence of AKI, ARDS were independently found be significantly associated with mortality in our cohort studies on dengue patients. We may recommend to identify the severity of dengue patients with these complications for monitoring and to make appropriate interventions to prevent mortalities in dengue. More studies are warranted with larger sample size and other cofounding factors associated with dengue are warranted.

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