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# Gender Bias in Dengue The Lab Perspective

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**Abstract**

*Background*: Dengue infection can occur as epidemics in India. If early treatment is not instituted it has high mortality. Currently there is no specific antiviral drug or vaccine available for treatment of dengue, preventive measures play a crucial role in controlling the infection and reducing mortality. Sex and gender are major factors which impact incidence, severity and response to vaccination and therapy in dengue, so that preventive measures may be targeted to the at risk population.

*Aims:* The aim of the study is to analyse gender patterns in dengue and its impact on the severity of dengue.

*Materials and Methods:* A total of 132 seropositive cases of dengue were analysed for the haematological parameters (haematocrit, blood counts) and serology in association with gender and age of the patients over one month period in November 2016 at KIMS hospital Bengaluru.The relevant data obtained from the microbiology register and haematology report forms was tabulated for analysis.

*Results:* Our patients were aged 5months-65years with an average of 32years. 30% constituted paediatric group with 70% in non paediatric (>12years) group. There was a male predominance with 55% males, 45% females and male to female ratio of 1.2:1. In the paediatric group we had 45% males (18/40) and 55% females (22/40). The lab parameters showed a rise in haematocrit in 54% of females as against 49% of males and was more marked in paediatric group. Leucopenia was significantly seen in higher proportion of males (44%) as against females (34%). The differential counts showed marginally higher proportion of lymphocytes especially atypical lymphocytes in females compared to males (56%vs 49%). Neutropenia and thrombocytopenia were seen in marginally higher proportion of males than females were 29% vs 24% and severe thrombocytopenia was 59% and 54% respectively. NS1 antigen positivity was noted in higher proportion of males compared to females (33% vs 22%) whereas association with antibody was seen in higher proportion of females compared to males 44% vs 35%).

*Conclusion:* Gender differences play an important role in prevalence and severity of dengue. Awareness of this factor and implementing preventive measures targeted at the risk population helps to reduce mortality and morbidity of disease.

**Keywords:** Dengue; Gender; Hematocrit; Leucopenia; Thrombocytopenia; Serology.

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## Introduction

Dengue, an arboviral infection presents with undifferentiated fever, dengue fever, Dengue haemorrhagic fever and Dengue Shock Syndrome [1].

It occurs as epidemics in India and affects 50 millions worldwide annually [2]. Dengue fever is self limiting but complications may be lethal. Hematological parameters are crucial prognosticators in dengue [3], early and rapid diagnosis is therefore vital for patient [4].

Age, sex, genetics, race, certain clinical & lab parameters serve as predictors of severity ]5]. It was believed that infectious diseases affect both sexes equally, it is now known that biological differences between males and females based on genetic immunological and hormonal factors may determine the susceptibility to disease and clinical outcome [6]. A few studies have claimed that the disease is severe in women due to heightened immune response and increased permeability of capillary bed. Pregnancy also increases the risk of developing severe dengue [7,8]. Health seeking behaviours also increases severity in women [6]. Other authors have claimed that due to occupational andoutdoor exposure and as testosterone down regulates the TH cells with antibody mediated responses, the prevalence and severity of dengue is increased in men [9,10]. It has been observed thatgender has role in biological responses to vaccine or therapy.

Few studies across the world have reported gender related differences in serohaematological parameters in Dengue. There is limited data on this subject in Indian population [11]. Our study is one of few focussing on impact of gender on serohaematological changes in dengue in Indian population.

## Materials and Methods

This is a prospective study conducted on 132 patients with Dengue positive serology in KIMS Hospital Haematology Department Bengaluru over a one month period in November 2016.

All patients with dengue positive serology (NS1, IgM, IgG or all) by Rapid card method (Standard diagnostics – BiolineAlera) with results of relevant haematology tests – haematocrit, blood counts (obtained by automated hematology analyser – Symex 1800i) with differential counts obtained from leishman stained peripheral smears (done as per hospital protocol to verify platelet counts) with age and sex details were included in the study.

The result of dengue serology was received from Microbiology ledgers. These were tabulated and analysed against patient's unique hospital number.

Patients with concomitant infections like malaria and typhoid along with dengue, those with normal, high platelet counts and those without gender and age details were excluded from study

## Results

Our study showed an age range of 5months-65years the average being 32years. The majority of patients were in 12-25years group (Table 1).

There was a male predominance with male: female ratio of 1.2:1 (Table 2).

The analysis of lab parameters in association with gender showed a rise in hemaocrit in increased proportion of cases on females than males (Table 3).

Our study shows an increased proportion of females with rise in haematocrit for age and sex [12]. The highest haematocrit in males was 59.6% as against 48% in females. The lowest haematocrit was 20.8% in males and 26.5%in females (Table 3).

The lowest count was 1,100cells/cumm in females as against 1400cells/cumm in males and highest TC in females was 14300 cells/cumm as against 13500 cells/cumm in males. The differential count pattern

**Table 1:** Age distribution

| Age group | Number | Percent |
|---|---|---|
| Pediactric <12years | 40 | 30 |
| Non pediatric | 92 | 70 |
| Total | 132 | 100 |

**Table 2:** Gender Distribution

| Gender | Number | Percent |
|---|---|---|
| Males | 73 | 55 |
| Females | 59 | 45 |
| Total | 132 | 100 |

**Table 3:** Hematocrit variation and gender

| Pattern of Hematocrit | Male | | Female | |
|---|---|---|---|---|
| | Number | Percent | Number | Percent |
| Normal | 37 | 51 | 27 | 46 |
| Increased | 36 | 49 | 32 | 54 |
| Total | 73 | 100 | 59 | 100 |

was categorised as lymphocytosis (> 60% lymphocytes ≤ 12 years & > 45% lymphocytes > 12 years), neutrophilia ( > 40% neutrophils ≤ 12 years & > 75% neutrophils > 12 years) and normal pattern. There was an increased proportion of cases of lymphocytosis in both genders, with marginally higher proportion in females. Leucopenia was seen in higher proportion in males. More number of females had normal count (Table 4 & 5).

Highest lymphocyte count in males was 90% & in females 84% (Table 5). An estimate of atypical lymphocyte was done categorised as <20% and ≥ 20% which was considered significant (Table 6). There were higher proportion of females showing significant atypical lymphocytosis. Neutropenia (age adjusted) was noted in 29% in males as against 24% females. The lowest neutrophil count was 10% in males and 15% in females (Table 6).

Severe thrombocytopenia with counts ≤ 0.5 lakhs/cumm was more in males compared to females (Table 7). The lowest platelet count in females was 8000cells/cumm and 11000cells/cumm in males. Analysis of serology with gender showed higher number of increased proportion NS1 positivity (33%) in males vs 22% in females (Table 7).

The antibody pattern showed higher proportion of females 44% in contrast to 35% of males (Table 8).

**Table 4:** WBC counts and gender

| Total WBC Counts | Males | | Females | |
|---|---|---|---|---|
| | Number | Percent | Number | Percent |
| <4000CELLS/CUMM | 32 | 44 | 20 | 34 |
| 4000-11000CELLS/CUMM | 35 | 48 | 34 | 58 |
| >11000 CELLS/CUMM | 06 | 08 | 05 | 08 |
| TOTAL | 73 | 100 | 59 | 100 |

**Table 5:** Differential white cell counts and gender

| Differential white cell type | Males | | Females | |
|---|---|---|---|---|
| | Number | Percent | Number | Percent |
| Lymphocytosis | 47 | 64 | 41 | 69 |
| Neutrophilia | 09 | 12 | 05 | 08 |
| Normal | 17 | 24 | 13 | 23 |
| Total | 73 | 100 | 59 | 100 |

**Table 6:** Atypical lymphocyte counts and gender

| Atypical Lymphocytic Count (Of Total Dc) | Males | | Females | |
|---|---|---|---|---|
| | Number | Percent | Number | Percent |
| < 20% | 37 | 51 | 26 | 44 |
| ≥ 20% | 36 | 49 | 33 | 56 |
| TOTAL | 73 | 100 | 59 | 100 |

**Table 7:** Thrombocytopenia – distribution

| Degree of Thrombocytopenia | Males | | Females | |
|---|---|---|---|---|
| | Number | Percent | Number | Percent |
| Severe (≤ 0.5 Lakhs/CUMM) | 43 | 59 | 32 | 54 |
| Moderate (≤1 LAKH/CUMM) | 29 | 40 | 23 | 39 |
| MILD (<1.5 LAKH/CUMM | 01 | 01 | 04 | 07 |

**Table 8:** Serology patterns with gender

| Serology Patterns | Males | | Females | |
|---|---|---|---|---|
| | Number | Percent | Number | Percent |
| NS1 Antigen Positivity | 24 | 33 | 13 | 22 |
| NS1 + Ab positivity | 23 | 32 | 20 | 34 |
| Ab only positivity | 26 | 35 | 26 | 44 |
| Total | 73 | 100 | 59 | 100 |

## Discussion

Our study showed an age range of 5 months to 65 yearswith male predominance(M:F- 1.2:1) in accordance with few studies [11] due to differences in outdoor activity and health care seeking behaviour between the gender [6,11,13].

There was an increase in haematocrit above reference range for age & sex in females (54%) in comparison to males (49%). One study reported a higher intrinsic susceptibility to capillary permeability in females than males [7,14] with increased haemoconcentration.

Other studies showed increased incidence of dengue haemorrhagic Fever in males [15]. Our study noted that there was a higher proportion of males with haematocrit ≥ 50% and the highest haematocrit 59.6% in males.

There was a higher proportion of cases with leucopenia in males as against females (44% vs 34%) in accordance with few studies [11], others showed higher proportion in females [7]. Some found no difference between gender [6].

The lowest total white cell count was noted in females. There was a higher proportion of lymphocytosis and atypical lymphocytosis in females. We did not find data to compare our findings. However our findings was in agreement with few studies which suggested that in females estrogen promotes TH cells and antibody dominated responses [9] and mounts a more vigorous immune responses than in males [6,7,14]. Neutropenia was marginally higher number of males (29%) than females (24%).

Thrombocytopenia was marginally higher in males especially with counts ≤ 0.5 lakhs/cumm when compared to females (59% as against 54%) in accordance with few studies [6,13], others showed higher proportion in females [7] where as some showed equal distribution between the genders [11].

The lowest platelet and lowest white cell count was observed in females, indicating that bone marrow suppression could be more severe in females than males, in accordance with few studies which suggested that dengue was severe in females than males [6,7].

Higher proportion of leucopenia and thrombocytopenia in males suggest that dengue is more severe in them [10,15]. A few studies found no significant association between haematological findings and gender [11].

There was a higher proportion of males with NS1 antigen positivity (33%) in comparison to females (22%). However antibody positivity was noted in higher proportion of females than males (44% vs 35%). A few studies noted that NS1 antigen positivity was higher in females than males while IgM response was seen in a higher proportion of males [7].

From haematocrit analysis we deduced that since capillary permeability is more in females, the incidence of dengue haemorrhagic fever and dengue shock syndrome is more in females, but severity of dengue shock syndrome is more in males. The WBC and platelet counts show increased number of cases with low counts in males with increased severity in females. The serology analysis shows antibody pattern predominates in females with lymphocytosis and atypical lymphocytosis suggesting vigorous immune responses in them.

The limitation of the study includes small study size and limited data to compare and confirm the findings.

## Conclusion

Dengue can occur in epidemics in India and may lead to high mortality if not managed appropriately. The sex of a person can impact the clinical outcome of the disease as they tend to influence the sero-haematological parameters differently. Also the response to vaccine and therapy differs. A knowledge of these variables produced by the different sexes may help reduce mortality and morbidity and allows for preventive measures to be targeted to the risk popululation.

*Ethical Committee Clearance*

This study consists of analysing data against the patients unique hospital identification number with age and sex details only. The anonymity of patients was maintained. The study was approved by Ethical Committee of hospital.

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