Social, health system and clinical determinants of fever mortality during an outbreak of dengue fever in Kerala, India

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ABSTRACT

Background and Objectives: The morbidity and mortality spectrum of the south Indian state of Kerala is dominated by chronic non-communicable diseases, yet febrile illnesses because of neglected tropical diseases and emerging viral infections are often reported. As fever deaths are mostly avoidable, understanding the determinants of mortality is essential for implementing preventive measures. **Methods:** A case-control study was done during an ongoing dengue outbreak in Thiruvananthapuram district, Kerala during 2017–18. Cases included all fever deaths from the line list of Integrated Disease Surveillance Program (IDSP). Data were obtained from hospital case records and by interviewing patients or care givers. The theoretical model for determinants of mortality was constructed at three levels namely sociodemographic factors, access to health care and health seeking behavior, and clinical determinants. **Results:** This study confirmed association of mortality with age above 40 years ($P = 0.010$, OR = 3.48), being heavy built ($P = 0.029$, OR = 13.25), clinical symptoms of breathlessness ($P < 0.001$, OR = 24.89), restlessness ($P < 0.001$, OR = 97.26), clinical signs of drowsiness ($P = 0.024$, OR = 7.97), hypotension ($P < 0.001$, OR = 42.22), complications such as ARDS ($P = 0.047$, OR = 171.56), and myocarditis ($P = 0.012$, OR = 16.59). A low occupation status of semiskilled work or less ($P = 0.012$, OR = 0.30), choosing a nearby hospital for treatment ($P = 0.018$, OR = 0.48) and shortening the time gap between onset of symptom and final diagnosis ($P = 0.044$, OR = 0.72) was found to be protective. **Conclusion:** Along with biological and clinical factors, distal determinants like social factors, health seeking behavior, and health system factors are associated with fever mortality.

Keywords: Dengue, Fever Mortality, Risk Factors, Social and health system determinants, Kerala

Introduction

Kerala, an Indian state with a 33 million population is in a stage of high epidemiological transition. The burden of non-communicable diseases is huge, while the health system reels under several outbreaks of communicable diseases almost every year.[1,2] The worst among the fever outbreaks over the past few years was the dengue epidemic in 2017–18 which was

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unprecedented in terms of morbidity as well as mortality.[3] The major cause of mortality was dengue fever, both confirmed and suspected followed by Leptospirosis and H1N1. In a substantial number of cases, laboratory confirmation for the infecting agent was missing and those deaths were accounted as unspecified fever deaths.[4] Hence, there is an urgent need to prioritize available healthcare services with added symptom-specific focus for decreasing mortality because of infectious diseases.[5] Understanding the determinants of mortality, both proximal factors like clinical characteristics and distal factors like sociodemographic characteristics, health-seeking behavior, and health system determinants will help plan preventive measures. This study aims to find out the determinants of mortality in patients hospitalized with fever in Thiruvananthapuram district of Kerala during an outbreak of dengue in the year 2017–18, to provide a comprehensive policy perception to tackle mortality because of infectious diseases.

Methods

A case-control study was undertaken during an ongoing dengue outbreak in Thiruvananthapuram district of Kerala state, India in 2017–18. Thiruvananthapuram, the capital of Kerala was the worst affected district. Study settings were government and private hospitals reporting to the Integrated Disease Surveillance Program (IDSP) of the Government of India. IDSP is the public health program of the Government of India, which captures surveillance data on communicable diseases from all the states. All 36 fever deaths reported during the period were from the two tertiary level government hospitals of the district. This was because of the practice of referring fever cases admitted in other government and private hospitals to these hospitals upon worsening of symptoms. Cases and controls were selected respectively from the line list of fever deaths and fever cases reported in IDSP. Fever death was defined as a death in the IDSP line list, due to confirmed or suspected dengue fever, H1N1 Influenza, Leptospirosis, or unspecified fever. Controls were patients hospitalized with confirmed or suspected dengue fever, H1N1 Influenza, Leptospirosis, or unspecified fever, who had recovered. Patients less than 18 years of age, patients whose records were unavailable, or for whom there was ambiguity regarding the cause of death and patients or relatives who were not willing to participate in the study were excluded. All deaths because of fever, meeting eligibility criteria were included. Altogether, there were 36 fever deaths during the study period. For each case, two controls were randomly selected from the same hospital from the IDSP line list. The final sample included 36 cases and 72 controls.

A structured proforma developed and validated qualitatively by a team consisting of public health and infectious diseases specialists was used for data collection. Details of cases and controls were obtained from the case records at hospitals and by verifying treatment records available with the patients. Patients and/or caregivers were visited and interviewed at their houses for ensuring data quality. Clarifications were obtained from treating clinicians regarding information available in-hospital records. Information regarding sociodemographic variables, health-seeking behavior, access and utilization of healthcare services, clinical presentation, laboratory parameters, complications, and management were obtained.

The measures of strength of associations between independent factors and outcome used were the crude odds ratio with 95% confidence interval (CI). Chi-square test, Fisher's exact test, and *t*-test were used for univariable analysis. For multivariable analysis, a logistic regression model was constructed and adjusted odds ratios with 95% CI were used to demonstrate the strength of association. All exposure factors with a significance of 0.25 or less were put in the original model and the variables losing significance were removed one by one using "backward" method in SPSS. The statistical level of significance was set at $P < 0.05$. The theoretical model for determinants of mortality was constructed at three levels to include proximal and distal determinants. The first level was sociodemographic variables, the second level was access to health care and health-seeking behavior, followed by clinical determinants at the third level. SPSS version 25.0 (SPSS IBM, Armonk, NY) was used for data analysis.

The study proposal was approved by the Human Ethics Committee (HEC) of our institution (IEC No 07/21/2017/MCT). Written informed consent was obtained from all participants.

Results

We report findings from 36 cases (fever deaths) and 72 controls (recovered fever patients) recruited from the IDSP line list of Thiruvananthapuram district during 2017–18. Laboratory confirmed diagnoses were there for 29 cases (90.6%) and 59 controls (81.9%). Most of the patients, both in the case group ($N = 27$, 75.0%) and the control group ($N = 50$, 69.4%) were diagnosed as having dengue fever. Eighteen patients had a diagnosis of short febrile illness (unspecified), six in case group and 12 among controls. H1N1 influenza and Leptospirosis were diagnosis for seven (two in case group and five in control group) and six patients (one in case group and five in control group), respectively.

Sociodemographic variables and personal history

Mean age of cases and controls was 40.36 (standard deviation 18.38) years and 32.59 (standard deviation 19.56) years, respectively. Significant association with mortality was found for persons with age more than 40 years. Male was the predominant gender among those who died (cases) ($N = 19$, 52.8%) while the proportion of males among survivors were only 37.5% ($N = 27$). Above Poverty Line families and those with urban residence were more in case group but the associations were not statistically significant. Statistically significant association was found between high occupational status (professional/skilled workers) and fever deaths.

Significant association with mortality was found for those patients in whose case sheets the treating physician had mentioned "heavy built persons" in general examination and with history of alcohol use. Smoking, diabetes, and chronic respiratory disease were more among cases than controls but the associations were not statistically significant. None of the study subjects had renal disease, tuberculosis, or any condition causing immune compromised state. One patient in the control group was pregnant. History of previous dengue infection was present in 2 (5.9%) cases and 7 (9.9%) controls. History of family members affected by dengue fever was elicited among 10 (29.4%) cases and 20 (28.2%) controls. Sociodemographic factors, substance use, comorbid conditions, and personal history among study subjects is shown in Table 1.

Multiple logistic regression to model the sociodemographic determinants identified a positive association of mortality with age category above 40 years (*P* = 0.010, OR = 3.48 [95%CI: 1.35–8.98]) and reported "heavy built" (*P* = 0.029, OR = 13.25 [95%CI: 1.31–134.21]), whereas a low occupation status of semiskilled work or less (*P* = 0.012, OR = 0.30 [95%CI: 0.12–0.77]) was found to be protective.

Health-seeking behavior and access to health care

Self-medication, inadequate bed rest, and inadequate oral fluid intake were significant risk factors for mortality. Health-seeking behaviors which were protective included giving priority to physical closeness of the hospital, and initiating treatment from government sector hospitals. System of medicine chosen for first consultation was modern medicine in about 95% of both cases and controls. Out of the three patients who took Ayurveda treatment in the study, two were in the case group. Two patients in the control group initially went for homeopathic treatment but both of them later changed to modern medicine.

Table 1: Socio-demographic factors and Personal history				
Variables	Cases (36) *n* (%)	Controls (72) *n* (%)	OR (95%CI)	*P**
Age >40 years	20 (55.6)	21 (29.2)	3.03 (1.32-6.96)	0.008
Gender				
Male	19 (52.8)	27 (37.5)	1.86 (0.83-4.19)	0.13
Socioeconomic status#				
Low SES	15 (41.7)	35 (48.6)	0.75 (0.33-1.69)	0.49
Place of residence				
Rural	17 (47.2)	46 (63.9)	0.51 (0.22-1.14)	0.098
Education status				
Secondary or less	18 (50)	35 (48.6)	1.05 (0.47-2.35)	0.892
Occupation status				
Semiskilled or less	17 (47.2)	50 (69.4)	0.39 (0.17-0.89)	0.025
Health insurance				
Available	17 (47.2)	44 (61.1)	0.56 (0.25-1.27)	0.170
Type of Health Insurance				
Government Medical insurance	14 (77.8)	38 (86.4)	Not calculated	0.674
Private medical insurance	1 (5.6)	2 (4.5)		
Other social insurance	3 (16.7)	4 (9.1)		
Tobacco Smoking				
Present	8 (22.2)	7 (9.7)	2.65 (0.87-8.02)	0.07
Alcohol use				
Present	11 (30.6)	10 (13.9)	2.72 (1.03-7.22)	0.039
Built				
Thin	0 (0)	4 (5.6)	Not calculated	0.031
Moderate	32 (88.9)	67 (93.1)		
Heavy	4 (11.1)	1 (1.4)		
Diabetes mellitus				
Present	10 (27.8)	11 (15.3)	2.13 (0.80-5.63)	0.122
Hypertension				
Present	5 (13.9)	12 (16.7)	0.80 (0.26-2.49)	0.709
Cardio Vascular Disease				
Present	2 (5.6)	2 (2.8)	2.05 (0.27-15.24)	0.471
Chronic lung disease				
Present	6 (16.7)	5 (6.9)	2.68 (0.75-9.47)	0.115
H/o dengue				
Present	2 (5.9)	7 (9.9)	0.57 (0.11-2.91)	0.496
Family members reported to be affected by Dengue				
Yes	10 (29.4)	20 (28.2)	1.06 (0.43-2.61)	0.89

**P*<0.05 considered significant, obtained from Chi square test. #As ascertained by government criteria of above and below poverty line

Mean distance of treatment facility from home, time gap between onset of symptoms, and first medical consultation in days, time gap of onset of symptoms and final diagnosis and duration of symptoms in days at time of in-patient admission were significantly higher in case group. The proportion of households where pre-monsoon activities had been done, field health workers had visited in last 2 months and information on preventive measures given by authorities was less than 50% among both cases and controls. Health-seeking behavior, access and utilization of health care of study subjects is shown in Table 2.

Multivariable logistic regression to model health seeking and health care access related determinants identified that choosing a nearby hospital for treatment (*P* = 0.018, OR = 0.48 [95%CI :0.26–0.88]) and shortening the time gap between onset of symptom and final diagnosis (*P* = 0.044, OR = 0.72 [95%CI: 0.53–0.99]) are protective.

Clinical determinants

Fever was the first symptom in all cases, except one case, in which fatigue was the first symptom. In the control group, fever was the first symptom in 58 (80.6%) subjects. In the control group, myalgia (8.3%), headache (6.9%), and fatigue (4.2%) were the other first symptoms. All reported complications except Hepatitis, Polyserositis, and Pancreatitis were significantly more among cases.

Table 3 shows the proportion presenting with particular symptoms and complications in each group. Respiratory distress (30.6%) was the most common reason for referral to a higher center among cases, whereas for controls, thrombocytopenia (54.2%) and bleeding manifestations (15.3%) were the predominant reason. The difference in reason for referral noted was statistically significant with a *P* value < 0.001 with Odds Ratio 10.12 (2.61–39.28). The complication leading to death in more than one-third of cases (38.9%) was Acute Respiratory Distress Syndrome (ARDS) followed by shock (19.4%), Multi-Organ Dysfunction Syndrome (MODS) (13.9%), and Myocarditis (13.9%). Others were Pneumonia, Disseminated Intravascular Coagulation (DIC), and intracranial bleed.

Multiple logistic regression confirmed positive association of mortality with symptoms of breathlessness (*P* < 0.001, OR = 24.9 [95%CI: 4.51–137.34]), restlessness (*P* < 0.001, OR = 97.26 [95%CI: 7.16–182]), and signs of drowsiness (*P* = 0.024, OR = 7.97 [95%CI: 1.31–48.61]), and hypotension (*P* < 0.001, OR = 42.22 [95%CI: 4.19–424.86]). ARDS (*P* = 0.047, OR = 171.56 [95%CI: 11.07–275.20]) and myocarditis (*P* = 0.012, OR = 16.59 [95%CI: 1.85–148.78]) were the two complications found to be significantly associated with death on adjusting for confounders.

Leukocytosis, hypoalbuminemia, abnormal liver function test, elevated blood urea nitrogen, and serum creatinine were significant risk factors of mortality. There was a significant

Table 2: Health seeking, access and utilization of health care				
Variable	Frequency, *n* (%) or mean (SD)		OR (95%CI)	*P**
	Cases (36)	Controls (72)		
Self-medication				
Present	12 (33.3)	11 (15.3)	2.77 (1.07-7.13)	0.031
Oral fluid intake before hospitalization				
Adequate	18 (51.4)	56 (77.8)	0.30 (0.12-0.71)	0.006
Bed rest before hospitalization				
Adequate	20 (57.1)	59 (81.9)	0.29 (0.12-0.72)	0.006
Treatment initiated from				
Govt sector hospital	17 (47.2)	50 (69.4)	0.39 (0.17-0.89)	0.025
System of medicine from where treatment was initiated				
Modern medicine	34 (94.4)	69 (95.8)	Not calculated	0.286
Ayurveda	2 (5.6)	1 (1.4)		
Homeopathy	0	2 (2.8)		
Reason for choosing health facility				
Nearby	11 (30.6)	55 (76.4)		<0.001
Good doctor	4 (11.1)	5 (6.9)		
Good facility	6 (16.7)	9 (12.5)		
Routine	15 (41.7)	3 (4.2)		
Distance of health facility from home (in kms)	3.6 (1.6)	2.9 (1.5)		0.036
Time gap between onset of symptoms and first medical consultation (in days)	2.4 (1.2)	1.5 (0.8)		<0.001
Time gap between onset of symptoms and final diagnosis (in days)	6.5 (3.0)	4.3 (1.7)		<0.001
Time gap between onset of symptoms and terminal event (in days)	11.2 (6.1)	9.7 (3.7)		0.196
Number of consultations till final diagnosis	2 (0.7)	1.6 (0.7)		0.017
Total number of consultations	2.7 (0.7)	2.4 (0.7)		0.066
Duration of symptoms at time of admission (in days)	5.2 (1.9)	4.3 (1.4)		0.004
Total duration of hospital stay (in days)	6.1 (5.8)	5.7 (3.6)		0.775
Field health workers visited in last two months	12 (33.3)	36 (50)	0.50 (0.22-1.15)	0.100
Information on preventive measures given by authorities	10 (27.8)	33 (45.8)	0.45 (0.19-1.07)	0.071

*P<0.05 considered significant, obtained from Chi square test and independent sample *t*-test

Table 3: Clinical presentation and Complications				
Variable	**Cases (36) *n* (%)**	**Controls (72) *n* (%)**	**OR (95% CI)**	***P***
Fever	35 (97.2)	71 (98.6)	0.49 (0.03-8.11)	0.614
Headache	14 (38.9)	44 (61.1)	0.41 (0.18-0.92)	0.029
Myalgia	21 (58.3)	49 (68.1)	0.65 (0.28-1.50)	0.319
Fatigue	22 (61.1)	43 (59.7)	1.06 (0.46-2.40)	0.889
Vomiting	18 (50)	49 (68.1)	0.47 (0.21-1.06)	0.068
Abdominal pain	10 (27.8)	32 (44.4)	0.48 (0.20-1.14)	0.094
Loose stools	10 (27.8)	9 (12.5)	2.69 (0.98-7.39)	0.049
Cough	14 (38.9)	9 (12.5)	4.45 (1.69-11.72)	0.002
Breathlessness	28 (77.8)	10 (13.9)	21.7 (7.73-60.85)	<0.001
Chest discomfort	11 (30.6)	3 (4.2)	10.12 (2.61-39.27)	<0.001
Palpitation	5 (13.9)	1 (1.4)	11.45 (1.28-10.12)	0.008
Restlessness	19 (52.8)	2 (2.8)	39.12 (8.29-108.37)	<0.001
Jaundice	12 (33.3)	1 (1.4)	35.50 (4.38-128.54)	<0.001
Oliguria	7 (19.4)	2 (2.8)	8.44 (1.65-43.12)	0.003
Drowsiness	23 (63.9)	7 (9.7)	16.43 (5.84-46.23)	<0.001
Altered consciousness	15 (41.7)	4 (5.6)	12.14 (3.63-40.58)	<0.001
Seizures	8 (22.2)	0		<0.001
Abnormal reflexes	4 (11.1)	0		0.004
Skin bleed	5 (13.9)	3 (4.2)	3.71 (0.83-16.51)	0.069
Epistaxis	3 (8.3)	2 (2.8)	3.18 (0.51-19.96)	0.195
Gum bleeding	6 (16.7)	6 (8.3)	2.20 (0.65-7.39)	0.194
Hemoptysis	1 (2.8)	1 (1.4)	2.03 (0.12-33.4)	0.614
Hematemesis	1 (2.8)	3 (4.2)	0.66 (0.06-6.55)	0.719
Malena	5 (13.9)	12 (16.7)	0.81 (0.26-2.49)	0.709
Increased menstrual flow than usual	1 (2.8)	5 (6.9)	0.38 (0.04-3.41)	0.373
Intracranial bleed	4 (11.1)	0		0.004*
Hypotension	19 (52.8)	1 (1.4)	79.5 (9.92-193.76)	<0.001*
Abdominal tenderness	9 (25)	7 (9.7)	3.09 (1.05-9.15)	0.035*
Edema	9 (25)	3 (4.2)	7.67 (1.92-30.48)	0.001*
Ascites	4 (11.1)	3 (4.2)	2.87 (0.61-13.61)	0.167
Pleural effusion	6 (16.7)	3 (4.2)	4.60 (1.08-19.62)	0.027*
Hemorrhagic syndrome	8 (22.2)	3 (4.2)	6.57 (1.62-26.58)	0.003
Shock	12 (33.3)	0	4 (2.28-5.65)	<0.001
Disseminated Intravascular Coagulation (DIC)	5 (13.9)	0	3.32 (2.47-4.46)	0.001
Expanded dengue syndrome	21 (58.3)	4 (5.6)	23.8 (7.12-79.54)	<0.001
Acute Respiratory Distress Syndrome (ARDS)	23 (63.9)	1 (1.4)	12.6 (15.5-101.1)	<0.001
Acute kidney injury	15 (41.7)	1 (1.4)	50.71 (6.3-80.7)	<0.001
Hepatitis	13 (36.1)	21 (29.2)	1.37 (0.58-3.21)	0.464
Myocarditis	12 (33.3)	3 (4.2)	11.5 (2.99-44.26)	<0.001
Polyserositis	5 (13.9)	3 (4.2)	3.71 (0.83-16.50)	0.114
Encephalitis	6 (16.7)	2 (1.4)	14.2 (1.64-42.08)	0.002
Pancreatitis	2 (5.6)	1 (1.4)	4.18 (0.36-47.68)	0.214
Multi Organ Dysfunction Syndrome (MODS)	15 (41.7)	1 (1.4)	50.71 (6.3-98.7)	<0.001

*P<0.05 considered significant, obtained from Chi square test

difference in polymorph count, lymphocyte count, ESR, and total protein between the two groups. S Ferritin, procalcitonin, and urine myoglobin were done for very few cases only. Elevated blood urea ($P = 0.006$, OR = 11.52 [95%CI: 2.0, 66.23]) was the single laboratory parameter that had significance on multivariable analysis. The laboratory parameters are shown in Table 4.

Discussion

This study tried to find out the proximal and distal determinants of fever mortality in a low- and middle-income setting with more emphasis on distal determinants. Age was significantly associated with fever mortality in our study, similar to reports from other studies in Kerala.[6] Patients with dengue who were more than 50 years of age had a two-fold greater chance of dying than younger patients as reported by a study in Brazil.[7] A study in California found that the risk of mortality due to H1N1 is higher in persons aged 50 years or more.[8] In addition to comorbidities, the chance of prolonged hospitalization is more common in this age group due to rehabilitation issues which can lead to bacteremia and multiorgan involvement.[9,10] In this study, the fatality was more among males with the association being not significant. Similar findings has been reported in previous

Table 4: Laboratory parameters				
Variable	Cases (36) *n* (%)	Controls (72) *n* (%)	OR (95%CI)	*P*
WBC Count per µl				
More than 10,000	8 (22.2)	4 (5.6)	4.85 (1.3-17.4)	0.009
Serum Albumin (g/dL)				
3 or less	14 (38.9)	13 (18.1)	2.89 (1.1-7.1)	0.018
ALT (units/L)				
More than 300	12 (33.3)	10 (13.9)	3 (1.18-8.11)	0.018
AST (units/L)				
More than 300	13 (36.1)	10 (13.9)	3.5 (1.35-9.01)	0.008
Blood Urea (mg/dL)				
More than 50	16 (44.4)	2 (2.8)	28 (5.9-132.1)	<0.001
Serum Creatinine (mg/dL)				
More than or equal to 2	11 (30.6)	1 (1.4)	31.2 (3.8-94.4)	<0.001

studies.[8,11–13] This is in contrast with the findings of studies from Malaysia and Vietnam which reported a preponderance of deaths among females.[14,15] Equal distribution of gender among fatal cases have also been reported in some studies.[16] There is conflicting evidence on the influence of gender on fever mortality due to infectious diseases. In contrast to other studies, high occupational status was found to be an important determinant of mortality in our study.[7,17] Being overweight and having the habit of regular alcohol use was associated with higher mortality, consistent with other studies. Even though smoking habits, diabetes, and chronic lung disease were more among the deceased, our study failed to detect a significant association with mortality unlike reported by other studies.[11,18] History of previous dengue infection was more among survivors than cases, but the association was not significant.

Self-medication was found as significant risk factor for mortality. Fever is one of the commonest symptoms for which self-medication is being practiced.[19] Self-medication as a risk factor for mortality in infectious diseases like dengue is well documented.[20] Association of mortality with self-medication practice are often attributed to delay in health care seeking which ends up in delayed diagnosis of the underlying condition and appropriate treatment and also results in worsening of condition by the time they seek health care. The role of fluid intake and bed rest in preventing complications, hospitalization, and death from infectious diseases is well established.[21] Similar findings were obtained in this study as well. Health-seeking behaviors like choosing a nearby hospital and initiating treatment from government sector hospitals were found to be protective. Early diagnosis, protocol-based management, timely referral, and knowledge among health staff may be the contributing factors. Another major determinant of mortality was the time gap between onset of symptoms and first medical consultation. Delayed care seeking has been documented in studies as a determinant of mortality, with death being more often in patients who sought care after the fourth or fifth day of fever compared to recovered who sought care during the first three days.[17] Care-seeking behavior may determine the possibility of receiving opportune treatment and thereby avoiding fatal outcomes. Time gap of onset of symptoms and final diagnosis, number

of consultations till final diagnosis, and duration of symptoms at time of admission were risk factors for mortality. Difficulties of opportunity were noted in diagnosis, case management, and the referral process in previous studies. When care is not offered opportunely, the risk of dengue fatal outcomes is theoretically doubled.[17] The health system related determinants should be addressed and must figure prominently in any strategy targeting a decrease in mortality.

Headache was found to be less frequent among cases in our study in contrast to that documented in other studies.[8,14] Breathlessness was identified as a risk factor for mortality similar to that reported by Louis *et al.*[8] Symptoms which were significantly higher among cases were cough, breathlessness, chest discomfort, palpitation, and loose stools. These alert symptoms indicate an important opportunity for adequate case management at a time early enough when treatment interventions would be most efficacious in preventing death. A study on leptospirosis in Kerala has identified abdominal pain as a risk factor for mortality.[13] Acute abdomen as an unusual presentation in DHF is also documented.[22] In our study, abdominal pain was not a significant determinant, whereas abdominal tenderness was found to be associated with mortality. Lethargy/restlessness was identified as a determinant of mortality in line with another study done in Malaysia.[14] Impaired consciousness was reported among more than 50% of dengue cases and seizures were found among more than one-third of dengue cases in previous studies.[23,24] Similarly altered mental status was found to be associated with mortality for H1N1 and Leptospirosis.[8,13] As evidenced in these studies, brain involvement was associated with a higher incidence of mortality in this study as well.

Hemorrhagic manifestations like epistaxis, gingival bleeding, and intracranial bleed were more common among those patients who died from fever similar to that reported by other studies on dengue.[25,26] This is one of the warning signs of dengue according to the WHO 2009 case definition.[27] Consistent with other studies, the probability of death was more among those who had jaundice and oliguria.[13] These features are early signs of multiple organ involvement and warrant immediate actions to prevent progression to severity and death. A study from Sri Lanka reports bleeding

at admission, acute kidney injury (AKI), and elevated hepatic transaminase >500 IU/L as independent predictors of mortality.[28] As evidenced in this study and suggested in other studies, cavitary effusion was associated with an increased incidence of mortality.[7] Presence of cavitary effusions is a sign of plasma extravasation which is the main pathologic change in severe dengue.[27] Edema was found to be frequent among cases which contrast with reports from other studies.[6,14] Complications like hemorrhagic syndrome, shock, disseminated intravascular coagulation, expanded dengue syndrome, acute respiratory distress syndrome, AKI, myocarditis, encephalitis, and multiple organ dysfunction syndrome were frequent among deceased than survivors.[6,14,16]

Hypoalbuminemia and elevated liver enzymes were found to be significant determinants of mortality as suggested in previous studies.[29] Elevated liver transaminases and hypoalbuminemia could be good indicators of vascular leakage or hepatic dysfunction in DHF and could be used to identify severe cases.[30] Uremia and elevated serum creatinine were found to be significantly associated with mortality. Similar findings suggestive of AKI have been documented in other studies as well.[16,29] In contrast to other studies, thrombocytopenia and hematocrit were not found to be a determinant of mortality in our study.[7] The usual practice of monitoring platelet count for predicting severity has to be reassessed based on this evidence since patients may progress to severity even without having thrombocytopenia. The major complication leading to death was acute respiratory distress syndrome as evidenced in previous studies.[31]

Primary care physicians as first contact doctors, can identify early, clinical determinants of mortality among fever cases and start appropriate management. In addition, knowledge of sociodemographic factors, health-seeking behavior, and health system factors associated with fever mortality can inform decision making in individual patient care as well as improving health care system and services.

Limitations

A major limitation of this study is that it was retrospective in nature. As there were only 36 deaths during the study period, we had a limitation of sample size. Study subjects included in this study were reported fever cases and deaths and this may not be representative since underreporting and lack of diagnosis for those who are brought dead is a reality.

Conclusion

Along with clinical factors, death because of fever is determined by sociodemographic factors, health-seeking behavior, and health system factors. To bring about a decrease in fever mortality, these factors should be addressed along with clinical determinants and generating awareness among the public regarding the same is a need. Patients with clinical risk factors should be identified and referred promptly from the primary and secondary levels of care and should be given special care and attention at tertiary levels of health care to decrease mortality.

Summary

Lower middle-income countries are burdened by several infectious diseases which initially presents with symptoms like fever and body ache and cause considerable mortality which is often avoidable. Understanding the determinants of mortality, both proximal clinical factors and distal determinants like sociodemographic factors, health-seeking behavior, and health system factors are essential for implementing effective preventive measures. Health-seeking behaviors like choosing a nearby hospital and initiating treatment from government sector hospitals are found to be protective. Mean distance of health facility from home, the time gap between the onset of symptoms and first medical consultation in days and time gap of onset of symptoms and final diagnosis were significantly associated with mortality. Significant association of mortality was found with symptoms of breathlessness, restlessness and signs of drowsiness and hypotension. ARDS and myocarditis were the two complications found to be significantly associated with death.

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Conflicts of interest

There are no conflicts of interest.

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