CORRELATION OF ALBUMIN-GLOBULIN RATIO AND PLATELET COUNT WITH DENGUE SEVERITY: A RETROSPECTIVE CROSS-SECTIONAL OBSERVATIONAL STUDY IN PATIENTS ADMITTED IN INTENSIVE CARE UNIT IN NORTH INDIA

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ABSTRACT

Introduction: Dengue fever is a significant public health concern, particularly in tropical and subtropical regions, with potentially severe complications such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). This study aims to investigate the association between albumin-globulin ratio and platelet count with the severity of dengue among patients admitted to the intensive care unit (ICU) in North India. **Methods:** This retrospective cross-sectional observational study was conducted at Max Super Speciality Hospital, Vaishali, Uttar Pradesh, between July 2023 and November 2023. The study included 120 adult patients diagnosed with dengue admitted to the ICU. Clinical and laboratory data, including albumin-globulin ratio, platelet count, and severity of dengue, were collected from medical records. Statistical analyses were performed to assess correlations and differences in parameters between patients with varying degrees of dengue severity. **Results:** Among the 120 patients included, significant associations were observed between albumin-globulin ratio, platelet count, and dengue severity. Patients with severe dengue exhibited lower albumin-globulin ratios and platelet counts compared to those with milder forms of the disease. Furthermore, severe dengue cases were associated with a higher incidence of complications such as respiratory distress, bleeding, and organ involvement. **Conclusion:** This study highlights the potential utility of albumin-globulin ratio and platelet count as prognostic indicators for assessing dengue severity in ICU-admitted patients in North India. Early identification of these markers may aid in predicting disease progression and guiding appropriate management strategies to improve patient outcomes.

KEYWORDS

dengue severity, critical care, tropical diseases, dengue fever, albumin-globulin ratio, severe dengue

INTRODUCTION

Dengue, a mosquito-borne disease, is one of the most common viral infections affecting mostly tropical and sub-tropical regions around the globe, and has become a major cause of morbidity and mortality. According to World Health Organization (WHO the incidence of dengue has increased from 0.5 million cases in year 2000 to 5.2 million cases in 2019 [1]. Caused by four different serotypes of Flavivirus genus, the dengue virus (DENV) is then transmitted to humans with the help of Aedes family mosquitos [2]. All 4 DENV (DENV-1,2,3,4) can cause disease, which can present as symptomatic or asymptomatic seroconversion infections. These can present in the form of mild self-limiting illness, to dengue fever (DF), or more severe form of disease, dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS) [3]. In 2009, WHO presented with a modified categorization of dengue, into non severe dengue: (a) dengue without warning signs (b) dengue with warning signs (abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, liver enlargement, increasing haematocrit with decreasing platelets) and severe dengue (with symptoms such as severe plasma leakage leading to shock or fluid accumulation with respiratory distress, severe bleeding, or severe organ impairment, including elevated transaminases, impaired consciousness, or heart impairment [4].

During the course of dengue infection, a series of haematological and biochemical changes takes place which vary according to the clinical severity of the disease. The hallmark pathological feature of DHF is plasma leakage, which indicates vascular endothelial damage [5]. The combination of common parameters haematological and biochemical parameters such as albumin concentration, haematocrit, aspartate aminotransferase ratio and platelet count, have shown to be effective in identifying severe dengue infection in patients with plasma leakage [6,7]. Hepatic involvement at varying severity is also related to dengue infection. Increased levels of bilirubin, aspartate transaminase (AST) and alanine transaminase (ALT), and decreased levels of serum albumin, could be used as early prognostic markers which could identify onset of leaking phase [8-11].

Haematocrit of 20% has been used to identify plasma leakage, however its is easily influenced by a number of factors. Thus, there is a need for more stable parameter. Albumin is extravasated during plasma leakage in severe dengue. Previous studies have shown that in patients with albumin levels <3.5 g/dL or if there is decrease of 0.5 g/dL from baseline, then it is significantly associated with progression of dengue [12,13]. Further, the ratio of albumin and globulin is also influenced by the plasma leakage and severity of DF [14-16]. However, the pattern of these changes is not well documented, which is the major lacunae in literature. Further, there had been very limited studies to establish correlation of serum albumin: globulin ratio and platelet counts with dengue severity in adult patients admitted in intensive care unit especially in North Indian population.

The present study was conducted with an aim to identify these patterns of changes in albumin/globulin ratio and platelet counts, and co-relate them with the severity of dengue. Additionally, we will look for the correlation of platelet count and albumin: globulin ratio on admission with length of ICU stay along with 28 days mortality to predict the outcome. This will help to predict the progression of disease to different clinical stages and thus help in early diagnosis and effective management of dengue.

MATERIAL AND METHODS

This cross-sectional retrospective observational study was conducted from July'2023-Nov'2023 at Max Super speciality Hospital, Vaishali, Ghaziabad, Uttar Pradesh, after taking approval from Institutional Ethics Committee. A total of 120 patients dengue serology patients admitted in medical ICU were included in the study.

The inclusion criteria were patients aged more than 18yrs and positive for dengue IgM or NS1. While patients who took treatment or were referred from another hospital, with pre-existing liver disease, chronic kidney disease or haematological disorders were not included in the study. Based on the WHO classification of 2009, the 120-dengue infection positive patients were divided into two groups: dengue with warning signs and severe dengue. Since dengue without warning signs were not admitted in our ICU they were not part of this study.

The following data was collected from the hospital medical records -

patient demographics, severity of dengue, presenting symptoms, clinical signs, laboratory parameters - complete blood count, serum albumin: globulin ratio at the time of admission.

Primary comparison is albumin: globulin ratio between dengue cases with warning signs and severe dengue cases. This comparison was done by student T test after computing mean and standard deviation in these two groups. We also investigated the platelet count in these two groups and test the difference between the groups by Wilcoxon test because the platelet count is likely to be highly skewed distribution. Correlation between albumin: globulin ratio and platelet count were obtained by spearman method in view of highly skewed distribution of platelet count. Statistical significance of this correlation was also obtained. In addition, various demographic characteristics and other biochemical parameters were also compared between the two groups as a secondary analysis. This comparison was mostly done by student t test since those are mostly quantitative measurement and the sample size is reasonable enough for this test to be valid. The level of significance for all comparisons was 5% and SPSS 22 was used for calculations.

RESULTS

The study included 120 patients, who met the inclusion criteria and were divided into two groups: dengue with warning signs (n =66) and severe dengue (n=54), with mean age of patients in the two groups, 37.61 ± 14.066yrs and 37.96 ± 15.227yrs, respectively. Overall, the ratio of males was higher than females in both the groups. At the time of admission, serological test was performed for each patient to confirm positivity for dengue virus. In was observed that in both the groups, maximum patients were positive for NS1 Ag (93.9% and 94.4%). In dengue patients with warning sign, 1.5% patients were IgM positive and 3% were both IgG and IgM positive. While in severe dengue patients, 1.9% were positive for IgM and 1.9% were positive for IgG and IgM (Table 1). No statistically significant co-relation could be derived between the two groups based on demographic parameters and DENV positivity.

Table 1: Demographic And Serological Parameters Of Patients

	Dengue with warning sign (n =66)	Severe Dengue (n =54)	P value
Age (yrs) Mean ± SD	37.61 ± 14.066	37.96 ± 15.227	0.894
Gender			
Female	25.8% (17)	25.9% (14)	0.983
Male	74.2% (49)	74.1% (40)	
Dengue serological parameters			
IgM	1.5%	1.9%	0.902
IgG AND IgM	3%	1.9%	
NS1 Ag	93.9%	94.4%	

Clinical parameters were recorded for each patient from their time of admission till the time they were hospitalized. Fever was the most common symptom present in all the patients in both the groups. Further, in patients with severe dengue, headache was present in 81.5% patients and myalgia in 94.4% patients, while in patients with warning signs of dengue, 74.2% had headache and 86.4% had myalgia. No statistically significant difference was observed between the two groups (Table 2).

A statistically significant difference was observed between the groups for the following clinical symptoms, with more number of patients with severe dengue having vomiting (88.9% vs 74.2%; p value 0.043), abdominal pain (92.6% vs 74.2%; p value0.008), respiratory distress (87% vs 6.1%; p value <0.001), bleeding (72.2% vs 21%; p value <0.001), shock (72% vs 0%; p value <0.001), polyserositis (96.3% vs 53%; p value <0.001), CVS involvement (74.1% vs 0%; p value <0.001), CNS involvement (59.3% vs 0%; p value <0.001), RS involvement (75.9% vs 11%, p value <0.001) and abdominal involvement (75.9% vs 27%, p value <0.001), respectively (Figure 1).
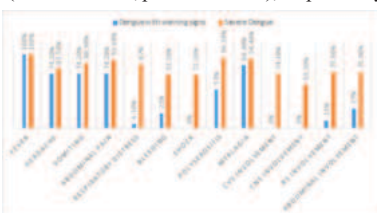
Figure 1: Co-relation Of Clinical Parameters In Patients With

Warning Sign And Severe Dengue (CVS- Cardiovascular System, CNS- Central Nervous System, RS- Respiratory System)

Blood samples were collected from all patients during hospital stay. It was observed that the mean platelet count was lower in severe dengue patients (41.31 ± 44.018 vs cells/mcL). A statistically significant difference was observed in the levels of albumin and globulin in severe dengue patients and patients with warning signs. Both albumin and globulin levels were lower in severe dengue patients (3.03 ± 0.54 vs 3.66 ± 0.41 mg/dL, p-value <0.001; and 2.23 ± 0.56vs 2.48 ± 0.42 mg/dL; p-value- 0.023; respectively). Further, the albumin to globulin ratio (A:G) was <1.5 in severe dengue patients, while >1.5 in dengue patients with warning signs. The difference was statistically significant (1.42 ± 0.36 vs 1.52 ± 0.29; p-value – 0.048) (Table 2).

Table 2: Co-relation Between Haematological Parameters Of Patients

	Dengue with warning signs			Severe Dengue			p value
	Mean ± SD	Min - Max	Median (IQR)	Mean ± SD	Min - Max	Median (IQR)	
Platelets (cells/ mcL)	42.17 ± 45.947	5-225	24.5 (15-48.5)	41.31 ± 44.018	5 - 213	24 (14.75 - 58.25)	0.732
Albumin (mg/dL)	3.6606 ± 0.41282	2.6 - 4.9	3.65 (3.375-4)	3.0306 ± 0.54161	2 - 4.3	3 (2.7 - 3.4)	<0.001**
Globulin (mg/dL)	2.4758 ± 0.4279	1.6 - 3.5	2.5 (2.2-2.8)	2.232 ± 0.55656	1 - 3.3	2.2 (1.8 - 2.7)	0.023*
A:G Ratio	1.5176 ± 0.28937	0.74 - 2.28	1.52 (1.328 - 1.743)	1.4191 ± 0.35709	0.88 - 2.5	1.37 (1.108 - 1.67)	0.048*

The overall survival outcome of the patients was determined based on need for ventilation, need for dialysis and 28 days mortality. None of the patients with warning signs required mechanical ventilation or dialysis, while 55.6% patients with severe dengue had to be shifted on mechanical ventilator and 38.9% required dialysis (P value <0.001). The mortality rate was significantly higher in severe dengue patients than in patients with warning signs (40.7% vs 0%, p value <0.001) (Figure 2).

Figure 2: Outcome Measures In Patients Enrolled For The Study

	Dengue with warning signs			Severe Dengue			p value
	Mean ± SD	Min - Max	Median (IQR)	Mean ± SD	Min - Max	Median (IQR)	
Length of ICU stay (days)	4.71 ± 2.96	2 - 24	4 (3 - 6)	5.87 ± 6.06	1-30	4 (2 - 7.25)	0.957

Need For Mechanical Ventilation	Dengue with warning signs		Severe Dengue		p value
	n	%	n	%	
No	66	100.0%	24	44.4%	<0.001**
Yes	0	0%	30	55.6%	
Total	66	100.0%	54	100.0%	

Need For Dialysis	Dengue with warning signs		Severe Dengue		p value
	n	%	n	%	
No	66	100.0%	33	66.1%	<0.001**
Yes	0	0%	21	38.9%	
Total	66	100.0%	54	100.0%	

Outcome (28 Day Mortality)	Dengue with warning signs		Severe Dengue		p value
	n	%	n	%	
No	66	100.0%	31	57.4%	<0.001**
Yes	0	0%	22	40.7%	
Total	66	100.0%	54	100.0%	

Further, the mean length of ICU stay in patients with warning signs was 4.71 ± 2.96 days, while in patients with severe dengue was 5.87 ± 6.06days. The difference was not statistically significant (P value- 0.957).

Group: Dengue with warning signs

Group: Dengue with warning signs

Group: Severe dengue

Group: Severe dengue
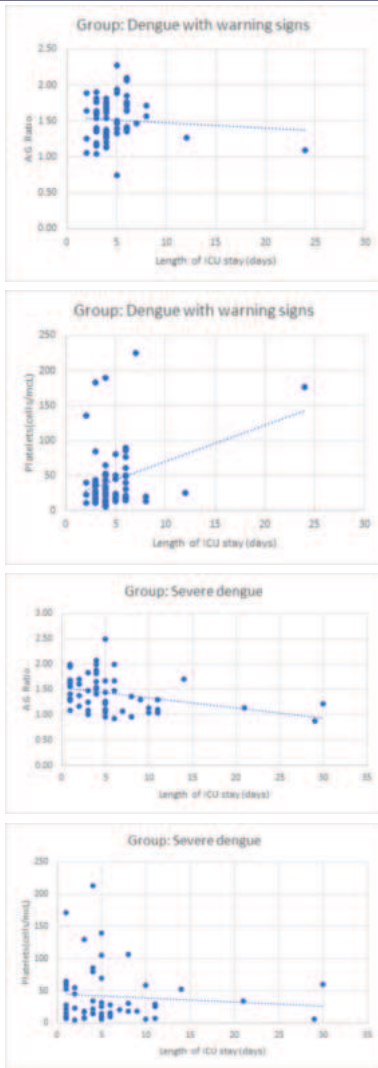
In present study, we correlated the A:G ratio and platelet count with our outcome measures, i.e, length of ICU stay and mortality. We observed a statistically significant negative co-relation between severe dengue patients with A:G ratio <1.5 and length of ICU stay (Table 3). As the A:G ratio decreased in severe dengue patients, the length of ICU stays increased.

We observed moderate positive correlation between A:G ratio and mortality in severe dengue but result was not statistically significant. The correlation between platelet count and length of ICU stay as well as platelet count with mortality was not found to be statically significant

Table 3: Correlation Of Albumin: Globulin Ratio And Platelet Count With Length Of ICU Stay And 28 Days Mortality In Dengue With Warning Signs And Severe Dengue Cases

			Platelets (cells/mcL)	A:G Ratio
Dengue with warning signs	Length of ICU stay (days)	Correlation Coefficient	0.203	0.156
		p value	0.105	0.214
Severe Dengue	Length of ICU stay (days)	Correlation Coefficient	-0.045	-0.390
		p value	0.749	0.004**
	Mortality	Correlation Coefficient	-0.006	0.250
		p value	0.965	0.068

DISCUSSION

Dengue, a mosquito-borne infection, has become increasingly prevalent in tropical and sub-tropical regions, affecting both rural and urban areas, posing a significant global health threat. Over the last few decades, the incidence of dengue fever has risen globally, with an estimated threat to around 25 billion people, or 40% of the world's population. According to the latest WHO estimates, there may be 50–100 million cases of dengue fever annually worldwide [1]. The acute infectious illness presents with symptoms such as biphasic fever, headache, bodily discomfort, prostration, rash, lymphadenopathy, and leucopenia. More advanced or severe cases often manifest as a severe febrile illness with complications in hemostasis and increased vascular permeability, occasionally leading to hypovolemic shock. Our study on demographic parameters revealed a higher male-to-female ratio among individuals affected by severe dengue and those with warning signs. These findings align with studies by Chandola I et al and Ahmed NH et al, where a higher number of males were reported to be affected by DENV [17,18]. Sandinirwan I et al's recent systematic review and meta-analysis demonstrated a significant association between low platelet count and progression to severe dengue (OR= 2.01 [95% CI 1.70 – 2.38]) [19]. Similar observations were made in our study, indicating a low platelet count in patients with severe dengue. Amancio FF et al reported that low levels of albumin are associated with severe dengue and high mortality [20]. Consistent with this, our study found an association between hypoalbuminemia and a higher incidence of severe dengue. Additionally, we noted that an A:G ratio of ≤1.5 was associated with severe dengue. Although different studies report varied cut-off values, the reversal in A:G ratio can be explained by the molecular size difference between albumin and globulin. Albumin, being smaller, tends to leak more easily during the early stages of dengue infection, causing the reversal of the A:G ratio. Further analysis revealed a significant correlation between the length of ICU stay and A:G ratio in severe dengue patients, along with a notable difference in mortality rates between severe dengue and patients with warning signs

CONCLUSION

Considering the above significant values, decreased albumin levels and A:G ratio of less than equal to 1.5 might help to differentiate severe dengue patients from patients with warning signs. These parameters could act as early predictors of severity of dengue infection. In conclusion, the present study highlights the importance of biochemical markers and clinical parameters in distinguishing dengue patients as well as their role in identifying severe dengue infection cases. These findings could play an important role in managing the public health and treatment regimen during dengue epidemics.

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