

Correlation of total leukocyte count and platelets with the recovery phase in children with dengue admitted in an urban tertiary care center

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ABSTRACT

Introduction: Dengue ranks among the most significant mosquito-borne viral diseases in the world. Anticipatory management and monitoring indicators are essential in effectively administering therapies in the critical phase. Only a few studies have explored and documented the relationship between laboratory parameters and convalescing children with dengue. **Objectives:** The objective of the study was to delineate correlation of total leukocyte count (TLC) and the onset of convalescence (recovery) phase in children with dengue, and second, to determine the correlation of platelet count and TLC with the duration of hospital stay. **Materials and Methods:** This prospective observational study was conducted in a tertiary care hospital in Nagpur from July 2018 to November 2018 when the dengue outbreak in the city and the vicinity of this central India region was at its peak. The inclusion criteria consisted of children of 1–18 years of age from either sex, fever of recent duration, and serological positivity for dengue (NS1 antigen and/or IgM and IgG antibody positivity) were included in the study. The exclusion criteria were febrile illness other than dengue, comorbid conditions such as HIV, bronchial asthma, congenital heart disease, and complicated dengue cases. **Results:** Out of 190 cases, 65.8% were males, the average duration of fever at the time of admission being 4.9 ± 2.2 days (Range 2–10 days). The average duration of illness was 10.1 ± 2.4 days (range 4–19 days). Eleven (5.79%) subjects had third spacing (capillary leak). The average TLC recovery time was 8.45 ± 1.57 days (7–12 days) from the onset of illness, while the mean capillary leak recovery time was 9.45 ± 1.57 days (8–11 days). A negative correlation was observed from a 2nd – day hospital stay with both TLC and platelets in patients with the capillary leak. **Conclusion:** In resource-limited settings, pediatricians can utilize TLC in predicting recovery, and thus can reduce the treatment costs.

Key words: Convalescent phase, Dengue, Platelets, Recovery, TL

Dengue ranks among the most significant mosquito-borne viral diseases in the world. During the past 50 years, the occurrence of dengue has risen 30-fold. For Southeast Asia, the caseload was comparable with that of meningitis, having twice the burden of hepatitis and one-third of the burden of HIV/AIDS [1,2]. The worst outbreak of dengue since 2006 was recorded in Delhi, India in 2015 with over 15,000 cases. Although the year 2017–2018 registered a drop in the number of cases, 2018–2019 witnessed a sharp rise. The goal of the global strategy is to reduce the burden of dengue with specific objectives to reduce its mortality by at least 50% and morbidity by at least 25% by 2020 [3]. The WHO recommended guidelines to focus on appropriate fluid therapy and has shifted preference from glucose-based fluids to normal saline [4] which has been observed as a paradigm shift in the management of dengue. This shift in the management of dengue has led to fewer incidences of pulmonary edema and third spacing, resulting in the decreased hospital stay.

With an aim to aid early identification of severe forms of dengue, the WHO has classified it into three categories, namely, dengue fever (DF), dengue with warning signs, and severe dengue [4]. Severe dengue includes clinical entities such as dengue hemorrhagic fever (DHF), which is characterized by mucosal bleeding and coagulopathy and dengue shock syndrome (DSS), characterized by hypotension. A moderate self-limited course is followed in DF, whereas DHF might appear as a benign condition, it can develop into a life-threatening situation as the fever abates.

Dengue progresses through its three predictable pathophysiological phases [4]:

1. Febrile phase (2–7 days): Viremia-driven high fever.
2. Critical/plasma leak phase: Sudden onset of varying degrees of plasma leak into the pleural and abdominal cavities. The onset is between 3 and 4 days after the fever, which generally lasts for 36–48 h.
3. Convalescence or recovery phase: Sudden arrest of plasma leak with concomitant reabsorption of extravasated plasma

and fluids. Onset is 6–7 days after the fever and lasts for 2–3 days. Early recognition of a patient's clinical phase is important to tailor clinical management, monitor the effectiveness of the treatment, and to anticipate when changes in are needed the management.

Anticipatory management and monitoring indicators are essential in effectively administering therapies as the patient enters the critical phase. New-onset leukopenia (white blood cell $<5000/\text{mm}^3$) indicates that the fever will likely to dissipate within the next 24 h and that the patient will be entering into the critical phase [5,6]. Moreover, assessing volume status is crucial to dengue management, and it entails using central venous monitoring and inferior vena cava Doppler ultrasonography. However, access to these sophisticated gadgets is limited in certain resource-limited health-care facilities, and thus, one has to rely on clinical parameters to titrate fluid therapy, especially during the transition from critical to convalescent phase.

Even though laboratory parameters are available to predict the onset of critical phase, data for anticipating convalescence phase is lacking. In dengue illness, changes in clinical and laboratory parameters can be protean; hence, there is a need to identify few laboratory parameters which can aid in predicting the onset of convalescence phase to avoid fluid overload and unnecessary use of blood and blood products.

With the above background, fortified by the fact that only a few studies have explored and documented the relationship between laboratory parameters and convalescing children with dengue in this tropical region of Central India known for excessive rainfall and high temperature; the present study was undertaken with the main objective of delineating correlation between total leukocyte count (TLC) and onset of convalescence (recovery) phase in children with dengue, and the secondary objective was to determine the correlation of platelet count and TLC with duration of hospital stay.

MATERIALS AND METHODS

This prospective observational study was conducted in a tertiary care hospital in Nagpur from July 2018 to November 2018 when the dengue outbreak in the city and the vicinity of this Central India region was at its peak. Consent from caregivers was taken, and ethical clearance was obtained from the Institutional Ethics Committee. The study sample was selected by non-probability, convenience sampling method and a detailed history and a thorough clinical examination were done in all the eligible cases.

Data were collected in a pre-designed, pre-tested pro forma that included demographics and clinical characteristics of the recruited case. The inclusion criteria consisted of children of 1–18 years age from either sex group, fever of recent duration (≤ 10 days), and serological positivity for dengue (NS1 antigen and/or IgM and IgG antibody positivity). The exclusion criteria were febrile illness other than dengue, comorbid conditions such as

HIV, bronchial asthma, congenital heart disease, and complicated dengue cases such as myocarditis, encephalopathy, renal failure, disseminated intravascular coagulopathy, and decompensated shock as they would have confounded the interpretation of capillary leak and hematological parameters.

Blood investigations, including TLC and platelet count, were done on a daily basis. Patients were treated conservatively with intravenous fluids and paracetamol as per the WHO guidelines [4]. Frequent monitoring of vitals (2 hourly), blood sugar levels (12 hourly), body weight (daily), and urine output (hourly) were monitored. The recruited subjects were tracked from the day of admission (day 1) until discharge, and the day-wise clinical measurements and observations were recorded in the proforma. The occurrence of other morbid conditions and any change in health status occurring during the 24-h period was also noted down.

TLC recovery time was defined as the number of days required to reach age-appropriate reference values [7]. Patients with rising hematocrit from the baseline and evidence of edema, ascites, or pleural effusion were considered to be having a capillary leak. None of the study subjects died during the entire duration of hospital stay.

Data were entered into MS Excel, coded, and analyzed in statistical software STATA, version 10.1, 2011. The data analysis included both descriptive and inferential statistics. The descriptive statistics were used to summarize quantitative variables with mean and standard deviation while frequency and percentages were used to summarize categorical (qualitative) variables. The inferential statistics mainly included Chi-square test and t-test for assessing the significance of the difference in outcomes expressed as proportions or means in comparison groups. Correlation between a hospital stay and TLC or platelet counts was assessed by Pearson's correlation coefficient ("r") significance of which was evaluated by t-test. $p < 0.05$ was considered statistically significant for all comparisons.

RESULTS

A sample of 230 cases with early manifestations (1–10 days) of fever was included in this study. Dengue was suspected in 190 (82.6%) children, who had two or more of the following symptoms: Fever, pain abdomen, headache, myalgias, arthralgias, skin rash, nausea, vomiting, and retro-orbital pain.

Out of these 190 children, 182 (95.8%) children who presented in early febrile period (1–10 days) and who were serologically positive for dengue took part in the study. The majority (66.8%) of them belonged to >5 years age group (mean age: 7.5 ± 5.1 years). The preponderance of male (65.79%) subjects was observed. The mean weight on admission was 25.9 ± 16.1 kg. Almost all (95.8%) had a fever; average duration of fever at the time of admission being 4.9 ± 2.2 days (range 2–10 days). The average duration of illness was 10.1 ± 2.4 days (range 4–19 days). Eleven (5.79%) subjects had third spacing (capillary leak) criteria with the presence of hemoconcentration and either edema, ascites, or puffiness (Table 1).

The trend of TLC with and without capillary leak (Fig. 1) showed a rise from day 2 of admission with average TLC recovery time, after initial leucopenia, as 8.45 ± 1.57 days (7–12 days) from the onset of illness.

While mean capillary leak onset was 7.45 ± 1.57 days (5–9 days) from the onset of illness, the mean capillary leak recovery time was 9.45 ± 1.57 days (8–11 days) from the onset of illness. Moreover, mean platelet count on day 1 for with and without capillary leak (Fig. 2) was $114,181.8 \pm 27,318.3/\text{mm}^3$ and $176,044.9 \pm 7304.23/\text{mm}^3$, respectively ($p=0.0417$). There was a significant decline in platelet counts among those who had a capillary leak ($p=0.0058$).

Although the lowest mean platelet count ($12,000/\text{mm}^3$) for capillary leak group was documented on day 5 of admission,

Table 1: Distribution of dengue cases with a capillary leak (n=190) by day of admission

Day after admission	n (%)
1.	11 (5.79)
2.	11 (5.79)
3.	4 (2.11)
4.	3 (1.58)
5.	1 (0.53)
6.	0 (0)

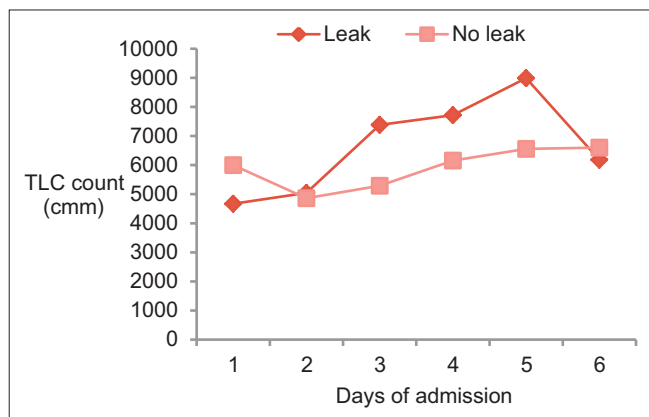


Figure 1: Trend in total leukocyte count with and without capillary leak by days of admission

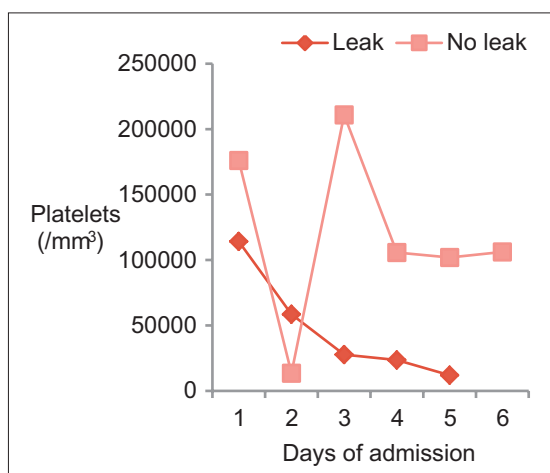


Figure 2: Trend in platelet count with and without capillary leak by days of admission

it was on day 2 in without capillary leak group with counts of $13,568.9/\text{mm}^3$.

Pearson's correlation coefficient for the duration of stay in the hospital with TLC and platelet counts is depicted in Table 2. A negative correlation was found from a 2nd day hospital stays with both TLC and platelets in patients with the capillary leak, and from 3rd day onward in those without the capillary leak. A similar pattern was found with both TLC and platelets in subjects having no capillary leak.

DISCUSSION

DF has a highly variable disease evolution and outcome. All 190 patients under the study were of proven DF, with 11 showing signs of capillary leak. The majority (79.5%) of patients belonged to the urban settings, largely due to the fact that Nagpur was witnessing large-scale construction work which presented challenges in implementing effective vector control measures. The slight male preponderance (Male: female ratio 1.92:1) could be due to increased risk of exposure to mosquito bites in males due to their preference for outdoor activities. In the present study, the critical phase onset was found to be from day 6 of illness and the convalescent phase characterized by the falling hematocrit accompanied by improving urine output and weight loss which started by day 8 of illness in the majority of children.

In the present study, the onset of critical phase was observed to be between 5th and 9th day, while recovery from critical phase coincided with the rise of TLC on the 7th–12th days of illness. This finding mirrors the observations from the adult study, where TLC starts to rise from day 5 of illness [8]. Many studies have been conducted to predict the critical phase, but few pediatric studies have evaluated the trend of TLC and platelet counts in the convalescence phase [9].

While the recent study conducted in Bengaluru [9] reported that any change in the values of TLC points toward the progression of the disease toward severity, the present study extends the current understanding and highlights the fact that the rise of TLC during the critical phase is not necessarily due to infection but in fact a sign of recovery. All patients in the current study displayed leukopenia on day 1 of admission. By day 2, TLC reached its nadir and then onwards, it kept rising, to be higher in children who have a capillary leak as compared to no leak group. Similarly, a recent study comprising subjects aged more than 14 years have reported TLC values to be significantly higher among leakers as compared to non-leakers during day 5 of illness and platelets were also reported significantly lower among leakers [10].

Thrombocytopenia was observed more frequently in patients with capillary leak syndrome. This can be due to the inflammation-dependent release of interleukin-1 β [11] aided by platelet-driven increased vascular permeability. A rapid decrease in platelet count, concomitant with a rising hematocrit, is suggestive of progression to plasma leakage [12]. However, platelet count failed to predict the recovery from the critical phase, as it continued to fall well past the critical

Table 2: Correlation of hospital stay with TLC and platelets

Hospital stay	TLC with capillary leak		TLC without capillary leak		Platelets with capillary leak		Platelets without capillary leak	
	r	p value	r	p value	r	p value	r	p value
Day 1	0.60	0.07	-0.01	0.97	0.23	0.49	0.2	0.01
Day 2	-0.09	0.81	0.10	0.18	-0.37	0.29	0.24	0.01
Day 3	-0.69	0.31	-0.03	0.74	-0.70	0.30	-0.09	0.25
Day 4	-0.88	0.31	-0.14	0.08	0.98	0.12	0.08	0.35
Day 5			0.04	0.68			0.04	0.84

r=Pearson's correlation coefficient, TLC: Total leukocyte count

phase. These findings resonate with those in the study by Ralapanawa *et al.* [10].

Moreover the comparison between the duration of hospital stay with TLC and platelet counts was made, overall, an inverse relationship was observed as TLC increased, hospital stays decreased and as platelets decreased, and hospital stays increased. In capillary leak group, this relationship started to show up from 2nd day onward for both TLC and platelet count. However, in no capillary leak group, a negative correlation was eminent from day 3 of admission. This can be due to the fact that thrombocytopenia occurs during the critical phase, and its lowest point coincides with day 2 of the capillary leak which needed intravenous fluids, thus prolonging the duration of hospital stay.

Furthermore, early decline and recovery of TLC occur in those children who do not suffer from capillary leak; hence, they recover much early resulting in a shorter hospital stay. Thus, the present study reveals that the onset of the recovery phase can be anticipated by keeping a close watch on the TLC.

It is common practice to start intravenous fluid therapy when the patient enters a critical phase. Pediatricians often fail to decrease the fluid rate as the patient enters the recovery phase. This is partly due to the fact that clinical findings such as edema, weight loss, and urine output takes time to show clinical improvement, and partly due to the lack of access to specific lab parameters to point toward the onset of the recovery phase. This can potentially increase the chances of fluid overload and pulmonary edema. By regularly monitoring the TLC trends during the critical and convalescent phase (5th – 7th days of illness), as demonstrated in the current study, doctors can start titrating their fluid therapy – especially in those with the capillary leak.

Another interesting finding which the present study brought to the fore was that, in children with the capillary leak, even though patients entered the recovery phase, platelets kept falling well past the 5th day of admission without associated complications. This insight can further be explored to utilize platelet transfusion sparingly. The study findings supplant the basic understanding of the disease process and clinicopathological underpinnings of the convalescent phase, thus encouraging researchers to embark on a larger study-designed to test these observations. The resource-deficient settings where hemogram analysis cannot be recommended regularly, TLC levels of day 2 and 3 could turn out to be vital parameters to anticipate the onset of recovery. This utilization will limit the cost of the laboratory tests.

Since this study was performed in a specified period where city inhabitants experienced an outbreak of dengue, the sample size was fixed. Hence, small sample size and exclusion of complicated dengue cases (thereby narrowing down disease spectrum) from the analysis are few of the limitations of the study. However, authors think that the study findings are pertinent, especially in regard to the settings and will certainly outscore the limitations.

CONCLUSION

In settings with limited resources-like central India, pediatricians, not only can utilize TLC in predicting recovery but also can help reduce the treatment costs. In addition, the study result implications may encourage treating doctors to rationalize expensive and potentially harmful platelet therapy.

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