

# Original Research Article

## Dengue Reinfection and Co-infection: A Study of Incidence and Outcomes in Adults Admitted to a Tertiary Care Hospital, Karachi, Pakistan

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### ABSTRACT

**Aims** To determine the incidence of re-infection and co-infection with dengue among adult population in Karachi, Pakistan. In addition, to determine the frequency of various medical complications among dengue patients with or without co-infection and reinfection. And to identify possible risk factors associated with dengue reinfection.

**Study design:** Retrospective cross-sectional study.

**Place and Duration of Study:** Department of Internal Medicine, Aga Khan University Hospital, Karachi, Pakistan, between January 2022 till August 2022.

**Methodology:** A total of 500 adult patients of age 18 years or above; admitted with confirmed diagnosis of dengue were included in the study. Information was collected regarding clinical and demographic

**Results:** The current study reported an incidence of 3.8% for dengue re-infection and an incidence of 19% for co-infection among adult dengue patients. The most common clinical symptoms were fever, nausea, vomiting and abdominal pain while bleeding, acute kidney injury and nosocomial infection were the most common complications with a proportion of 10.6% (n=53), 7.8% (n=39) and 4.2% (n=21). The study could not find any statistical association between the socio-demographic factors as well as disease related characteristics.

**Conclusion:** This study determines a low incidence proportion of dengue re-infection and co-infection among adult patients admitted with confirmed diagnosis of dengue infection at a private tertiary care hospital in Karachi. Bleeding, nosocomial infection and acute kidney injury were identified as the most frequent medical complications among hospitalized dengue patients. The study did show any statistically significant risk factors associated with dengue re-infection. Large scale multi-center studies are warranted with sufficient sample size and objective assessment methods to determine the incidence of dengue re-infection and co-infection as well as for the identification of risk factors associated with dengue re-infection among adult population of Pakistan.

**Keywords:** Dengue fever, re-infection, co-infection

### 1. INTRODUCTION

Dengue is a vector borne viral disease, transmitted by female Aedes mosquito. There are 4 serotypes of this virus. Every year millions of people suffer from this illness. However, severity of illness varies from mild symptoms like fever and body aches to severe dengue hemorrhagic shock syndrome. (1) Transmission of this viral illness is greatly influenced by temperature, rainfall, and urbanization. The primary pathophysiology of the disease is capillary leakage and hemoconcentration. This viral illness is known for causing multi-organ damage such as encephalopathy, respiratory distress syndrome, acute liver injury, renal failure, coagulopathy and much more. Previously thought to be a pediatric disease has

now shown trend towards young adult population. (2) In Pakistan rapid urbanization, climate change, population growth and various socioeconomic factors have resulted in increased burden and more frequent outbreaks of dengue infection. (3,4) Early identification of the disease is important in countries like Pakistan which are endemic for dengue and other illness which have similar clinical spectrum such as malaria or acute viral hepatitis, early recognition and treatment may sometimes be delayed. Various studies have also shown incidence of various viral and non-viral co-infection in patients with dengue fever. And such simultaneous infections not only complicate the diagnosis but also the treatment and overall outcome. (5,6). Rising burden of dengue infection also increases the likelihood of dengue re-infection which is known for relatively more severe illness and poor prognosis. Previous studies from Pakistan conducted in Lahore and Mardan have been reporting severe illness and relatively poor prognosis among dengue patients with re-infection or when patient had a positive history for previous dengue infection. (7, 8)

Various small-scale studies from Pakistan have been reported incidence of dengue and associated seasonal variation. However, there is a dearth of evidence regarding dengue re-infection and co-infection. Therefore, this study aims to determine the incidence of re-infection and co-infection with dengue among adult population in Karachi, Pakistan. The study also aims to determine the frequency of various medical complications among dengue patients with or without co-infection and reinfection as well as possible risk factors associated with dengue reinfection.

## **2. MATERIAL AND METHODS**

A retrospective cross-sectional study was conducted at Aga Khan University Hospital Karachi, between January 2022 till August 2022. All the adult patients of age 18 years or above; admitted with confirmed diagnosis of dengue i.e., either through antigen or antibody test for dengue infection through emergency department or out-patient-department were included in the study. Patients who were not admitted to the hospital despite medical advice and could not be followed were excluded from the study. Patients' personal and relevant clinical information was obtained from existing Health Information Management System established at Aga Khan University Hospital. Basic demographic characteristics, disease signs, symptoms and complications, laboratory investigations, critical care unit stay, treatment offered, demographic data and disease outcome were recorded as main study variables. All the data was collected using a purposefully designed structured questionnaire. Out of 520 patients 500 patient records full filling the eligibility criteria were included in this study.

Ethical approval for this study was obtained from Ethical Review Committee of Aga Khan University, Karachi. This study involved no direct interaction between patient and researcher. However, standard practices were followed to ensure anonymity and confidentiality of the study participants. Patients were assigned unique randomly generated three-digit codes to organize the data and no personal identifying information (including names and Medical Record numbers) were formally recorded. Access to the coded identifiers will be granted upon request only to those involved in data review and analysis upon request and a logbook will be maintained to keep track of requests.

Data was analysed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA). Descriptive statistics were calculated using mean or median for quantitative continuous variables and frequency or proportions for categorical variables. Incidence proportion was calculated for dengue re-infection and co-infection. Frequency of various medical complications was also calculated. Chi-square test of significance was also applied to identify possible factors associated with dengue re-infection and co-infection.

## **3. RESULTS AND DISCUSSION**

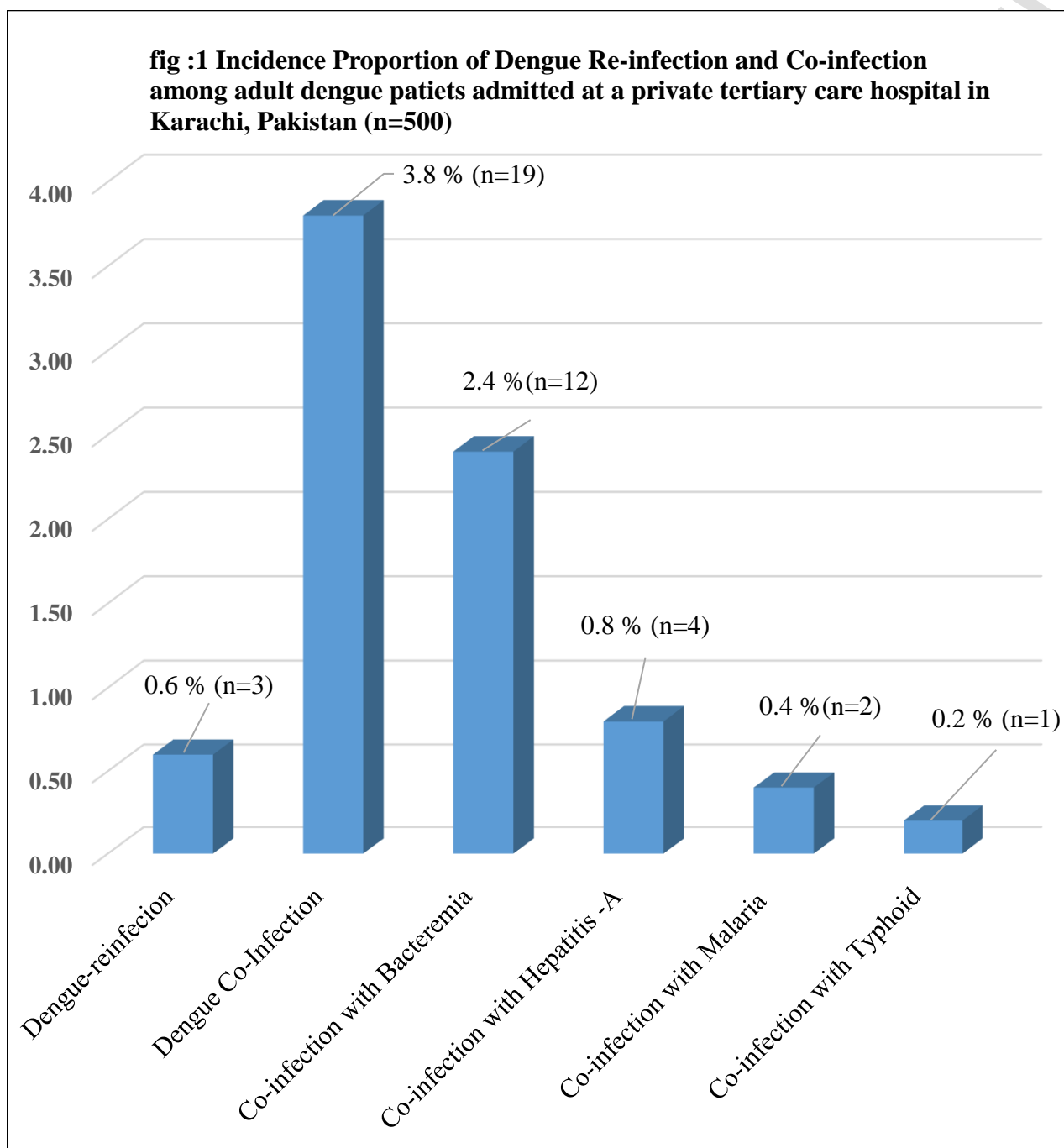
Total 500 eligible dengue patients were included in the study. Median age of patients was 36 years with an IQR of 22 years. 76.8% (n=384) of the patients were between age of 19-44. Around 59.4% of all dengue patients were male and 40.6% (n=203) were females. Majority of the patients were residents of Karachi. 60.8% (n=304) of all patients were diagnosed on the basis of positive rapid antigen test while 33.4% (n=167) of all dengue patients were diagnosed with positive IgM test. However, 1% of all IgM test showed equivocal results and for 4.8% (n=24) of the lab confirmed dengue patients the information regarding the type of test applied for diagnosis was not available as were tested outside before admission. 73.8% (n=369) of all dengue patients included in this study were tested and diagnosed with dengue at Aga Khan University Hospital. Hypertension was the most common co-morbid followed by Diabetes Mellitus with a proportion of 18% (n=90) and 13.4% (n=67) respectively. Fever was the most reported symptom followed by vomiting, nausea, diarrhoea, and generalised weakness. (Table:1)

**Table: 1 Socio-demographic characteristics of the adult dengue patients presenting at a private tertiary care hospital in Karachi , Pakistan (n=500)**

Variable	Frequency (n)	Percentage (%)
<b>Median Age: 36 years (IQR; 22 years)</b>		
<b>Age (in completed years)</b>		
19- 34years	223	44.6
35-50years	161	32.2
51-66years	80	16.0
67-82 years	31	6.2
83 years and above	05	1.0
<b>Sex</b>		
Male	297	59.4
Female	203	40.6
<b>Residence</b>		
Rural Sindh	06	1.2
Baluchistan	09	1.8
KPK	05	1.0
Punjab	01	0.2
Karachi	479	95.8
<b>Dengue diagnosed on:</b>		
Positive Rapid antigen test	304	60.8
Positive IgM test	167	33.4
Equivocal result on IgM test	05	1.0
Not sure about the diagnostic test applied	24	4.8
<b>Dengue diagnostic test conducted at:</b>		
Aga Khan University Hospital	369	73.8
Outside Aga Khan University Hospital	131	26.2
<b>Co-morbids</b>		
Hypertension	90	18.0
Diabetes Mellitus	67	13.4
Ischemic Heart Disease	27	5.4
Chronic Kidney Disease	10	2.0
<b>Symptoms</b>		
Fever	479	95.8
Headache	57	11.4
Shortness of breath	26	5.2
Nausea	106	21.2
Vomiting	161	32.2
Diarrhea	89	17.8
Abdominal Pain	80	16
Generalized weakness	78	15.6
Jaundice	03	0.6
Dizziness	26	5.2
<b>Clinical signs on examination</b>		
Pallor	09	1.8
Edema	05	1.0
Bruises	22	4.4
Hepatomegaly	02	0.4
Splenomegaly	04	0.8

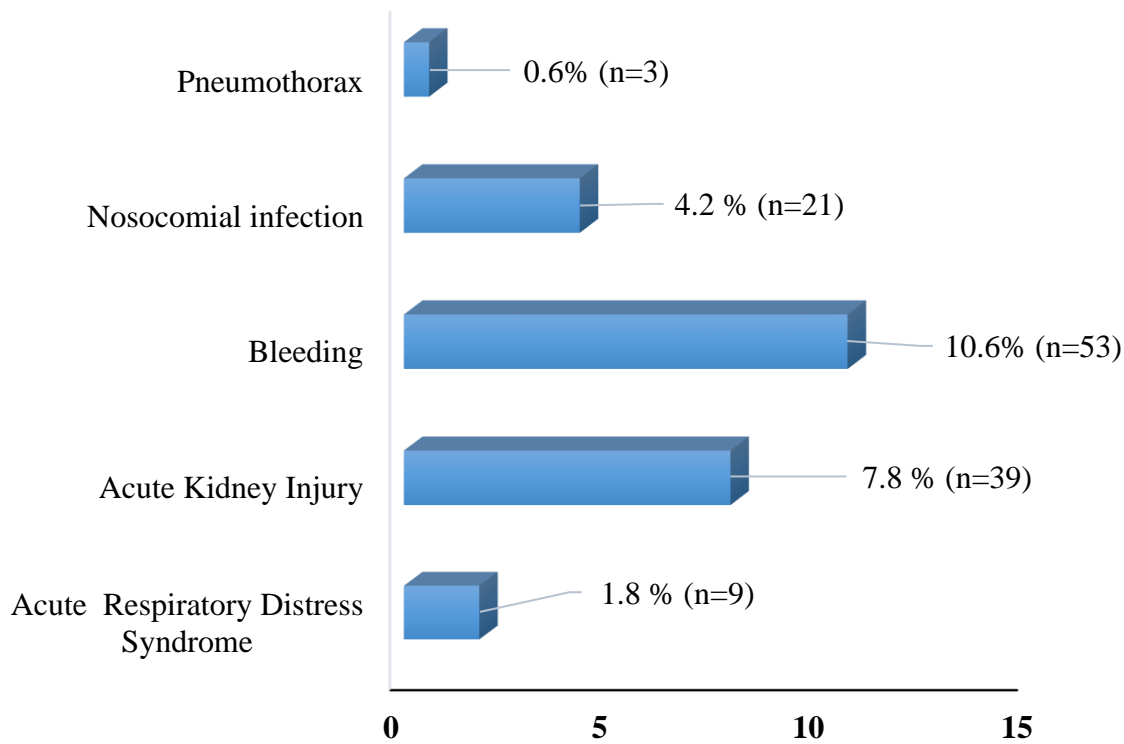
Disease outcome		
Recovered and discharged	476	95.2
Left against medical advise	13	2.6
Died	11	2.2

The study found an incidence proportion of only 0.6% for dengue-reinfection and an incidence proportion of 3.8% for dengue co-infection. The highest incidence for dengue co-infection was observed with bacterial infections and viral Hepatitis-A infection with an observed incidence of 2.4% and 0.8% respectively (Figure:1).



Bleeding and acute kidney injury (AKI) were the most frequent complications among dengue patients with a proportion of 10.6% (n=53) and 7.8 % (n=39); however the overall mortality due to dengue infection was only 2.2.% (n =11) (Figure:2).

**fig :2 Frequency of various medical complications among adult dengue patients admitted at a private tertiary care hospital in Karachi, Pakistan (n=500)**



To the best of our knowledge this is the first study estimating incidence proportion for dengue re-infection among adult patients with laboratory confirmed cases of dengue infection. The considerably higher frequency of dengue cases among male sex as compared to female sex is consistent with previous local evidence. [7, 8]

However the incidence of dengue re-infection and co-infection in this study was 3.8% i.e. 3.8 re-infection cases per 100 patients which was considerably low as compared to the frequencies of re-infection given in previous studies i.e. (ranging between 9.6 to 39.5% ) can be attributed to differences in the study population, age group selected and sample size of the study. [8-10] However, the overall burden of co-infection in our sample was 19% i.e. 19 dengue cases with co-infection per 100 cases of dengue infection which was considerably lower as compared to previous local as well as international evidence. These differences can be explained by the selection of dengue patients from a hospital representing a privileged population with relatively higher socioeconomic class, good health literacy and better living conditions. The most common co-infection was bacteraemia followed by Hepatitis A infection. On the contrary to previous local evidence the incidence of co-infection with Malaria in the current study was too low which can be explained by again the specific socioeconomic background of the study population. [11] It is obvious that difference in socioeconomic class is the main factor playing a direct role in malaria transmission owing to improved infrastructure and better environmental conditions. Not a single case of Chikungunya as co-infection is reported in our study. However, studies from public sector healthcare settings from Pakistan have shown considerable burden 11.1% of co-infection with Chikungunya.[9] The differences in epidemiology of dengue and other co-infections within Pakistan can be well explained by geographical and environmental condition within country as well as differences in lifestyle.

In this study, fever was the most common symptom followed by gastrointestinal (GI) symptoms including nausea vomiting, abdominal pain, and diarrhoea. Similar trend in symptoms is observed in other studies conducted in Karachi, Pakistan reporting fever, vomiting abdominal pain as the most reported symptoms. [10, 12, 13] The latest dengue classification by World Health Organization (WHO); introduced in 2009 also identifies the presence of GIT symptoms as an indicator of disease severity. [14] A meta-analysis of 39 published articles comprising of 1790 records ; published in 2021 concluded that, vomiting, abdominal pain or tenderness, pleural effusion, ascites, epistaxis, gum bleeding, GI bleeding, lethargy or restlessness and hepatomegaly (>2 cm) were associated with higher risk of severe dengue.[15] However, the actual frequency of various commonly reported GI and Non-GI dengue symptoms was relatively different in our study sample as many of them were partially treated outside at other facilities; hence may have passed the initial phase of illness identified usually identified by fever, myalgia and headaches.

The study did not show any statistical differences in the frequency of dengue re-infection based on differences in demographic characteristics such as age groups, sex, and place of residence. Similarly, no statistical differences were noted in presence of comorbidity i.e. diabetes mellitus, hypertension, ischemic heart disease and acute kidney injury among dengue patients with and without dengue re-infection. This can be explained by relatively very few numbers of cases with re-infection. This study found statistically significant differences in the frequency of acute respiratory distress syndrome and acute kidney injury as complications of dengue fever among patients with and without diabetes mellitus type 2. This finding is supported by previous study conducted in Punjab and KPK by Faiz Ahmed and colleagues reporting more severe disease among dengue patients with diabetes mellitus. [9]

Our study has some intrinsic limitations, such as providing information from only one private sector, tertiary care hospital in Karachi, which limits its generalizability. Moreover, as this data was taken from patients admitted to hospital hence it cannot represent less severe dengue cases which were asymptomatic and never required hospital admission as well as general community. Similarly, findings of this study may be different from previously studies conducted in public sector hospitals due to differences in healthcare environment as well as differences in socio-demographic status of patients attending public sector hospitals. All these differences further limit the generalizability of the study findings. Moreover, this study assessed re-infection on the basis of patients` self-reported medical history and didn't assess serum IgG test for confirmation of previous dengue infection. This limits the internal validity of the study and may have resulted in underestimation of the re-infection of dengue possibly due to recall issues as well as in cases where physician had treated them without identifying the dengue infection due to overlapping symptoms and self-limiting nature of the disease. Similarly, no data was available to assess con-current dengue infection which can be described as simultaneous infection with two different strains of dengue virus. In addition, probability of underestimating co-infection in this study cannot be ruled because a mild co-infection with dengue infection can be easily masked due to overlapping signs and symptoms and no-specific laboratory investigations especially among those who had no complication and overall stable hospital course.

Nevertheless, this study offers a valuable addition to the local evidence and provides further basis to conduct large scale studies in a community where dengue has become more like a regular occurrence rather than a seasonal infection. The researchers also need to study the factors associated with this changing behavior of the disease.

#### 4. CONCLUSION

This study determines a low incidence proportion of dengue re-infection and co-infection among adult patients admitted with confirmed diagnosis of dengue infection at a private tertiary care hospital in Karachi. Fever and GIT symptoms were among the most reported symptoms. Bleeding, nosocomial infection and acute kidney injury were identified as the most frequent medical complications among hospitalized dengue patients. Our study could not identify any statistically significant risk factors associated with dengue re-infection. Large scale multi-center studies are warranted with sufficient sample size and objective assessment methods to determine the incidence of dengue re-infection and co-infection as well as for the identification of risk factors associated with dengue re-infection among adult population of Pakistan.

#### ETHICAL APPROVAL (WHERE EVER APPLICABLE)

Ethical approval for this study was obtained from Ethical Review Committee of Aga Khan University, Karachi ( Ethical board review number 2022-8101-23102). This study involved no direct interaction between patient and researcher. However, standard practices were followed to ensure anonymity and confidentiality of the study participants. Patients were assigned unique randomly generated three-digit codes to organize the data and no personal identifying information (including names and Medical Record numbers) were formally recorded. Access to the coded identifiers will be granted upon request only to those involved in data review and analysis upon request and a logbook will be maintained to keep track of requests.

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