

Predictive Value of Thrombocytopenia in the Diagnosis of Dengue Infection in Outpatient Settings

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SUMMARY

Thrombocytopenia is often relied upon as an important criterion for the diagnosis of dengue infection among patients presenting with an acute non-specific febrile illness. This study was aimed to assess usefulness of thrombocytopenia in the diagnosis of acute dengue virus infection. This was a clinic based prospective cohort study from May to November 2003. Consecutive patients presenting with acute non-specific febrile illness of less than two weeks were selected from two urban primary care centres. We did full blood count examination (FBC) on the day of visit and dengue serology on day five of illness for all patients enrolled. We repeated the FBC examination for patients who had initial normal platelet counts. Thrombocytopenia was defined as platelet count $<150 \times 10^9/L$. Eighty-seven patients enrolled in the study. Complete data was available for 73 patients. The prevalence of acute dengue virus infection was 27.6%. The sensitivity and specificity were 88% and 71% respectively. The likelihood of acute dengue infection in the presence of thrombocytopenia was 2.52 and likelihood of not having dengue infection in normal platelet count patients was 5.22. Thrombocytopenia has fair predictive value in diagnosing acute dengue virus infection. It was more useful to exclude than to diagnose dengue infection.

KEY WORDS:

Dengue infection, Thrombocytopenia, Likelihood ratio, Sensitivity, Specificity

INTRODUCTION

Dengue infection is the commonest arboviral disease in the world. It carries a significant mortality if the diagnosis and treatment are delayed¹. Full blood count assessment is often done for early detection if there is clinical suspicion of acute dengue infection in an outpatient setting. Many clinicians rely on the presence of thrombocytopenia to diagnose acute dengue virus infection. This is because office dengue serology test kit is not widely available in all primary care clinics. Presence of thrombocytopenia is also the main reason for hospital admission². However, dengue infection is only one of the many causes of acute febrile thrombocytopenia. Other causes of febrile thrombocytopenia include scrub typhus, chikungunya fever, infectious mononucleosis, malaria, typhoid fever, leptospirosis and acute human immunodeficiency virus conversion disease³.

Although thrombocytopenia is an important finding in acute dengue infection among adults, the rate of its occurrence varies widely. It ranges from 40%-97%^{4,5,6,7}. Since the thrombocytopenia is given so much emphasis in the diagnosis of acute dengue virus infection, it is of interest to know how valid thrombocytopenia is, in diagnosing acute dengue virus infection in an outpatient setting. The objective of this study was to determine the validity of thrombocytopenia in diagnosing acute dengue virus infection among patients with acute non-specific febrile illness presenting to the outpatient clinics.

MATERIALS AND METHODS

We conducted a prospective cohort study of patients attending Primary Care Centre of Hospital Universiti Kebangsaan Malaysia (HUKM) and Batu 9 Health Clinic Hulu Langat, from May to November 2003. We invited consecutive patients who were age 12 years and above with a history of fever (oral temperature of $\geq 37.5^\circ C$) for less than two weeks to participate in the study. Patients were excluded if there was an apparent localized source of infection e.g. urinary tract infection, acute abdomen, or any illness with pathognomonic clinical features e.g. varicella infection, measles, rubella, scarlet fever and obvious dengue haemorrhagic manifestations. Ethics approval was obtained from the research and ethics committee of the Medical Research Unit, National University of Malaysia (UKM). Consent was taken from all eligible patients before enrolling them into the study.

Full blood count examination was done for every patient. Patients were assumed to have acute dengue virus infection if thrombocytopenia was detected and were managed by protocol for acute dengue virus infection⁸. All the other patients with normal platelet counts were called back on day 5 of illness for a repeat full blood count so as not to miss any patient with thrombocytopenia. We considered patients to have thrombocytopenia if any of the platelet count result was $< 150 \times 10^9/L$. We did dengue serology for all patients on day 5 of illness. If the patients were admitted, data was then collected from hospital records.

Dengue serology tests were done using PanBio Rapid Immunochromatography method in the virology laboratory, HUKM. Primary acute dengue virus infection is defined as a positive serology test of IgM alone. Secondary infection is defined as a positive IgG with or without a positive IgM. Collectively, both primary and secondary infections constitute acute dengue infection.

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Statistical analysis

Results were analysed as intention to treat with SPSS version 11. Sensitivity, specificity and likelihood ratio of the test (thrombocytopenia) in predicting the disease (acute dengue infection) was calculated. Likelihood of disease for a positive result, which was denoted by (+)LRd, calculated as [Sensitivity/(1-Specificity)] and Likelihood of no disease for a negative result, which was denoted by (-)LRn, calculated as [Specificity/(1-sensitivity)]⁹.

RESULTS

We screened 153 patients, of which 49 did not give consent for the study and 17 were excluded for not fulfilling the criteria. Fourteen patients defaulted follow up as they claimed to be well and refused reassessment. Hence, complete data was available for 73 patients. However, we have included all 87 patients (including 14 defaulters) enrolled in our data analysis. (Fig.1) Mean age of the patients in this study was 27.3 years (27.5, SD±12.0); and fifty-seven (65.5%) were males; Malay (73.6%) was the main ethnic group, followed by Chinese (11.5%), Indian (9.2%) and others (5.7%).

Patients presented to our clinics at different days of fever. They ranged from 2 to 10 days of fever. There were 37 patients who had thrombocytopenia on their first blood taking of which 15 presented with less than 5 days of illness (Fig. 2). On second blood taking which was on day 5 of illness, 5 more patients developed thrombocytopenia from their initial normal platelet count. These made a total of 42 (48.3%) patients had thrombocytopenia.

There were 24 patients (27.6%) with positive dengue serology testing. Among these patients with dengue infection, 21(87.5%) had thrombocytopenia. Fourteen patients who defaulted did not have dengue serology performed and they were assumed as not having dengue infection. Among the 14 defaulters, four patients had thrombocytopenia and 10 had normal platelet count.

We first cross tabulated and analysed on complete data from 73 patients. (Table I) The sensitivity and specificity of thrombocytopenia in diagnosing acute dengue virus infection were 88% and 65% respectively. The likelihood ratio for not having acute dengue virus infection, when there was normal platelet count, was two times higher than the

likelihood ratio for having acute dengue virus infection, when there was thrombocytopenia. (Table II) In order to study how precise this estimate of likelihood ratios could be, we further analysed the data, firstly assuming all defaulted patients had acute dengue virus infection and secondly, assuming they did not have dengue infection. The likelihood ratios were lower when we assumed the defaulters had acute dengue virus infection but the ratios did not change much if we assumed that they did not have dengue infection. (Table II)

DISCUSSION

Thrombocytopenia occurred in 87.5% of patients with acute dengue infection. The finding of high percentage of dengue patients with thrombocytopenia in our study was also noted in other studies involving adult dengue patients^{2,6,7,11}. It ranges from 67.9% to 97%. Studies that defined thrombocytopenia as less than 100X10⁹/L^{2,11} had lower percentage of dengue patients with thrombocytopenia compared to studies which define thrombocytopenia as less than 140 X10⁹/L^{6,7}. This is logical as the higher the level of thrombocytopenia used in its definition, the higher percentage of dengue patients with thrombocytopenia.

Even though there was high percentage of dengue patients with thrombocytopenia, we should still exercise caution in relying on the presence of thrombocytopenia in diagnosing a patient with dengue infection as it has low sensitivity and specificity (both were <90%) in diagnosing dengue infection. From our study, both the (+)LRd and (-)LRn were less than 10. Hence it reiterates that thrombocytopenia is not an ideal screening test to either rule in or rule out dengue infection^{9,10}. However, presence of thrombocytopenia among patients with acute non-specific febrile illness increases the odds of dengue by three times and absence of thrombocytopenia decreases the odds by almost six times among patients with acute non-specific febrile illness. This shows that thrombocytopenia is more useful as the criterion in ruling out acute dengue infection virus than diagnosing dengue infection. This is easily understood as only 8.57% of patients with normal platelet count had acute dengue virus infection, while there were as many as 44.7% of patients with thrombocytopenia who did not have dengue infection. However, in the absence of thrombocytopenia, we should consider other clinical features of dengue infection like nausea, vomiting, abdominal pain, duration of fever more

Table I: Platelet count results and their dengue serology status among 73 patients with complete data

Platelet count status	Dengue serology		Total
	Positive	Negative	
Thrombocytopenia (<150 X 10 ⁹ /L)	21	17	38
Normal platelet count	3	32	35
Total	24	49	73

Table II: Comparing validity and predictive values of thrombocytopenia in diagnosing acute dengue virus infection among different categories of analysis

Category of analysis	Sensitivity (%)	Specificity (%)	(+)LRd*	(-)LRn‡
Among 73 patients with complete data	88	65	2.52	5.22
Assuming defaulted patients had dengue infection	66	71	1.90	1.91
Assuming defaulted patients did not have dengue infection	88	67	2.63	5.33

* the likelihood ratio for disease for a positive result

‡ the likelihood ratio for no disease for a negative result

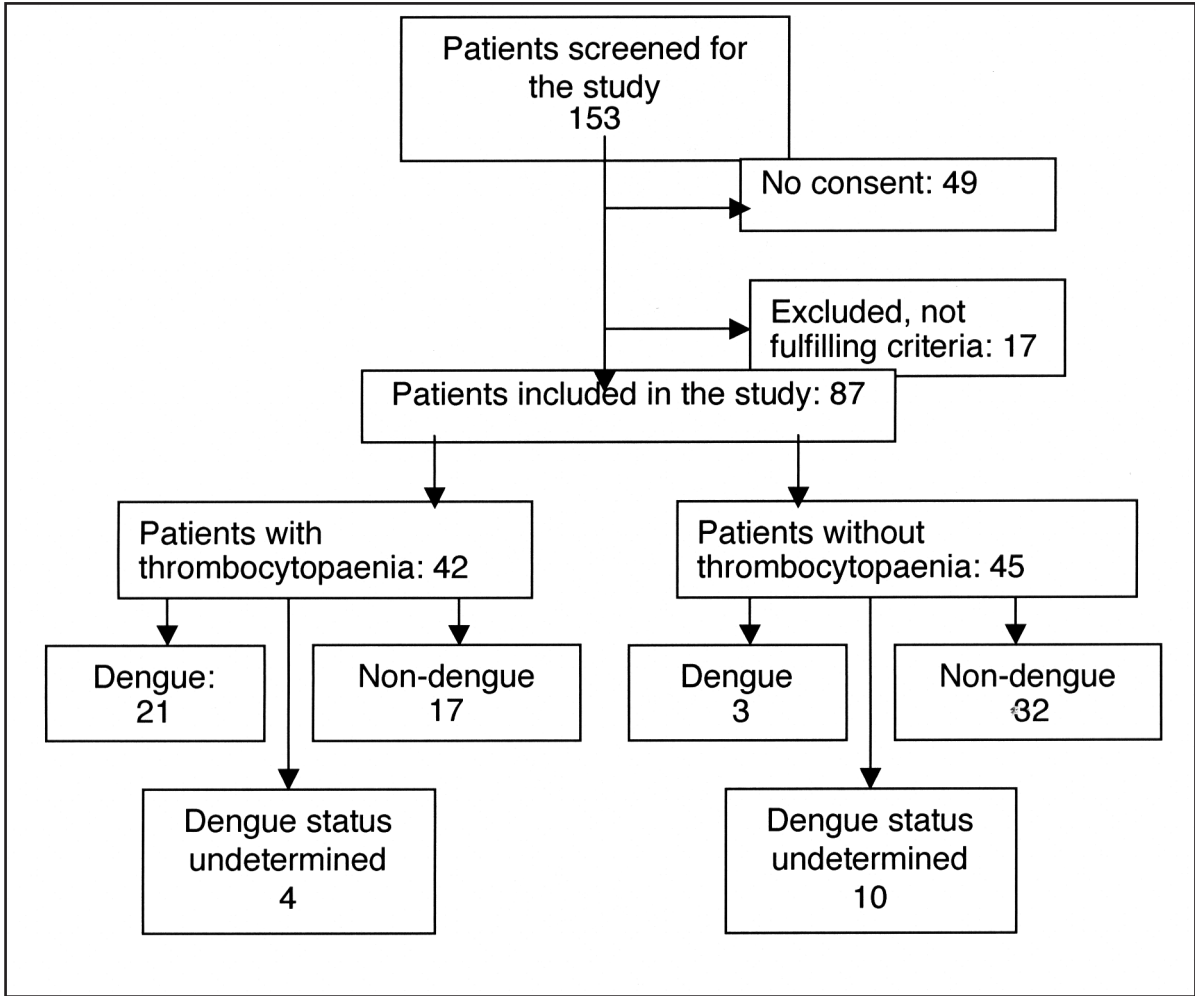


Fig. 1: Patient enrolment in the study.

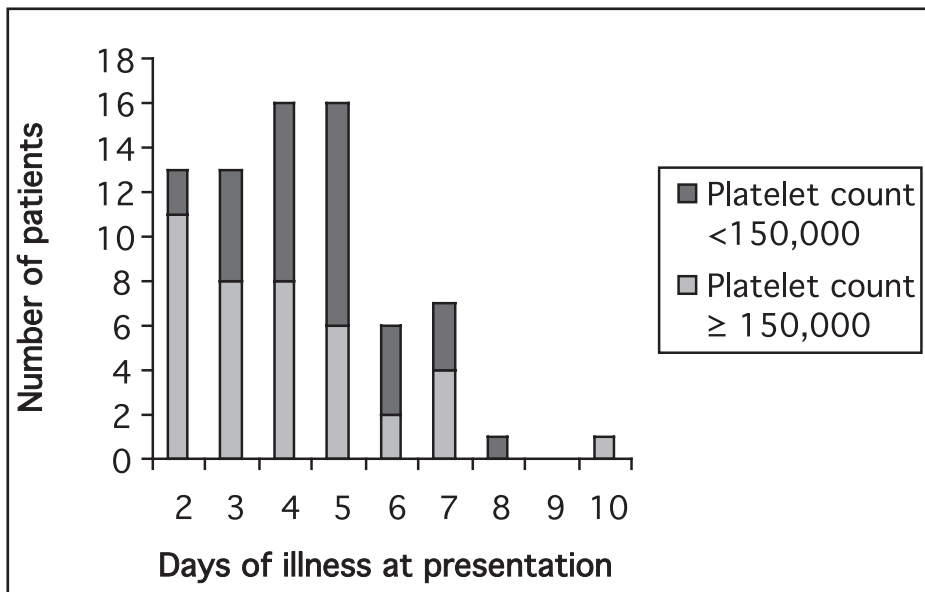


Fig. 2: Occurrence of thrombocytopenia with respect to days of illness at presentation.

then three days¹² and leukopenia¹³ before dismissing a case of dengue infection. These clinical features are significantly associated with acute dengue virus infection.

In the analysis of intention to treat, the likelihood ratios were reduced when all defaulters were assumed to have acute dengue virus infection but they remained unchanged when we assumed them not to have acute dengue virus infection. The later situation was more likely as all defaulters claimed to be well and refused reassessment. In this study a third of the patients had acute dengue virus infection. Assuming a third of the defaulters had acute dengue virus infection, the +LR(d) and -LR(n) improved to 3.10 and 6.64 respectively. This means thrombocytopenia is even a better criterion in excluding than diagnosing acute dengue virus infection. Hence, likelihood ratios estimated using the only available complete data would represent the true situation.

However, we have to be cautious in interpreting this data. Panbio Rapid Immunochromatography test kit was used as the diagnostic tool in this study. This test kit is routinely used in the microbiology laboratory of Hospital Universiti Kebangsaan Malaysia for the diagnosis of acute dengue virus infection. Serology results from this test kit are not the gold standard in the diagnosis of acute dengue virus infection. Antigen detection by polymerase chain reaction, viral culture or paired serology should be used instead¹⁴. Therefore, even though Panbio Rapid Immunochromatography test kit has very good sensitivity and specificity, false positive and negative test results do occur. In reference to a local study by Lam *et al.*, the false negative rate of this Panbio Rapid test for acute dengue virus infection was 0% (sensitivity of 100%) and the false positive rate was 11% (specificity of 89%)¹⁵. Whereas, Vaughn *et al.* demonstrated that 80% of dengue patients would show a diagnostic level of secondary dengue infection by day 1 of defervescence using haemagglutination-inhibition test (HAI, in detecting IgG) which gave a false negative of 20%. Day of defervescence was defined as the day when the temperature dropped below 38°C which commonly occurs around day 5 to 7 of illness¹⁶. In the present study, dengue serology was done on day 5 of illness. Hence, by considering all the above factors, we estimated the diagnostic error from Panbio Rapid Immunochromatography test kit to be 11 to 20%.

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