

The relationship between platelet count and the onset of leaking phase in dengue patients

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ABSTRACT

Introduction: The complications of dengue are related to reduced intravascular volume following plasma leakage. Thrombocytopenia or platelet dysfunctions are detected in all stages of the illness and are related to the clinical outcome. The main objective of the study was to correlate absolute platelet count to the onset of leaking phase in dengue patients who had entered into leaking phase after the hospital admission.

Methods: One hundred and sixteen patients (age range 14-74 years, median age 33 years) who entered the leaking phase after admission were recruited to the study. Dengue infection in patients was confirmed with either the presence of positive NS1 or positive IgM antibodies. Serial ultrasonography was done from admission until the leaking phase is detected. Platelet counts were assessed twice per day just prior to the ultrasonography.

Results: There were 47 (40.5%) females and 69 (59.5%) males among the recruited patients. The mean number of days at which leaking was detected following onset of fever was 4.9 ± 0.9 days. The mean platelet count at the onset of leaking phase was $30,051 \pm 17,023$ / μ L. Age and the platelet count at the time of onset of leaking phase was significantly negatively correlated (whole group $r = -0.323$ $p < 0.001$; in females $r = -0.369$, $p = 0.011$; males $r = -0.280$ $p = 0.020$). Platelet count at the time of onset of leaking phase was significantly lower in the patients older than 30 years of age ($27,577.5 \pm 17,361.4$) compared to those of the patients younger than 30 years ($33,955.6 \pm 15,888.8$) ($p=0.032$). Upper limit of the range of platelet count at the onset of leaking phase was 77,000/ μ L which was slightly lower in females.

Conclusions: According to this study, the value of platelet count as a predictor of the progression of dengue infection depends on the age of the patients. Young patients are more prone to develop leaking phase with higher platelet counts than the older patients.

Key words: *Thrombocytopenia, dengue, leaking phase*

Introduction

Dengue viral fever is the most prevalent mosquito-borne disease in the world.

The first case of dengue in Sri Lanka was reported in 1960 (1). During the past few decades, the Sri Lankan population has gone through several

epidemics and is currently experiencing annual dengue epidemics (2). The incidence and the severity of the disease are significantly increased during recent years resulting in high mortality.

Many dengue patients are asymptomatic and may not progress into the critical phase. The critical phase

occurs around the time of defervescence associated with an increased tendency for capillary leakage. The leaking phase manifests as a rise in haematocrit, pleural effusions, ascites or haemorrhage (3).

Therefore, dengue patients should be closely monitored for the development of plasma leakage. As a prognostic indicator, ultra sound scans (USS) could be used to assess patients at risk for entering the critical phase. Gallbladder wall thickening due to oedema which can be detected in USS is considered the earliest sign of plasma leaking in dengue haemorrhagic fever (4). The haematological parameters are useful in predicting the development of critical phase within the next 24 to 48 hours (5).

The platelet count has value as potential indicator of clinical severity in dengue (6, 7). A rapid decline in platelet count or a platelet count less than 150,000/ μ L blood is an alarming sign of dengue (6). The mechanisms involved in thrombocytopenia are not fully understood (8). Bone marrow suppression (9, 10) and increased peripheral destruction (11, 12) are the proposed mechanisms for thrombocytopenia. Furthermore, number of studies have documented platelet dysfunction in dengue (13, 14).

✎ The value of platelet count as a predictor of critical phase has been evaluated in several studies. The rapid decline of platelet counts before the critical phase has been reported in both adult and paediatric studies (15-17). Several studies showed gallbladder wall thickening which was significantly associated with lower platelet counts (17-20). Santhosh *et al.* have reported gallbladder wall oedema in 97.8% of patients whose platelet count was less than 40,000/ μ L (19).

There have been no studies done in Sri Lanka on the value of platelet count as a predictor of the critical phase. The main objective of this study was to assess the relationship between ultrasonographic evidence of earliest leakage and corresponding platelet count in dengue patients who had entered into leaking phase after the hospital admission.

Methods

This descriptive cross-sectional study was conducted at Teaching Hospital, Karapitiya, over a period of six months. All patients with confirmed dengue fever with positive NS1 antigen or IgM antibodies and developed leaking phase after the

admission into two medical wards were included in the study. Patients with dengue leaking phase on admission, patients with other aetiologies for thrombocytopenia such as cirrhosis, splenomegaly, autoimmune disorders, myelodysplastic syndromes or malignancies and patients who were on thrombocytopenic drugs were excluded from the study.

After obtaining informed written consent, the data were collected by the principal investigator using a pre-tested questionnaire.

All dengue patients underwent serial ultrasonography on admission and then twice a day until leaking phase was over. Ultrasonography was performed by a medical registrar experienced in detecting dengue leaking phase under the supervision of a consultant radiologist. The consultant radiologist repeated all doubtful scans. USS studies were performed with 6 hours of fasting to optimize gallbladder visualization. Gallbladder wall thickening was used as a radiological sign to detect the leaking phase. Wall thickness of more than 3 mm was considered as gallbladder wall thickening (18). All ultrasound examinations were performed with a portable machine (*L&T symphony model*) using 3.5 MHz and 5 MHz probes. Gallbladder wall thickness was measured by using a previously reported and validated ultrasound method (21). Blood samples were collected 30 minutes before each scan using standard procedures in to EDTA tubes and immediately analysed using Mindry 6068 and *Sysmex* XN 1000 automated full blood count analysers. Once the leaking was detected latest platelet count was taken for the analysis.

The data were analysed with *PSPP* version 0.83-g5f9212 statistical software (Free Software Foundation, Inc. <http://fsf.org/>). Mann Whitney U test was used to assess the significance between variables. $P < 0.05$ was considered statistically significant.

The ethical approval for the study was obtained from the Ethics Review Committee of Faculty of Medicine, University of Ruhuna. Approval was taken from the Director, Teaching Hospital, Karapitiya for data collection and written, informed consent was obtained from the patients or the guardian in case of patients less than 18 years of age.

Results

Of one hundred sixteen patients who had entered into leaking phase after the hospital admission, 47 (40.5%) were females and 69 (59.5%) were males. The median age of females was 36 years and males were 32 years. Majority (55%) of the patients were from Galle Municipality area. Demographic characteristics and variables related to the disease course are given in Table 1.

The duration of hospital stay was significantly higher in female patients than in male patients ($p = 0.043$). However, gender and the duration of the fever on admission was negatively correlated with the duration of the hospital stay ($r = -0.344$; $p = 0.018$). Furthermore, there was no gender-related difference in the duration of fever on admission.

The duration of fever on admission was negatively correlated with the duration of hospital stay ($r = -0.410$; $p < 0.001$) and platelet count at the onset of leaking phases ($r = -0.200$; $p = 0.031$). Furthermore, the duration of fever on admission was positively correlated with the duration of fever at the onset of leaking phase ($r = 0.201$; $p = 0.031$).

However, among the male patients, the duration of fever on admission was negatively correlated with the mean duration of hospital stay ($r = -0.490$;

$p < 0.001$) and mean platelet count at the onset of leaking phases ($r = -0.331$; $p = 0.005$). The platelet count at the onset of leaking phases was positively correlated with the duration of the hospital stay ($r = -0.252$; $p = 0.037$).

Correlation of the mean duration of fever on admission, during the hospital stay and at the onset of leaking phase according to the age group is given in Figure 1.

The mean number of days the leaking phase was detected after the onset of fever was 4.9 ± 0.9 days. There was no statistically significant association between the duration of fever at the onset of leaking phase and gender ($p = 0.247$) (Figure 2). Mean platelet count at the onset of leaking phase was $30,051 \pm 17,023$. There was no significant association of platelet count at the onset of leaking phase and the gender ($p = 0.478$).

There was a significant negative correlation between the age and the platelet count at the time of onset of leaking phase in the sample ($r = -0.323$ $p < 0.001$; females $r = -0.369$; $p = 0.011$ and males $r = -0.280$; $p = 0.020$) (Figure 3). Upper limit of the range of platelet count at the onset of leaking phase was slightly lower in females.

Table 1: Demographic characteristics and variables related to the disease course

Demographic characteristics	Male (n=69)	Female (n=47)	Total (n=116)
Age (median) in years	32	36	33
Age range (years)	14 - 69	15 - 74	14 - 74
Mean duration (SD) of the hospital stay (days)	5.1 (1.4)	5.6 (1.5)	5.3 (1.5)
Range of duration of hospital stay (days)	3 - 10	4 - 10	3 - 10
Mean duration (SD) of fever in days on admission	4.0 (1.5)	4.2 (1.6)	4.1 (1.5)
Mean duration (SD) of fever in days at the onset of leaking phase	4.8 (0.9)	5.0 (0.9)	4.9 (0.9)
Mean platelet count (cells/ μ L) (SD) at the onset of leaking phase	30449 (16554)	29468 (17855)	30051 (17023)
Range of platelet count at the onset of leaking phase (cells/ μ L)	3,000 - 77,000	7,000 - 74,000	3,000 - 77,000

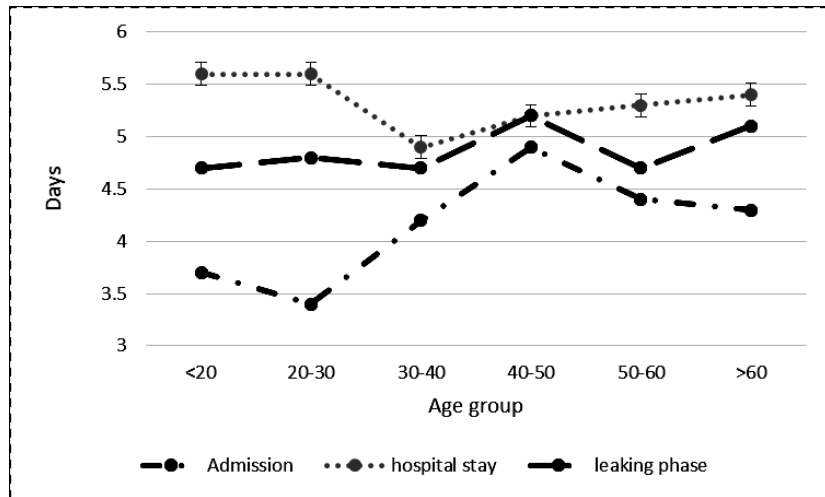


Figure 1: Mean durations of fever; on admission, during hospital stay and at the onset of leaving phase according to the age group

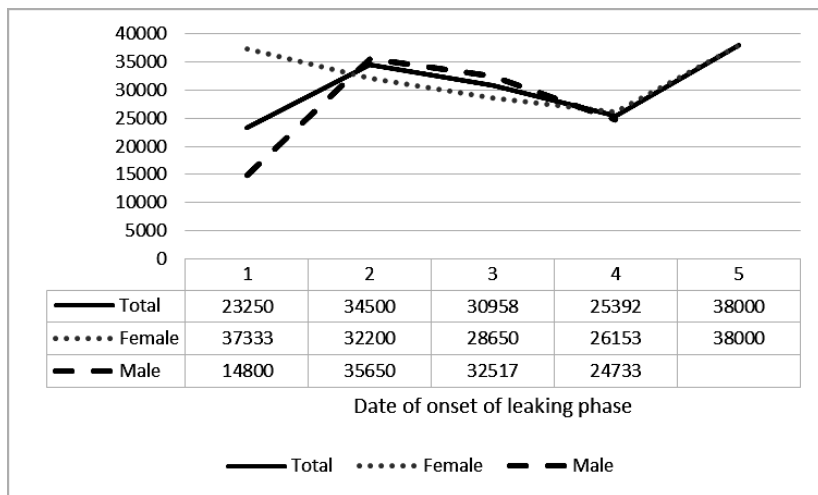


Figure 2: Correlation between mean platelet count at the onset of leaving phase and mean duration of the fever at the onset of leaving phase

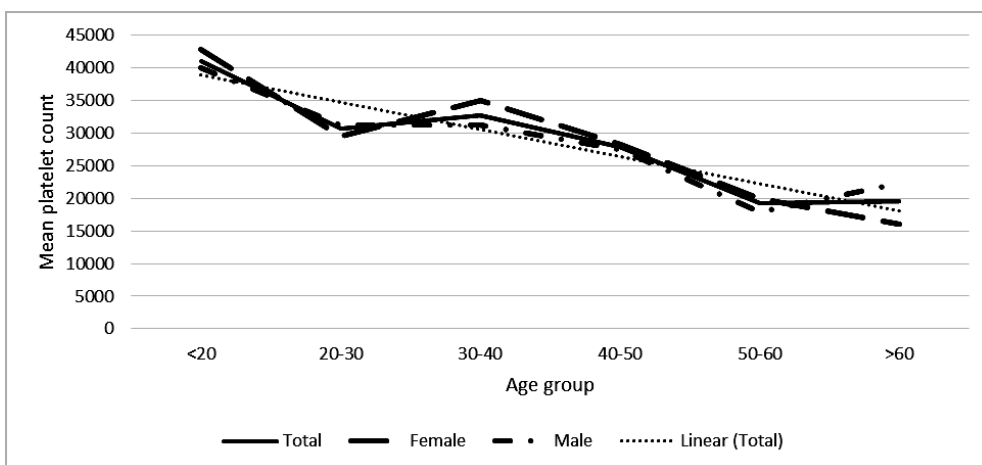


Figure 3: Correlation between age and the platelet count at the time of onset of leaving phase

The platelet count at the time of onset of leaking phase was significantly lower in patient older than 30 years of age (27,577.5, SD 17,361.4) than patients younger than 30 years of age (33,955.6, SD 15,888.8) ($p=0.032$).

Discussion

This study shows that the value of platelet count as a predictor of the progression of dengue fever depends on the age of the patients.

Age and gender have been studied as factors forecasting the severity of dengue. Female gender and young age have been found as risk factors for mortality (22). The duration of hospital stay was significantly longer in female patients than male patients in the current study which would support the finding of preponderance of females among severe dengue cases but not among mild cases (23). It has been suggested that risk of female gender reflects either a more robust cellular immune response or a higher intrinsic susceptibility to capillary permeability in females than males (24).

The age-stratified analyses in previous studies have demonstrated the difference in clinical and laboratory manifestations of dengue between elderly and younger adults. It was observed that children less than 10 years of age are more prone to increased vascular permeability, leading to shock (24). In our cohort, the age and the platelet count at the time of onset of leaking phase was significantly negatively correlated. This shows that the young patients are more prone to develop leaking phase with higher platelet counts than the older patients.

Similar to our findings, several studies have reported that platelet count $\leq 100,000/\mu\text{L}$ increased the risk of leaking (25, 26). Furthermore, platelet count decreases rapidly before patients enter the state of shock. This emphasizes that in young patients leaking phase may develop at higher platelet counts than in elderly patients.

Upper limit of the range of platelet count at the onset of leaking phase was in this study was $77,000/\mu\text{L}$, which was slightly lower in females. Considering the higher limit of the mean platelet count at the onset of leaking phase as observed in the current study, we propose that the leaking phase

must be anticipated when the platelet count reaches $80,000/\mu\text{L}$. National Guidelines recommend that platelet counts less than $100,000/\mu\text{L}$ indicate that the patient might enter the critical phase (onset of plasma leakage) and this is supported by many other studies (27, 29). This study further supports the above recommendation.

The mean duration of fever at the onset of the leaking phase was 4.9 ± 0.9 days with a wide range in platelet count. These findings emphasize the importance of early detection and continuous monitoring of dengue patients. Early identification of the patients with risk improves the outcome. Furthermore, it may enhance the efficient allocation of hospital resources by diverting resources for patient with impending threat for severe disease.

Conclusions

The value of platelet count as a predictor of the progression of dengue fever depends on the age of the patients. Younger patients are more prone to develop leaking phase with higher platelet counts than the older patients.

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