ASSOCIATION OF HEMATOCRIT-PLATELET INDEX AND HEMATOCRIT SHIFT WITH WARNING SIGNS AND HOSPITAL STAY IN DENGUE PATIENTS AT A TERTIARY CARE HOSPITAL

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ABSTRACT

Objective: To determine the relationship between hematocrit, platelet count, warning signs and duration of hospitalization in indoor dengue patients.

Study Design: Analytical, cross sectional study.

Place and Duration of Study: Department of Medicine, Pakistan Air Force Hospital Islamabad and Department of Biochemistry and Molecular Biology, Army Medical College, Rawalpindi, from Sep 2019 to Jun 2020.

Methodology: A total of 100 indoor patients were recruited using convenience sampling. Their platelets, hematocrit and warning signs were recorded on arrival in the hospital. First two parameters were checked every day for the whole duration of stay in the hospital. The WHO standard treatment of dengue was given to the patients. Patient were divided into two groups based upon duration of hospitalization using cut-off of 3 days. Linear regression was used to analyze association of hematocrit-platelet index and hematocrit shift with presence of one or more warning signs and duration of hospital stay.

Results: There was statistically significant difference in 3rd day Hematocrit Platelet Indices of patients with short and long hospital stay (p=0.003). 3rd day Hematocrit-platelet indices of patients with and without warning signs also showed statistically significant difference when compared with eachother (p=0.0001). It was stronger than Hematocrit Shift (p=0.82) and platelets considered alone.

Conclusion: Day 3 Hematocrit Platelet Indexis more strongly associated with warning signs and duration of stay rather than hematocrit alone. It means both need to be taken into account while monitoring dengue patients. Hematocrit platelet index for severity and duration of hospitalization while Hematocrit shift for fluid therapy.

Keywords: Hematocrit/platelet index, Hematocrit shift, Warning signs.

INTRODUCTION

Dengue viruses from family Flaviviridae, genus Flavivirus are mosquito-borne human pathogens which cause dengue infection ranging from asymptomatic phase to potentially fatal Dengue Shock Syndrome (DSS). The incidence of dengue has increased 30-fold over the last 50 years. Up to 50-100 million infections are now estimated to occur annually in over 100 endemic countries, putting almost half of the world's population at risk[1]. In 2009, the World Health Organization introduced a revised classification scheme consisting of the following categories: dengue without warning signs, dengue with warning signs, and severe dengue[2]. A total of 47,120 confirmed cases of denguefever, including 75 deaths were reported in Pakistan's recent epidemic from July to November 2019[3]. Our current study is based on this epidemic. DSS occurs once the patient transitions from stable phase to the leak (critical phase) of the illness. Identification of this transition to critical phase transition is important from diagnostic and management point of view because if unrecognized and mismanaged it can be fatal. So, hematocrit assumes an important role as its rise above the baseline value heralds leak phase. The aim of the fluid therapy is to normalize this shift above the baseline back to the baseline value. Both inadequate and excessive fluids lead to adverse outcomes. Fluid therapy needs close monitoring of patients' clinical condition as well as hematocrit for type,

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flow rate, volume and duration of fluids administered.

The onset of critical phase can be predicted clinically through warning signs which comprise clinical and biochemical features[4]. Here comes the role of a predictability index to predict warning signs and hospital stay the two most important parameters from therapeutic and administrative point of view. In our experience with dengue patients we were cognizant of the unpredictability of this disease with regards to the onset of the leak phase. While there are certain criteria reported in the literature[5] which predict leak phase in general terms but application to individual patients remains a challenge more so in our settings where resource and patients' clinical conditions preclude complex investigations. Secondly, we did not find in literature any attempt to date to unify these parameters into a simplified, user-friendly mathematical formula of predictability. In this background we tried to develop Hematocrit/platelet index as a predictability index for two parameters we mentioned before. We also compared it with hematocrit shift to see which of the two better correlated with the outcomes. Our basic premise was to check the validity of hypothesis that thrombocytopenia and rising hematocrit are associated with prolonged hospital stay.

METHODOLOGY

This cross sectional study analyzed data of indoor male patients admitted with dengue fever (diagnosed by NS1 Antigen) at PAF Hospital Islamabad over a period of 2 months, from September 2019 to October 2019. Study was endorsed by the hospital ethics committee (PERC/1/9/20). Our exclusion criteria were females and children less than 12 years of age. The records of all dengue patients aged more than 12 years were included and retrospectively scrutinized for variables including age, platelet count, hematocrit and duration of hospitalization. The sample size was calculated using standard statistical formula for sample size calculation based upon the reported prevalence of dengue in Pakistan which is about 3.1% according to a study[6]. Keeping standard error 0.05 the sample size comes out 44 while our sample size is 100. The hospital lab charts were customized to include hematocrit levels for ease of review of lab parameters. Entries of variables including name, patient's contact numbers, date, age, TLC count, Platelet count, presence or absence of warning signs and duration of hospitalization were made on standardized form. Al data were anonymized. All patients were managed according to the WHO guidelines on the subject. Serial monitoring was done for both hemodynamics and hematocrit of the patients and corresponding fluid adjustments were made based upon the evolution of these parameters over serial time. Where necessary clinical examination was supplemented by chest x-rays and abdominal Ultrasound exams to detect early leak phase marked by pleural effusions and ascites. Baseline blood complete pictures (Blood CP) were sent for all patients on admission day and then once daily. More frequent Blood CP was done in patients requiring frequent monitoring on clinical grounds or because of unstable hematocrits. Hematocrit-platelet index (HPI) was calculated for each day by dividing hematocrit (%) by platelet count/nl and matched with the patients' clinical status. Hematocrit shift % (HS) on each day was calculated as a % shift from the patient's baseline value on admission day (HCTA). For example, HS shift on a particular day (HCTD) was calculated as [(HCTD-HCTA)/ HCTA] × 100. In case of more than one value in a day maximum values for that particular day were recorded. Hospital duration was calculated from the day of admission (A) to the day of discharge. Day 1 was 24 hours after admission, day 2, 48 hours after admission and so on. Throughout the course of their admission the patients were closely monitored for the development of warning signs as per WHO guidelines.

All the data was enteredinto Microsoft excel sheet for basic computation. Mean and standard deviation were calculated for the nominal data. Pearson two tailed bivariate correlation analysis was used to study correlation between HPI, HS, Warning signs and hospital stay. Two-tailed

equal variance independent samples t-test was used to compare 3rd day HPI of patients with and without warning signs and also for those with stay of 3 days or less and those with stay of more than 3 days.

RESULTS

A total of 100 patients were studied. Fifty four (54%) had stay of 3 days or less. Eleven (11%) developed warning signs. Mean HPI was 1.09 SD ± 0.47. Mean HS 1.37% SD ± 0.04. Mean daily HPI and HS are shown (fig-1 & 2).

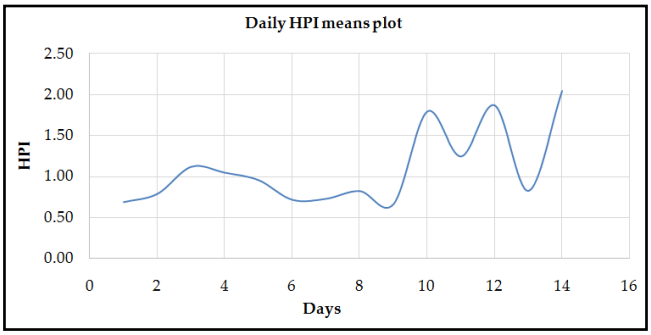

Figure-1: Daily hematocrit platelet index means plot.

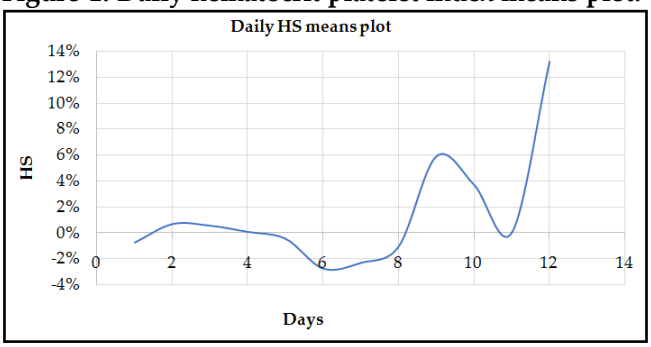

Figure-2: Daily hematocrit shift means plot.

Association was determined with linear regression and Pearson's formula using SPSS-22 (table-I). Among the parameters studied, none of the parameters was predictive of the duration of hospital stay and development of clinical warning signs (abdominal pain/tenderness, vomiting, lethargy, restlessness, mucosal bleed, enlarged liver or clinical fluid accumulation) during the hospital stay except a limited utility promised by HPI index.

We divided data of our patients into two groups based upon hospital stay with an arbitrary cutoff of less than or equal to 3 days used to define a group (A) with short stay and those with higher number of days group (B). Student's t-test showed statistically significant (p=0.003) difference between 3rd day HPIs of the two groups with

Table-I: Pearson two tailed bivariate correlation analysis.

Laboratory Parameters	Days Indoor	Warning Signs
Hematocrit (on day 1)		
p-value	0.761	0.311
n	100	100
Hematocrit Shift in percent (from day 1 to 2)		
p-value	0.364	.606
n	100	100
Platelets Count (on day 1)		
p-value	0.615	0.619
n	100	100
Hematocrit on day 4		
p-value	0.137	0.877
n	68	68
Hematocrit on day 5		
p-value	0.643	0.129
n	46	46
Hematocrit on day 6		
p-value	0.812	0.181
n	35	35
Platelets on day 4		
p-value	0.006	0.010
n	67	67
Platelets on day 5		
p-value	0.157	0.108
n	46	46
Platelets on day 6		
p-value	0.066	0.301
n	35	35
Hematocrit-Platelet Index (HPI) on day 1		
p-value	0.361	0.950
n	100	100
Hematocrit-Platelet Index (HPI) on day 2		
p-value	0.192	0.454
n	100	100
Hematocrit-Platelet Index (HPI) on day 4		
p-value	.003	0.003
n	66	66
Hematocrit-Platelet Index (HPI) on day 5		
p-value	0.156	0.005
n	46	46
Hematocrit-Platelet Index (HPI) on day 6		
p-value	0.266	0.485
n	35	35

mean value 1.30 for patients with stay more than 3 days (table-II). HPI day 3 ≥1 PPV 100% NPV 43%, sensitivity 39%, specificity 100% for duration of stay more than 3 days. There was also a statistically significant difference (p=0.0001) between 3rd day HPIs of patients with (group A') and without warning signs (group B') (mean HP3 for patients with warning signs was 1.96) PPV 44%, NPV 94%, Sensitivity 72%, specificity 82% (table-III).

Table-II: Comparison of 3rd day hematocrit platelet indices of patients with short and long duration of stay.

Baseline Characteristics	Study Groups		*p*-value
	Group A (n=21)	Group B (n=46)	
Hematocrit platelet index Day 3	0.48 ± 0.04	1.30 ± 0.06	0.003

Table-III: Comparison of 3rd day hematocrit platelet indices of patients with and without warning signs.

Baseline Characteristics	Study Groups		*p*-value
	Group A' (n=10)	Group B' (n=36)	
Hematocrit platelet index Day 3	1.96 ± 0.08	0.76 ± 0.05	<0.001

DISCUSSION

This study was pilot study which has introduced association of hematocrit-platelet index (HPI) with warning signs including (clinical: Abdominal pain or tenderness, Persistent vomiting, Clinical fluid accumulation (ascites, pleural effusion), Mucosal bleeding, Lethargy or restlessness, Hepatomegaly >2 cm and Laboratory: Increase in hematocrit concurrent with rapid decrease in platelet count)[4] and duration of hospitalization.

HPI consists of easy to obtain variables as platelet count and hematocrit which are part of the complete blood count (CBC) routinely done in all dengue patients. We tried to have an index which could alert the physician not only to the warning signs but also give an idea of short or prolonged hospital stay wherein a cutoff of 3 days was used to differentiate between the two. Eleven percent of our patients had warning signs as compared to 77% in another study by Rathakrishnan *et al*[7]. It could be explained by early admission and close fluid monitoring of patients. Mean HPI and HS of our patients rise with the stay in the hospital with maximum mean recorded at 3 day (excluding the outliers). It is because of generally low threshold for admissions at our setups resulting in admissions at early stage of disease because of fear for disease complications or lack of transportation facilities in case patient gets serious. Alternatively, it could be because of patients seeking medical care at an early stage. Higher HPI index is more strongly correlated with development of warning signs in dengue patients indoors as compared to the platelets count, hematocrit or hematocrit shift alone. It is an interesting observation as rise in hematocrit value of ≥20% is reported in literature[8,9] to be strongly associated with severe dengue. Our study does not contradict this claim but rather shows that HPI is more strongly associated with warning signs. It could be because of vigilant fluid therapy which was instituted based upon dynamic hematocrit trends when even small positive shifts in hematocrit were timely addressed by appropriate fluid adjustments. The PPV in our study is comparable with international studies especially for duration of stay and less for warning signs (100% vs 82-95%) as reported in studies[10,11]. Detailed analyses reveal that from the initial first- or second-day data, none of our parameters could help predict the duration of stay of a dengue patient in hospital neither the data could predict the development of warning signs during the stay at hospital. In another study comparing patients with non-severe dengue and severe dengue the researchers did not find any significant difference in the clinical manifestations of the two groups on the first two days. Notable differences started from 3rd day 12 onwards. It is observed that if hematocrit platelet index is used, which is obtained by simple division of hematocrit by platelet count/nl, it can effectively indicate patients developing clinical warning signs despite fluid therapy and standard

management during hospital stay. There is statistically significant difference of 3rd day HPIs of patients with and without prolonged stay (p=0.003) and those with and without warning signs (p=0.0001). Hematocrit-Platelet Index (HPI) on day 4 and 5 is also clearly significantly associated with development of one or more warning signs in admitted patients. As in normal course of disease, dengue patients develop warning signs from day 4-5 so the same duration shows a strong link of it with HPI. It is also evident that no other parameter mainly, hematocrit, percent hematocrit shift or platelet count is significantly associated with warning signs. That means these parameters cannot be used reliably to indicate development of clinical warning signs. The apparent superiority of HPI over simple HS may be because it incorporates two instead of a single variable. Wherein HS remains as the prime guide for fluid therapy but clinician also needs to know the expected trajectory of a particular patient in terms of hospital stay and development of warning signs. HPI offers a simple tool which can guide clinicians working in resource-constrained settings to gauge a fair idea about the direction their individual cases are taking with regards to the two parameters just mentioned. We suggest that HPI of 1.0 or more on day 3 is likely associated with prolonged hospital stay and development of warning signs.

Although work has been done regarding predictability of severe dengue[13] like in a study by Park[14] *et al* structural equation modeling (SEM) was used for prediction but the number of variables was high and difficult to execute in our settings. Lam *et al* studied the platelet dynamics of children with dengue[14] but yet they did not integrate platelet and hematocrit values into one mathematical index. We did not find isolated platelet values of any statistical significance for two outcomes studied. Tamibmaniam *et al*[16] included in their algorithm for severe dengue three parameters including vomiting, pleural effusion and low systolic BP. The diagnosis of pleural effusion at times needs ultrasound which may not be technically feasible in certain of our settings. Lee *et al*[17] have proposed a very practical scoring model but our study uses hematocrit as a variable since it's a mandatory monitoring variable also in Dengue so clinicians are spared the task of having to resort to other variables in order to monitor their cases. Retnam *et al*[18] have also studied association of hematocrit, platelets and duration of stay but again as separate and not as integrated variables unlike in our study. The results of our study are also validated by Ajlan *et al*[5] who demonstrated that out of WHO warning signs only hemoconcentration with concurrent drop in the platelet count was a significant predictor of severe outcome and the need for advanced healthcare. The limitations of this study are that all of our patients were males so we cannot extrapolate these results onto females. Secondly, in WHO warning signs the use of term lethargy is subjective and therefore subject to variation in interpretation. Thirdly, high-powered statistics could not be employed because of system limitations.

CONCLUSION

Hematocrit Platelet Indexof ≥ 1 on day 3 is associated with development of warning signs and a hospital stay of more than 3 days. Hematocrit Platelet Index is superior to Hematocrit Shift and platelets alone in this regard. Given our resource limited settings it offers a simple and convenient method for treating physicians to have an idea about clinical course of the disease in their individual patients.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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