International Journal of Mosquito Research

ISSN: **2348-5906**
CODEN: **IJMRK2**
IJMR 2018; 5(6): 05-09

Received: 02-09-2018
Accepted: 03-10-2018

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Survival analysis of dengue patients of Pakistan

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Abstract
Objective: The present study is carried out to explore relationship between dengue fever and demographic factors, initial symptoms and severe symptoms. It is used to estimate the survival function with respect to age and gender respectively and to predict time to survive of dengue fever on the basis of number of factors.
Methods: The study was conducted by taking data from Services Hospital Lahore from the year 2013 to 2016. A sample of size 708 is included. Pearson chi square test, Mann Whitney test is applied and survival analysis using Kaplan Meier test and Cox-regression model respectively.
Results: The symptoms of dengue fever like headache, eye pain, muscle pain, joint pain, abdominal pain, nausea and vomiting, sweats, haematuria, chills and vaginal bleeding had significant association with fever. From Mann Whitney U test, it is concluded that HCT and Hb in died group was statistically significantly higher than the survival group. Cox regression demonstrated that abdominal pain and petechlae was significant in predicating the survival rate for DF (Dengue Fever) patients and abdominal pain was significant in predicating the survival rate for DSS (Dengue Shock Syndrome) patients. Kaplan Meier showed that estimated survival time for the male, female and others are same whereas it is different among children, adults and elderly.
Conclusion: The present study has revealed that dengue is more common in adults whereas estimated survival time was same for males and females. In DSS abdominal pain was significant in predicting the survival rate and nausea and vomiting show greater hazard for DSS patients whereas petechlae and abdominal pain were also significant in predicting the survival rate in DF (Dengue Fever).

Keywords: Survival analysis, dengue fever (DF), dengue shock syndrome (DSS), cox regression, Kaplan Meier

Introduction
Dengue fever is a quick developing pandemic-prone disease which is usually caused by a mosquitoes bite, the viruses is transmitted to human being by the female mosquito *Aedes aegypti*. The common symptoms among dengue patients are high grade fever, skin rash, headache and severe muscle and joint pains. The dengue is also known as "break bone fever" or "dandy fever". It affects infants, children and adults alike and could be fatal [3, 4]. The mosquitoes causing dengue infection bite most frequently during daytime and in the outdoors [20].

The dengue virus (DEN) includes four distinct serotypes (DEN-1, DEN-2, DEN-3 and DEN-4). Most of the people suffer from Dengue fever (DF), Dengue hemorrhagic fever (DHF) and Dengue Shock Syndrome (DSS). Infant, young children and adults are equally affected by the dengue fever but deaths were less common in most of the cases [10]. Unplanned urbanization is the primary factor that lead to the widespread increase in the occurrence of disease in most of the developing countries where as the travel factor is believed to have the larger impact on the global spread of dengue [7].

It is believed that the patients suffering from DSS symptoms should visit a medical facility as soon as possible because it leads to death within 24 hours [8].Dengue prospers in urban poor areas, rural areas and in addition it affects tropical and subtropical countries. The rate (occurrence) of dengue has expanded 30-fold over the last 50 years. Every year a large number of severe cases of dengue, about 20,000 people lead to death [6, 20]. Occurrence of dengue fever has increased since past decade, it is more common in China, Sri Lanka, India, Maldives, Bangladesh and Pakistan [5].

In Pakistan, the occurrence of DHF was first reported in Karachi in 1994 [18]. Pakistan has sub-tropical climate, it consist of huge population whereas due to poor sanitation and less precautionary measures lead to the occurrence of dengue fever [11]. Over the past few years, the dengue fever has been rapidly increasing in different regions of Pakistan especially in the urban areas of Punjab. In Punjab, the heavy monsoon rains has provided the best conditions for the mosquitoes to flourish in the stagnant waters. Around 2,661 and 1,440 cases of dengue fever were reported in 2013 and 2014 respectively whereas 4,348 cases of dengue fever were reported in 2015

Fever, purpura, epistaxis, haematemesis (blood in vomiting) and ecchymosis were generally present manifestations. At the initial presentation, it was observed that 94 patients had a platelet count below 100,000/mm3 [17]. The warning symptoms in majority of the severe cases were abdominal pain and vomiting. Mortality was associated with adult dengue virus infection [12].

The main symptoms of fever on admission which fall under the fatal category were chills and rigor myalgia, nausea and vomiting and diarrhea, systolic blood pressure (mmHg 105.0 – 230) and fever. Under the warning signs abdominal pain and persistent vomiting came out to be insignificant [19]. Symptoms like bleeding, abdominal pain, vomiting and rash were strongly associated with DSS. The warning signs in some cases were severe and persistent vomiting and diarrhea about 4 days before the death of the patients [16]. The most common associated risk factor with fever was nausea and vomiting, it was being followed by abdominal pain, diarrhea, cough, body aches, bleeding gums, hematemesis [1]. Dengue fatalities were seen mostly in adult females [15]. The fever was most common with the symptoms, anorexia and abdominal pain [2]. The patients died due to severe dengue infection, with the associated risk factors, hematuria, gastrointestinal bleeding, and thrombocytopenia compared to survivors [14]. The probability of survival of Demam Berdarah Dengue (DBD) patients among males and females does not differ significantly [9]. The dengue patients suffered from diabetes and hypertension and those of east Indian origin were found to be at shorter hospital stay prior to death [13].

In past, less number of researches has been carried out on identification of risk factors among dengue patients whereas less focus is paid on the survival analysis of dengue patients. This study has focused on identifying the risk factors and survival of dengue patients admitted at Services hospital Lahore.

Materials and Methods

The aim of the study was to assess the survival of dengue patients**.** The target population of this analytical study was dengue patients of different age groups (children, adult, and elderly) of Lahore. The sampled population of this study was the dengue patients that were admitted at the Services Hospital Lahore from the year 2013 to 2016. A sample of size 708 dengue patients was taken for the study. The collected data was secondary and was retrieved from patient's reports that were consisted of information relating to demographic factors, initial and severe symptoms and laboratory investigations respectively. Data was analyzed using chi-square test of association, Mann Whitney test and survival analysis was carried out using Kaplan Meier test and Cox-regression model respectively.

Results

Table 1: Percentage of initial and severe symptoms in patients and chi Square test of associations between fever and gender, age group, education and different symptoms.

Percentage of symptoms in dengue patients		Significant Association of symptoms with dengue fever
Headache	83.90%	0.00**
Eye pain	72.88%	0.00**
Muscle pain	84.04%	0.00**
Joint pain	68.36%	0.00**
Nausea and vomiting	64.41%	0.01*
Diarrhea	14.83%	0.903
Irritability in infants	4.10%	0.523
Chills	53.95%	0.00**
Cough	28.53%	0.863
Petechlae	17.37%	0.611
Purpura ecohymosis	4.24%	0.455
Abdominal pain	43.64%	0.001*
Sweats	31.50%	0.00**
Epistaxis	7.63%	0.087
Bleeding gums	13.28%	0.158
Hematuria	1.69%	0.005*
Vaginal bleeding	1.99%	0.003*
Hypotension	12.95%	0.465
Platelets		0.398
Gender		0.528
Education		0.065
Age-group		0.084

**Significant at 0.05 and 0.01 significance level

* Significant at 0.05 significance level

Table 1 has reported percentage of symptoms that were present in the dengue patients. Chi square test has revealed that headache, eye pain, muscle pain and joint pain, chills, abdominal pain, sweats, hematuria and vaginal bleeding respectively are significantly associated with the dengue fever.

Table 2: Mann Whitney U test

	WBC	HCT	Hb	Systolic_BP	Distolic_BP	Pulse Pressure
Mann-Whitney U	3381.000	2488.500	2036.000	3380.500	2842.000	3751.500
Wilcoxon W	246634.00	245741.500	245289.000	3446.500	2908.000	247004.500
Z	-.672	-1.999	-2.671	-.676	-1.481	-.123
Asymp. Sig. (2-tailed)	.501	.046	.008	.499	.139	.902

According to table 2 Mann Whitney U test showed that HCT and Hb in died group was statistically significantly higher than the survival group.

Table 3: Mann Whitney U test

	WBC	HCT	Hb	Systolic_BP	Distolic_BP	Pulse Pressure
Mann-Whitney U	34784.000	30752.500	34477.000	35418.50	34803.500	33918.000
Wilcoxon W	206189.00	38378.500	42103.000	43044.500	206208.500	41544.000
Z	-.579	-2.535	-.728	-.272	-.572	-1.010
Asymp. Sig. (2-tailed)	.563	.011	.467	.786	.567	.312

Table 3 has reported HCT in yes group was statistically significantly higher than the no group of petechlae.

Table 4: Mann Whitney U test

	WBC	HCT	Hb	Systolic_BP	Distolic_BP	Pulse Pressure
Mann-Whitney U	34784.000	30752.500	34477.000	35418.500	34803.500	33918.00
Wilcoxon W	206189.00	38378.500	42103.000	43044.500	206208.500	41544.00
Z	-.579	-2.535	-.728	-.272	-.572	-1.010
Asymp. Sig. (2-tailed)	.563	.011	.467	.786	.567	.312

According to table 4, Systolic BP in yes group was statistically significantly higher than the no group of joint pain.

Table 5: Mann Whitney U test

	WBC	HCT	Hb	Systolic_BP	Distolic_BP	Pulse Pressure
Mann-Whitney U	50714.00	53790.000	54631.000	57085.500	54964.500	56043.500
Wilcoxon W	82592.00	157986.00	158827.00	161281.500	159160.500	87921.500
Z	-2.588	-1.407	-1.084	-.143	-.961	-.548
Asymp. Sig. (2-tailed)	.010	.159	.278	.887	.336	.584

Table 6: Mann Whitney U test

	WBC	HCT	Hb	Systolic_BP	Distolic_BP	Pulse Pressure
Mann-Whitney U	24963.000	28164.50	28744.500	28392.000	27536.000	26984.500
Wilcoxon W	213768.00	32629.50	217549.500	217197.000	216341.000	31449.500
Z	-2.110	-.376	-.061	-.253	-.720	-1.026
Asymp. Sig. (2-tailed)	.035	.707	.951	.800	.472	.305

Table 5 and 6 indicate that WBC in yes group was significantly higher than the no group of nausea and vomiting as well as bleeding gums.

Cox regression was applied to risk factors of Dengue Fever (DF), Dengue Shock Syndrome (DSS) and DHF as well as with the initial symptoms. It showed that abdominal pain and petechlae was significant indicating that these predictors were significant in predicating the survival rate for Dengue Fever (DF) patients and abdominal pain was significant in predicating the survival rate for Dengue Shock Syndrome (DSS) patients and nausea and vomiting showed greater hazard rate as compared to survival in DSS (Dengue Shock Syndrome).

Table 7: Kaplan Meier Test

	Chi-Square	Degrees of Freedom	Significance
Log Rank (Mantel-Cox) for Gender	1.294	2	0.524
Log Rank (Mantel-Cox) for Age Groups	7.10	2	0.025

According to Kaplan Meier test, the estimated survival time for all the categories of the gender was same whereas it was different among children, adults and elderly.

Discussion

According to the current study approximately 68% of individuals were males and 31% were females where as 0.2% were categories as others. It was observed that approximately 94.63% of patients suffer from dengue fever which include initial symptoms such as headache, eye pain, muscle pain, joint pain, nausea and vomiting, diarrhea, irritability in infants, chills, cough, petechlae, purpura ecohymosis, abdominal pain, sweats, epistaxis, bleeding gums, haematuria, vaginal bleeding, and hypotension, the results are in line with

the other reports [2]. The symptoms of dengue fever were almost the same that is in contrast with [12] where as it was in contradiction with other studies [17, 1].

The current study revealed that about 4% cases have platelets count <10,000, about 73% cases have platelets count ranging between 11,000 to 40,000 whereas about 17% cases have platelets count that are less than100,000 that is in contradiction with the study that has reported the platelets count less than 100,000 in 93% of the cases, 5% cases have platelets count less than 10,000 and 173 cases having platelets ranging between 11,000 to 40,000 respectively [16]. The study was also in contrast with other reports according to which 94 patients had a platelets count below 100,000/mm3 whereas the platelets count was less than 100,000/mm in four patients [17].

The present study showed that the mortality rate was 1.55% that was approximately the same as reported in another study [1]. The present study revealed that the clinical symptoms of deceased cases was fever experienced by all patients, chills, headache, eye pain, and hematuria and diarrhea that is consistent with a study, according to which the clinical symptoms of deceased cases were fever experienced by all of the patients, chills, headache and breathlessness [16]. The current study and another study [2] have reported the common symptoms of deceased patients such as chills, headache, eye pain and hematuria, diarrhea, whereas a study has reported hematuria as a common symptom of deceased cases [14]. The current study reported nausea and vomiting as well as diarrhea occurred right before the death of the patient that is in line with a study according to that some cases have suffered from persistent vomiting and diarrhea about 4 days before the death of the patients [16].

The current study has reported that survival time or the average length of the stay of dengue patients at hospital was two days that was also in contrast with the other studies [9, 15].

The present study has revealed that fever was more common in adults compared to children and elderly, it is in line with the study that has reported the fatal dengue haemorrhagic fever (DHF)/dengue shock syndrome (DSS) occur more in elders [12]. The present study is also in line with some studies that has depicted the clinical profile of DHF in adults whereas mortality was associated with adult dengue virus infection [12, 18]. The present study is in contradiction with the study according to which dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) fatality and hospitalization rates were the highest among young infants and elderly [19].

Kaplan Meier technique revealed that the estimated survival time for the male, female and other gender category is same (p-value < 0.05) whereas nine out of ten fatal cases included adult females with a median age of 32 years [15]. The current study concluded that dengue fatalities were seen basically in adult females [9].

Cox regression technique was applied that has explored the petechlae and abdominal pain as significant factors in predicting the survival rate, the cox regression has also reported that the patients suffering from nausea and vomiting have greater hazard compared to survival. The current study is in line with the study that has reported some cases who have suffered from persistent vomiting before the death of the patients [12, 16].

Conclusion

The present study has revealed that dengue is more common in adults whereas estimated survival time was same for males and females. The hazardous factors for the deceased patients were fever, headache, eye pain, muscle pain, joint pain, nausea and vomiting, chills, haematuria and diarrhea respectively. For dengue shock syndrome, abdominal pain was significant in predicting the survival rate and nausea and vomiting show greater hazard for dengue shock syndrome patients whereas petechlae and abdominal pain were also significant in predicting the survival rate in the patients suffering from dengue fever.

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