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Original Article

Hematocrit Spectrum in Dengue: A Prospective Study

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Abstract

Aim: Dengue occurs in epidemics in India, severe forms are lethal. Hematocrit aids in prognosis and effective management of dengue. Our study is to assess the impact of age and gender on hematocrit values, and the effect of varying hematocrit values as a prognostic indicator in dengue.

Materials and Methods: A total of 132 serologically proven dengue cases were analyzed over 1 month in November 2016, along with hematocrit and relevant hematology data (obtained from analyzer).

Results: The age range was 5 months to 65 years with male preponderance. Hematocrit ranged from 20.8% to 59.6% (mean 40.2%). Male showed lowest and highest hematocrit.

55% had hematocrit >40%, 27%, had >45%, 58% showed hemocrit above reference range for age and sex, 8% showed hematocrit more than/equal to 20% above the reference range. A higher proportion of males showed increased hematocrit overall. 56% with increased hematocrit over reference range were associated with thrombocytopenia (<1 lakh/cumm).

A comparison of varying hematocrit values with reference range adjusted for age and sex showed a high proportion of false positive in males and false negative in children and females.

Conclusion: Hematocrit is an effective, simple diagnostic and prognostic tool and helps in the early appropriate management of dengue; however, guidelines need to be established to increase its accuracy.

Key words: Dengue, Hematocrit, Prognosis

INTRODUCTION

Dengue is an arboviral infection dengue virus (DENV 1–4) transmitted by aedes mosquito.[1] It shows a wide range of clinical presentation from asymptomatic cases to undifferentiated fever, dengue hemorrhagic fever (DHF)/ dengue shock syndrome (DSS) or non-severe and severe dengue.[1-3] Most cases of dengue are self-limited; however, severe dengue has high mortality if not diagnosed and managed early during the disease.[4] The overall incidence of dengue is 100 million with 2,50,000 cases with DHF and 25,000 deaths per year.[5] The incidence has increased manifold in India due to many causes.[5,6] The diagnosis and management (mostly supportive fluid therapy)[7] are based on clinical and lab parameters with certain lab tests aiding in the early forecast of severe dengue.[8] While serological tests (detection of nonstructural protein 1 [NS1] antigen, immunoglobulin (Ig) M, and IgG antibodies) aid in diagnosis of dengue,[4,7,9] simple, cost-effective, easy tests such as hematocrit and platelet counts have great utility in resource-poor healthcare systems in India[9] for predicting onset of severe dengue.

It is known that there is a rise in hematocrit (due to vascular leakage) before the onset of severe dengue/DHF-DSS. Clinical identification of vascular leakage is difficult and delayed until shock develops.[7] Many studies have focused on hematocrit changes, especially the increase in hematocrit in dengue; however, its utility has not been fully exploited as there are no clear-cut guidelines for hemoconcentration[10] with different studies putting forth varying cutoff values such as >40%,[6,11,12] >45%,[2,5,13-15] and >2% over reference range for age and sex[3] or with other values.[16-19] Some studies have used the more accurate cutoff of a rise in

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hematocrit of ≥20% above baseline for age and sex.[20-22] A few have suggested more than 10% above baseline value.[23]

Hematocrit rises 3–5 days after fever just before the critical period which lasts for 1–3 days[7,9] the test is most accurate if properly timed test values are considered.[21]

Our study explores the impact of age and gender and varying thresholds of hematocrit[16,24-27] and is a step toward increasing the sensitivity of this lab parameter to aid in better management of dengue cases.[9,21,22]

The aim of our study was

- To analysis of hematocrit values, its comparison with other studies of same and different cutoff values.
- To analyze the factors which influence its accuracy (age and sex) and draw parallels with clinical risk factors in other studies.
- To analyze the impact of these on diagnosis and prognosis in dengue.

MATERIALS AND METHODS

This is a prospective study done on 132 patients with dengue positive serology in hematology section of Kempegowda Institute of Medical Sciences Hospital and Research Centre, Bengaluru, over a 1 month period in November 2016.

All patients with serological confirmation of dengue (NS1/IgM and/or IgG positivity by rapid card method) tested for hematocrit were included in the study.

The patients with concomitant infections such as Malaria and Typhoid along with dengue were excluded from the study.

The hematocrit values along with relevant data (obtained from automated hematology analyzer-Sysmex 1800i) were analyzed. The patient's unique hospital identity number were noted with age and sex. The results of dengue tests were retrieved from microbiology register.

Ethical Committee Clearance

The patients' anonymity was maintained as only the unique hospital identification number of the patient was recorded for the purpose of study along with age and sex. The data available of dengue patients was analyzed. This study was approved by the Hospital Ethical Committee.

RESULTS

In a total of 132 dengue serology positive cases analyzed, the age of patients ranged from 5 months to 65 years with the majority in 12–25 years group. The average age was 32 years [Table 1].

The gender distribution showed a slight male predominance with male:female ratio of 1.2:1 [Table 2].

An analysis of the hematocrit spectrum revealed a range of 20.8–59.6% with an average value of 40.2% in our study. The hematocrit distribution is shown in Table 3. The maximum number of cases were noted in the range of 35–40%. 75/132 (57%) had a hematocrit ≥40%, whereas 37/132 (28%) had a hematocrit ≥45%.

A high hematocrit adjusted for gender in adults and pediatric cases are shown in Tables 4 and 5. This shows an increased proportion of pediatric cases and males with higher hematocrit.

A point of significance that our data showed was that the lowest and highest hematocrit in both adults and pediatric group was seen in males as compared to females of the respective group [Table 6].

An analysis of hematocrit rise over 20% above reference range for age and sex[25] (>45% for pediatric age

Table 1: Adult versus pediatric age pattern distribution

*Age group (years)	Number of cases (*n*) (%)
Adult	86 (65)
Pediatric	46 (35)

*Adult>14 years, pediatric≤14 years

Table 2: Gender wise distribution

Gender	Number of cases (132) (%)
Males	73 (55)
Females	59 (45)

Table 3: Hematocrit distribution

Hematocrit range (%)	Number of cases (132) (%)
20–25	01 (01)
≥25–30	06 (04)
≥30–35	08 (06)
≥35–40	42 (32)
≥40–45	38 (29)
≥45–50	23 (17)
≥50–55	10 (08)
≥55–60	04 (03)

Table 4: *Pediatric age and gender distribution of increased hematocrit

Gender	*n* (%)
Male	20/22 (91)
Female	19/24 (79)
Total pediatric	39/46 (85)

*Pediatric reference range for hematocrit>38%

(≤14 years), >48% for adult females, and >54% for adult males) is shown in Tables 7 and 8.

A analysis was also done with cutoff hematocrits of >40% for age and sex, and of >45% similarly to check their impact as a prognosticator [Table 9].

A analysis was also done on the number of cases with a rise in hematocrit ≥20% over reference range for age and sex[25] and compared with hematocrit over range for age and sex[25] associated with thrombocytopenia ≤1.0 lakhs/cumm as both these are some of the criteria suggestive of onset of dengue hemorrhagic fever/DSS and is shown in Table 11.

Platelet count <1.0 lakhs/cumm is one of the criteria for diagnosis of DHF/DSS. It may be noted that the hematocrit over reference range most correlates with platelet counts of <1.0 lakhs/cumm on comparing with other hematocrit cutoffs (>40% and >45%) as seen in Tables 10 and 11.

DISCUSSION

The study shows a maximum number of cases in young age in accordance with other studies[2,16] with a slight male predominance,[2,12] probably due to occupational exposure and increased recreational activity in men.[28]

Table 5: *Adult gender distribution of increased hematocrit

Gender	*n* (%)
Males	25/51 (49)
Females	13/35 (37)
Total adults	38/86 (44)

*Adult reference range for hematocrit - Males >, Females >

Table 6: Age and gender distribution for highest and lowest hematocrit values

Gender	Age group			
	Adults >14 years		Pediatric ≤14 years	
	Low hematocrit	High hematocrit	Low hematocrit	High hematocrit
Males	26.6	59.6	20.8	51.0
Females	29.7	48.0	27.6	43.3

Table 7: Age distribution of hematocrit rise >20% over reference range

Age group	Number of cases (*n*) (%)
+Adults	06 (07)
++Pediatric	05 (11)

+It included 5 of 51 adult males and 1 of 35 adult females, ++there were 4 of 22 pediatric males and 1 of 24 pediatric females

The hematocrit range was 20.8–59.6%, the average being 40.2%. Studies in adults by Kailash *et al.* and Geethika *et al.* showed ranges of 20.3–51.5% (mean 39.8%) and 25.4–53.2% (mean 38.7%), respectively. Gurdeep *et al.* observed a mean of 35.5% in children.

Our study showed 55% of cases with hematocrit >40% in accordance with others,[12] few recorded a lower proportion of cases.[6,11] We had 27% of cases with hematocrit >45% in accordance with others,[13,15] some showed a lower proportion of cases.[2,5] 8% of cases had hematocrit ≥20% above reference range for age and sex,[25] in accordance

Table 8: Gender distribution of hematocrit rise >20%, above reference range

Gender	*n* (%)
Males	09 (12)
Females	02 (03)
Total	11 (08)

Table 9: Hematocrit distribution (>40% and>45%)

Hematocrit >40%		
Hematocrit >45%		
Group	*n* (%)	*n* (%)
Adults		
Male	40/51 (78)	25/51 (49)
Female	14/35 (40)	05/35 (14)
Pediatric		
Male	11/22 (50)	05/22 (23)
Female	08/24 (33)	01/24 (04)
Total		
Adults	54/86 (63)	30/86 (42)
Pediatric	19/46 (41)	06/46 (13)
Total		
Male	51/73 (70)	30/73 (41)
Female	22/59 (37)	06/59 (10)
Overall	73/132 (55)	36/132 (27)

Table 10: Comparison of different hematocrit cutoff values

Hematocrit values			
Group	>40 (%)	>45 (%)	>Reference range for age and sex (*n*) (%)
Adults			
Male	78	49	25 (49)
Female	40	14	13 (37)
Pediatric			
Male	50	23	20 (91)
Female	33	04	19 (79)
Total			
Adults	63	42	38 (44)
Pediatrics	41	13	39 (85)
Total			
Male	70	41	45 (59)
Female	37	10	32 (53)
Overall	55	27	77/132 (58)

Table 11: Comparison of hematocrit ≥20% above reference range

Group	Hematocrit reference range for age and sex with thrombocytopenia, *n* (%)	
	Hematocrit ≥201%	Hematocrit >reference range with platelet count ≤1.0 lakhs/cumm
Adults		
Male	05/51 (10)	24/51 (47)
Female	01/35 (03)	13/35 (35)
Pediatric		
Male	04/22 (18)	18/22 (82)
Female	01/24 (04)	18/24 (75)
Total		
Adults	06/86 (07)	38/86 (43)
Pediatrics	05/46 (11)	36/46 (78)
Total		
Male	09/73 (12)	42/73 (58)
Female	02/59 (03)	31/59 (53)
Overall	11/132 (08)	74/132 (56)

with others,[5] few showed a higher proportion of cases.[1] The increase in hematocrit in dengue is due to hemoconcentration attributed to plasma leakage induced by cytokine-mediated increase in vascular permeability and damage to vascular endothelium.[26]

Cytokines are produced by DENV infected monocytes, B lymphocytes, and mast cells.[6,21] Endothelial cell dysfunction by virus also leads to increased capillary permeability.[29] This phase of plasma leakage is the critical phase, the onset of which (marked by circulatory and perfusion changes leading to shock) can be predicted with the rise of hematocrit 10–15% above the baseline value. This is considered a significant predictor of severe disease.[17,23,29]

A few studies have noted that there is a higher proportion of cases with increased hematocrit in severe than non-severe dengue[10,18] and also the mean hematocrit values are higher in severe compared to non-severe dengue.[8]

The key issue in the management of dengue lies in the identification of onset of critical phase[17] by continuous monitoring of hematocrit to check for the rise in hematocrit above baseline/reference values. The reference values vary at different ages and between the genders. Thus, accurate hematocrit values obtained from correct interpretation of the result extrapolated against the particular age and gender plays a crucial role in diagnosing precisely the progression to severe dengue and thus treatment of these cases.[22] However, the use of uniform hematocrit values across all ages, both sexes and non-standardization of cutoff values could impact management of dengue adversely.

Our study showed that there was a higher proportion of cases with increased hematocrit in males than in females in accordance with few studies.[24] This was observed across all hematocrit threshold values.

On comparison with adults, children showed a higher proportion of cases in the group where hematocrit was above reference range for the age and sex, and where it was ≥20% above the reference range.

A fewer studies have observed that there is greater vascular permeability in children[8,26,27] and the risk of severe dengue is higher in children and develops faster than adults.[4,6,21,25,26,30,31] While a few studies have noted increased severity in males, this has been disputed by others.[8]

Our study also reveals that the lowest and highest hematocrit values were noted in males (both in adults and children). These observations emphasize the importance of using age and sex-matched hematocrit values[7] for accurate prediction of progression to severe dengue and minimizing error in the diagnosis (attributed to false positives and negatives) which could limit the utility of this test.

Our study noted a higher proportion of false positives in males on comparing with the values obtained by reference range and a higher proportion of false negatives in children and females.

A few studies have observed that timing and frequency of monitoring also influence the accuracy of hematocrit test in diagnosis.[17,21] Daily testing from 3rd day routinely, but 4th–6th hourly for 2 days in DHF has been suggested by few[17] while others recommend testing before and after fluid therapy and every 6th–12th hourly.[21]

A study was done on single, random hematocrit value as baseline value could not be obtained and uniformity in testing was not implemented.

A stable hematocrit over 24 h is considered criteria for discharge by few studies.[9,17]

Limitations of our study reflects pitfalls in the utility of hematocrit in dengue[7,11,20,32] and includes

- Non-availability of baseline and timed hematocrit values.
- Increased prevalence of anemia in India.
- Blunting of hemoconcentration due to fluid therapy.
- Fall in hematocrit due to significant blood loss due to dengue.
- Concomitant conditions causing increased (malignancies) or decreased (other causes of hemorrhage) hematocrit.
- Other limitations exclusive to a study was the relatively small sample size and lack of other similar studies to conform our conclusions.

CONCLUSION

Hematocrit is a highly effective, simple, diagnostic, and prognostic tool in dengue if utilized correctly. It also gives therapeutic guidance by aiding inappropriate selection of fluids.

However, proper guidelines need to be enforced with regard to timing, frequency and threshold values to prevent overdiagnosis of non-severe and underdiagnosis of severe cases which could impact morbidity and mortality in dengue.

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