



ASSOCIATION BETWEEN DENGUE VIRUS RELATED COMPLICATIONS AND PATIENTS' DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Kamran Amir Khan¹, Sameed Ullah Qureshi¹✉

ABSTRACT

OBJECTIVE: To explore the association between observed complications in patients diagnosed with dengue fever and patients' demographic and clinical characteristics.

METHODS: This cross-sectional analysis of data collected from prospective study conducted in a private hospital in Peshawar, Pakistan and comprised data of dengue patients admitted from June 2018 to December 2019. Laboratory parameters and clinical outcomes were studied. STATA 16 was used for data management and analysis.

RESULTS: Out of 200 diagnosed patients of Dengue fever, 135 (67.5%) were males and 65 (32.5%) were females. The median age of diagnosis was 36 years and 67.5% were males. Only 6 (3.0%) patients were diagnosed with severe dengue disease. Forty-two (29.0%) patients experienced one or more complication(s). Most common complications observed were coagulopathy (n=16; 8%), dengue shock syndrome (n=15; 7.5%) and sepsis with infection (n=6; 3%). Median (interquartile range-IQR) of platelet count ($\times 10^9/l$) was 72.9 (41.1-129.9) and 144.0 (100.4-205.0) in patients with and without complications respectively ($p < 0.001$). Platelet transfusion was done in 27 (13.5%) and folic acid supplementation was given to 171 (85.5%) patients. Median (IQR) duration of hospital stay was 4 (3-6) and 3(2-4) days in patient with and without complications (< 0.001). Overall mortality rate was 2.0% (n=4/200). There was a statistical difference in proportion of platelet transfusion, duration of hospital stay (number of day) and survival between those who had complications and those who didn't ($p = < 0.001$).

CONCLUSION: Platelet transfusion and duration of hospital stay in the hospital were significantly associated with higher risk of dengue complications.

KEYWORDS: Dengue (MeSH); Dengue Virus (MeSH); Severe Dengue (MeSH); Dengue Shock Syndrome (MeSH); Complications (Non-MeSH), Blood Platelets (MeSH); Thrombocytopenia (MeSH)

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INTRODUCTION

Dengue fever is caused by dengue viruses (DENV) of the genus *Flavivirus*. It is transmitted by *Aedes* mosquitoes and presents as an acute febrile illness (AFI). Four serotypes of the dengue virus have been identified i.e., DENV-1, DENV-2, DENV-3, and DENV-4. The DENV is a major cause of disease in tropical and subtropical areas. Annually, over 50 million infections are reported.¹ All four serotypes of DENV are endemic in Pakistan with peak

incidence of infection between September to December.^{2,3} The Although these infections are self-limiting, some patients suffer serious complications or even die as a result.⁴⁻⁷ The clinical signs and symptoms vary, and the complications include neurological impairment, organ failure, hemorrhagic fever, liver failure, acute kidney failure, acute respiratory distress, dengue shock syndrome.

Majority of studies in Khyber Pakhtunkhwa province of Pakistan are

1: Northwest General Hospital, Peshawar, Pakistan

Email✉: sameedqureshi92@gmail.com

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epidemiological and only limited studies are conducted to address the clinical aspects of dengue fever.^{2,3,8-10} This study was conducted to explore the association between the observed complications in patients diagnosed with dengue fever and patients' demographic and clinical characteristics, and to help identify these patients with early complications and prompt treatment.

METHODS

This cross-sectional study was conducted at Northwest General Hospital, a tertiary care hospital of Peshawar, Pakistan. Non-probability convenient sampling technique was used, and a structured format was used for data collection. Patients who presented with acute febrile illness (AFI) in the emergency room and in-patient departments from June 2018 to December 2019 were included in the study. Laboratory tests including dengue serology, complete blood count and ALT were performed as a part of initial evaluation. Patients with clinical presentation of viral illness and supported by positive serology of dengue tests including via detection of viral antigen nonstructural protein and antibodies were labeled as dengue confirmed cases. All the cases with negative dengue serology were excluded from the study. Two milliliter of blood in EDTA anticoagulant, 2 ml blood in 0.2 ml citrate anticoagulant and 2 ml blood in plain bottle was collected for blood counts, dengue serology and aminotransferase (ALT). Dengue specific NS1, IgG, IgM were performed by standard enzyme linked

TABLE I: DEMOGRAPHIC INFORMATION ABOUT THE RESPONDENTS (N=794)

| Variables | | Total N = 200 [N (%)] | Complication(s) | | P value |
|----------------------------------|-----------------------------|-----------------------------|--------------------------|--------------------------|---------|
| | | | No n = 158 [N (%)] | Yes n = 42 [N (%)] | |
| Gender | Male | 135 (67.5) | 105 (66.5) | 30 (71.4) | 0.583 |
| | Female | 65 (32.5) | 53 (65) | 12 (28.6) | |
| Dengue | Mild/Moderate | 194 (97.0) | 154 (97.5) | 40 (95.2) | 0.608 |
| | Severe | 6 (3.0) | 4 (2.5) | 2 (4.8) | |
| Platelets Transfused | No | 173 (86.5) | 149 (94.3) | 24 (57.1) | <0.001 |
| | Yes | 27 (13.5) | 9 (5.7) | 18 (42.9) | |
| Given folic acid supplementation | No | 29 (14.5) | 25 (15.8) | 4 (9.5) | 0.459 |
| | Yes | 171 (85.5) | 133 (84.2) | 38 (90.5) | |
| Survival | Stable | 193 (96.5) | 156 (98.7) | 37 (88.1) | <0.001 |
| | Left against medical advice | 3 (1.5) | 2 (1.3) | 1 (2.4) | |
| | Died | 4 (2.0) | 0 (0) | 4 (9.5) | |
| Age (years) | Median (IQR) | 36 (25-49) | 35 (25-47) | 38 (26-52) | 0.360 |
| Duration of hospital stay (days) | Median (IQR) | 3 (2-4) | 3 (2-4) | 4 (3-6) | <0.001 |

*E= Fisher's exact *C= Chi Square *R= Wilcoxon rank sum

TABLE II: COMPLICATIONS AND THE PRESENTING SYMPTOMS OF THE STUDY SUBJECTS

| Variables | Frequency (n=200) | Percentage | |
|-----------------------|------------------------|------------|------|
| Presenting symptoms | Generalized body aches | 144 | 43.0 |
| | Anorexia | 98 | 49.0 |
| | Vomiting | 29 | 14.5 |
| | Fever | 28 | 14.0 |
| | Headache | 25 | 12.5 |
| | Altered mental status | 7 | 3.52 |
| | Rash | 3 | 1.50 |
| Complications (n=42*) | Coagulopathy | 16 | 8 |
| | Dengue Shock Syndrome | 15 | 7.5 |
| | Sepsis with infection | 6 | 3 |
| | Renal dysfunction | 3 | 1.5 |
| | Cardiomyopathy | 2 | 1 |
| | Seizure | 1 | 0.5 |

*patients experienced one or more complication(s)

immunosorbent assay (ELISA). Baseline information on patient's name, age (years), registration number, and clinical presentation (fever, generalized body ache (GBA), vomiting, anorexia, headache, rash, and altered mental status) were obtained. Subsequent information on treatment therapy antipyretic, antibiotics if needed and supplementation), survival (survival, expired), complications (dengue shock syndrome (DSS), malaria, sepsis with infection, cardiomyopathy, seizures, and coagulopathy) platelet transfusion (yes/no), and creatinine levels were recorded. Acute kidney injury (AKI) was

defined by increase in creatinine >1.2mg/dl and coagulopathy were described as International normalized ratio (INR) of more than 1.5.

The ethical certificate for this study was obtained from the ethical committee of the Hospital. Each patient was given a unique identifier to ensure anonymous data. Continuous variables were presented as median (25%–75% interquartile range [IQR]) and were compared using Wilcoxon's ranked sum test; this was because the variables were not normally distributed. Categorical variables were presented as

numbers (n) or proportions (%) and were compared using Fisher's exact or Chi Square test, where appropriate. Multivariate logistic regression model was used to determine risk of dengue diagnosis between male and female, odds ratio and 95% confidence interval were obtained. Two-sided P < 0.05 was considered as statistically significant. STATA 16 was used for data management and analysis

RESULTS

A total of the 200 patients were via detection of viral antigen nonstructural protein and antibodies of Dengue fever. Of this, 158 (79.0%) did not experience any complication, while 42 (21.0%) experienced one or more complication(s). The median age of diagnosis was 36 years and 67.5% were males. Only six (3.0%) patients had severe dengue. The overall mortality rate was 2.0%. Platelet transfusion and folic acid supplementation was done in 27 (13.5%) and 171 (85.5%) patients, respectively. There was a statistical difference in proportion of patient's platelets transfusion and survival between those who had complications and those who didn't (p = <0.001) [Table I].

The predominant presenting symptoms were generalized body aches (n=144; 43.0%) and anorexia (n=98; 49.0%). Most common complications observed were coagulopathy (n=16; 08%), dengue shock syndrome (n=15; 7.5%) and sepsis with infection (n=6; 3%) [Table II].

The laboratory values are presented in [Table III]. The median concentration of platelet and creatinine were different among patients with and without complications on arrival and during the course of admission (p < 0.001). Median (IQR) platelet count ($\times 10^9/L$) was 130 (79.7-195); 144.0 (100.4-205.0) and 72.9 (41.1-129.9) in total patients, patients without complications and patients with complications respectively (p < 0.001). Similarly, Median (IQR) of serum Creatinine (mg/dl) was 0.8 (0.6-1.1), 0.8 (0.6-1.1) and 1.1 (0.8-1.6) in total patients, patients without complications and patients with complications respectively (p < 0.001).

Multivariable analysis of the factors associated with complications in dengue

TABLE III: HEMATOLOGIC AND BIOCHEMICAL PARAMETERS OF THE STUDY SUBJECTS

| Parameters | Total (N = 200) | Complication(s) | | P value |
|---|---------------------|------------------------|----------------------|---------|
| | | No (n=158) | Yes (n=42) | |
| | Median (IQR) | Median (IQR) | Median (IQR) | |
| Hemoglobin (g/dl) | 14.0 (12.4-15.2) | 13.9 (12.3-15.2) | 14.3 (12.7-15.4) | 0.488 |
| Platelet Count ($\times 10^9$ /l) | 130 (79.7-195) | 144.0 (100.4-205.0) | 72.9 (41.1-129.9) | <0.001 |
| Packed Cell Volume (%) | 41.9 (38.2-45.3) | 41.8 (38.1-45.6) | 42.1 (38.4-45.0) | 0.821 |
| Alanine Transaminase (U/L) | 39.5 (22.5-68.5) | 38.5 (23.0-65.0) | 42.5 (22.0-75.0) | 0.671 |
| Creatinine (mg/dl) | 0.8 (0.6-1.1) | 0.8 (0.6-1.1) | 1.1 (0.8-1.6) | <0.001 |
| Total Leukocyte Count ($\times 10^9$ /l) | 5.8 (3.9-8.1) | 5.6 (3.9-7.79) | 7.3 (4.2-9.4) | 0.051 |

*Interquartile range

TABLE IV: MULTIVARIABLE ANALYSIS- FACTORS ASSOCIATED WITH COMPLICATION(S) IN DENGUE PATIENT

| Variable | | Odds ratio | 95%CI | P value |
|----------------------------------|--------|------------|-----------|---------|
| Platelet Transfusion | No | Reference | | |
| | Yes | 8.14 | 2.54-26.0 | <0.001 |
| Duration of hospital stay (days) | | 1.65 | 1.26-2.17 | <0.001 |
| Platelet count | | 0.99 | 0.99-1.00 | 0.144 |
| Creatinine | | 1.33 | 0.91-1.93 | 0.137 |
| Survival | Stable | Reference | | |
| | LAMA | 0.55 | 0.0-191.7 | 0.840 |
| | Died | - | - | - |

LAMA: Left against Medical advice

patient revealed that only platelet transfusion (OR 8.14, 95% CI 2.54–26.00) and number of stay (OR 1.65, 95% CI 1.26–1.00) in the hospital were significantly associated with higher risk of complication(s) ($p < 0.001$) [Table IV].

DISCUSSION

In this study, dengue virus related complications were observed in 21% cases with common complications like coagulopathy, dengue shock syndrome and sepsis with infection. Generalized bodyaches and anorexia were the common complaints. Platelet transfusion and duration of hospital stay were associated with complications in patients diagnosed with dengue fever.

A wide spectrum of illness exists. It can range from imperceptible to mild to a severe or sometimes fatal dengue fever.¹¹ For diagnosis of dengue virus, the gold standard is the virus isolation in cell culture and the subsequent identification

using fluorescent antibody. This method is however, rarely used in the clinical setting. Acute dengue infection is diagnosed by detecting viral antigen and RNA or dengue specific antibodies in blood.¹¹ The antibody detection (IgM and/or IgG) is commonly achieved by using the enzyme-linked immunosorbent assay (ELISA) – this is because of its sensitivity and specificity. Our study obtained the viral antigen (NS1), IgG, IgM using the ELIZA. Most of the patients included in the study presented with acute dengue infection, while anorexia and generalized body aches were the most common presenting symptoms. In a study in Brazil,¹² the researchers found that some of the most persistent symptoms of Dengue infection were weakness, fatigue, anorexia – this is consistent with our study. Other studies have reported similar findings in Thailand and Madeira island.^{13,14}

There are limited studies on the factors associated with Dengue virus

complications. This is either because dengue virus is known commonly to resolve without treatment or due to the limited cases of complicated dengue infection.⁴ However, a number of studies have associated Dengue infection to several neurological disturbances in recent times. The neuropathogenesis of dengue virus infection is not well understood. It may seem like the viral and the host factors may have a role in the neurological disorders associated with Dengue.¹⁵ A study in Lucknow, India among 26 confirmed patients with dengue infection, recorded that six neurological disorders associated with dengue virus after two years of infection – brachial neuritis, encephalopathy, Guillain Barre syndrome, hypokalemic paralysis, viral myositis, Opsoclonus-myooclonus syndrome, myelitis, and encephalomyelitis were identified.¹⁶ Apart from subsequent neurological impairment, other complications have been recorded.

Dengue hemorrhagic fever or Dengue shock syndrome is another complication that has been reported. Dengue infected children in the pediatric intensive care unit in a hospital in South India had complications including hepatic dysfunction.¹⁷ As such, it can be observed that hepatic involvement is common in dengue. Previous studies have found elevated liver enzymes, especially ALT to be associated with dengue fever.¹⁸⁻²⁰ A recent study in Pakistan found that the occurrence of liver dysfunction was higher in dengue fever than in dengue hemorrhagic fever (38.15 vs 18.6%).²¹ However, in our study, liver functions were normal in both dengue patients and in those patients with complications. Another study also found that ALT levels failed to show any involvement in hepatic dysfunction.⁵

Creatinine level is also an important indicator of acute renal failure has been reported to be associated with dengue fever.⁵ Rhabdomyolysis was reported in a study by Davis and Bourke where two patients who had dengue infection²² Rhabdomyolysis is a complication of dengue virus infection might be less recognized and thus, underreported. We, however, did not find significant association between dengue complications and creatinine levels. Other complications found in our study patients were sepsis, malaria, seizures, coagulopathy, and cardiomyopathy.

In this study, 200 patients were included. Platelet transfusion and duration of stay in the hospital were significantly associated with higher risk of complication(s). Previous studies have found that platelet transfusion is a management of the hemorrhagic manifestation of dengue fever i.e., such as petechiae, gum-bleeding, epistaxis etc.²³⁻²⁵ However, unnecessary and empirical uses of platelet transfusion should be monitored or avoided in cases of mild episodes of bleeding.²⁵ Also, patients who stay longer in the hospital are more likely to have been ill and experiencing complications, hence their longer stay in the hospital.^{26,27}

LIMITATIONS OF THE STUDY

The study population may not be representative of the total dengue population during the time period studied. Also, there is a lack of information about other known complications of Dengue virus.

CONCLUSION

Platelet transfusion and number of days in the hospital were significantly associated with higher risk of dengue complications. However, there is a need for a study with larger sample size to fully explore the association, as cases of severe dengue conditions are increasing in recent times.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

KAK: Concept and study design, acquisition, analysis and interpretation of data, drafting the manuscript, critical review, approval of the final version to be published.

SUQ: Analysis and interpretation of data, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request



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KMUJ web address: www.kmu.edu.pk

Email address: kmu@kmu.edu.pk