

Comparison of Clinical and Biological/ Laboratory Findings of Malaria and Dengue Infection in Karachi. A Cross Sectional Survey

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ABSTRACT

Background: Malaria and dengue fever are among the most prevalent infectious diseases in tropical countries, with an approximated 219 and 50 million cases in the world, respectively. The proposed study sought to identify distinguishing clinical and biological variable of falciparum malaria and dengue.

Methodology: Between September and October 2021, a cross-sectional questionnaire survey was distributed to participants in Karachi via Google form. The closed ended, self-administered questionnaire assessed symptoms of malaria, and dengue fever.

Results: Of the 100 patients 67 tested positive for dengue, while 33 tested positive for falciparum malaria. Dengue positive patients had skin rash, arthralgia, retro-orbital pain, mild bleeding, thrombocytopenia and leucopenia whereas malaria positive patients had fever with chills along with splenomegaly. Other symptoms such as headache, fatigue, nausea, vomiting, myalgia, and dizziness did not differ significantly.

Conclusion: In conclusion, it is possible to distinguish between dengue and malaria infections using clinical and laboratory data. These findings must be confirmed through additional study across a range of geographic locations and time periods.

Keywords: Dengue, Malaria, Mild Bleeding, Retro-orbital pain, Thrombocytopenia, Leucopenia

INTRODUCTION

Dengue fever and malaria, the two prevalent arthropod-borne diseases, which has emerged as the significant public health problems in tropical areas (1, 2). Dengue viruses and Plasmodium parasites are common in American and Asian inter - tropical convergence regions, in which their highly prevalent areas overlap significantly. Even though their pathogenesis varies, but their clinical and biological manifestations are similar, which makes it difficult to differentiate between the two infections (3).

Dengue virus (DENV) is caused by a member of the Flaviviridae family and is spread by one of four serotypes: DENV-1, DENV-2, DENV-3, and DENV-4 (4). According to WHO estimates, approximately 50 to 100 million people in the world are infected with DF each year, leading to 500,000 hospitalizations and 20,000 deaths with 2.5 billion living in high-risk areas (5). Pakistan is at significant risk of dengue endemics due to its dense cities, water contamination, unsanitary conditions, large number of refugees, and low vaccination coverage (6).

Dengue virus disease ranges from a mild febrile illness known as dengue fever (DF) to a potentially fatal condition known as dengue haemorrhagic fever (DHF)/Dengue shock syndrome (DSS) (7). Dengue Fever begins with a sudden onset of a high fever after an incubation period of 3-15 days (usually 5 to 8). It is a self-limiting infection characterized by incapacitating symptoms such as headache, retro-orbital pain, myalgia, arthralgia, petechiae rash, and leucopenia. A macular-papular recovery rash appears 3-5 days after fever onset and usually begins on the trunk before spreading peripherally (8).

Malaria is a protozoan that belongs to the Plasmodium species group which consist of multiple subspecies. Of these, four are believed to infect humans: P. falciparum, P. vivax, P. ovale, and P. malaria (9). In terms of morbidity and mortality, P. falciparum is the most severe of the four Plasmodium species, followed by P. vivax (10), with proportions of 60% and 40%, respectively, in several developing countries (11, 12). Malaria is a major health concern in tropical and subtropical regions, affecting approximately 3.3 billion people around the world (13). Malaria mortality rates range from 0.3-2.2% worldwide, with cases of severe malaria ranging from 11-30% in tropical climate regions (14). According to WHO in 2015, P.vivax malaria accounts for up to 75% of all malaria cases, with the majority of cases occurring in South East Asia (74%)(15).

Malaria is an acute febrile illness occurring at all age groups. A non-immune person experiences symptoms seven days or longer (typically between 10 and 15 days) following the infectious mosquito bite. The initial signs of malaria, including fever, headache, chills, and vomiting, can be mild and challenging to identify. P. falciparum malaria can advance to a serious infection that frequently is fatal if not managed within 24 hours. A few of the following symptoms are frequently present in children with severe malaria: cerebral malaria, severe anemia, respiratory distress related to metabolic acidosis (16).

Although rapid laboratory tests have recently been developed (17, 18), their availability is costly, and in endemic areas, the majority of diagnoses are made using clinical and epidemiological criteria in Southeast Asia (19). Although there is some evidence that clinical signs and symptoms change as the disease progresses, only a small number of those studies included information on the disease's stage at the time of clinical evaluation (19). As a result, it was challenging to compare the results and identify features that would help with early diagnosis.

The proposed study, "Differentiating clinical and laboratory features in malaria and dengue patients," was conducted in order to determine the feedback which could be of assistance in the differential diagnosis of dengue and malaria because many symptoms and clinical features are shared by falciparum malaria and dengue.

MATERIAL AND METHODS

Participants: A self-administered online questionnaire was used to collect data for a cross-sectional observational study on participants from Karachi who had previously experienced dengue fever or malaria and were between the ages of 10 to 70. Over the course of three weeks questionnaires were distributed in the presence of the study teams. After being fully informed of the study's goals and their participation in it, the participants verbally consented to participate. Between September and October 2021, the information was gathered using a web-based survey created with Google Forms. The sampling was done at random. The selective age group does not discriminate against anyone or have pre-determined standards for gender or marital status.

Inclusion criteria: All the diagnosed participants in the study ranged in age from 10 to 70 years old, were Karachi residents, regardless of gender, and had experienced dengue or fever in the previous three months.

Exclusion criteria: Participants who have a chronic medical condition or other febrile illness.

Design of the questionnaire: A questionnaire was created in order to meet the study's objectives. All of the survey questions were closed-ended.

The first section of the questionnaire included about their general demographics, such as their age, gender and marital status. The second section focuses on the clinical symptoms of dengue and malaria. The third section included the laboratory findings

Statistical analysis: The data entry and analysis of the collection data were done using SPSS version 23.0 on mac OS X (operating system). Before each questionnaire was submitted, it was extensively examined for missing data or information. All surveys that were missing relevant information were cleansed. The mean and standard deviation were employed for continuous variables, whereas data, \pm The Chi-Square test was performed to assess the time spent by the participant on his/her phone at home with pain in joints, pain in participant's muscles, hearing discomfort, headache private life of the participants

A p value of 0.05 was implemented as a threshold for significance.

RESULTS

The age, gender, and marital status criteria were mentioned in the demographic analysis. There were 100 participants in total with a mean age of 29.64 ± 9.93 , divided into five age groups: 10-20 years, 21-30 years, 31-40 years, 41-50 years, and 51-60 years.

Table 1: Demographic Data of the study Participants

Factor	Mean \pm S.D. / n (%)
Mean \pm S.D. Age (years)	29.64 ± 9.93
Gender	(n) %
Male	74 (74)
Female	26 (26)
Marital Status	(n) %
Married	78 (78)
Unmarried	22 (22)
Total subjects: 100 Data is presented as Mean \pm SD and percentage	

Table 2: Comparison between clinical variables of Dengue and Malaria

Clinical Variables	Dengue	Malaria	p-value
Fever			
> 5 days	33	24	0.04
< or = 5 days	34	9	
Headache			
Yes	54	26	0.76
No	13	07	
Retro-orbital pain			
Yes	58	19	0.005*
No	09	14	
Fatigue/Tiredness			
Yes	58	26	0.218
No	09	07	
Arthralgia			
Yes	61	18	0.000*
No	06	15	
Myalgia			
Yes	63	27	0.154
No	04	06	
Chills			
Yes	15	29	0.000*
No	50	04	
Rash			
Yes	61	02	0.000*
No	06	31	
Nausea/Vomiting			
Yes	57	27	0.773
No	10	06	
Dizziness			
Yes	48	27	0.505
No	19	06	
Mild bleeding			
Yes	36	09	0.044*
No	31	24	

Sore-throat/Dry cough			
Yes	23	21	0.013*
No	44	12	
Data is presented as Mean \pm SD Chi-square was applied p value < 0.05 was considered significant			

Table 3: Comparison between Biological/laboratory parameter of Dengue and Malaria

Laboratory Parameters	Dengue	Malaria	p-value
Hemoglobin	33	24	0.04
< 11	34	9	
> 11			
Platelet per microliter	52	15	0.025*
< 150,000	14	17	
150,000 to 450,000	01	01	
> 450,000			
WBC per microliter	45	11	0.000*
< 4000	20	22	
4000 to 11,000	02	00	
> 11,000			
Splenomegaly			0.002*
Yes	09	28	
No	56	05	
Data is presented as Mean \pm SD Chi-square was applied p value < 0.05 was considered significant			

Patients with malaria were significantly older than those with dengue (32.3 years (± 7.4) vs. 26.0 years (± 7.32) respectively; $p < 0.05$). Our survey found that 11% of participants were between the ages of 10 and 20, 50% were between the ages of 21 and 30, 26% were between the ages of 31 and 40, 7% were between the ages of 41 and 50, and only 6% were between the ages of 51 and 60.

Fever > 5 days and $\geq 40^\circ\text{C}$, chills, dizziness, and splenomegaly were more frequent in malaria patients. On the contrary, retro-orbital pain, arthralgia rash, mild bleeding, thrombocytopenia and leucopenia were associated with DF. However, there were no differences between the two groups in terms of headache, fatigue, myalgia, nausea and vomiting.

DISCUSSION

In terms of prevalence and mortality rates, malaria and dengue are both regarded to be growing exponentially. These mosquito-borne diseases present a global public health concern due to their ease of spread around the world (20, 21).

In the present study, males outnumbered females, as they have in other studies from Pakistan, India, and other South East Asian countries. It's possible that males are spending more time outside than females in these areas, increasing the likelihood of mosquito bites (22). However, a research performed in Vietnam disclosed a small difference in male female ratio, most likely due to equal access to mosquito bites as a result of their social and cultural differences from our study (23).

Dengue and Malaria fever are difficult to diagnose in patients due to clinical similarities. Patients with malaria and dengue fever usually had high grade fevers, as had previously been observed in Saudi Arabia, Pakistan, and India. (24-26). The main clinical features of *P. vivax* and *P. falciparum* malaria patients were fever with chills, and rigour. Our findings were consistent with those of et Tangpukdee et al., who observed similar symptoms in malaria patients (27).

In our study, dengue had slightly higher rates of headache, nausea, and vomiting than falciparum malaria and these symptoms were reported in 80% and 82% of dengue patients in Karachi, respectively. Similarly, a study conducted in Makkah found that patients had a higher incidence of headache (75%) and nausea (69%) (28). Another significant finding from our study, when compared to malaria, was the manifestation of retro-orbital pain, skin rash and mild bleeding as a predictor of dengue in all age groups. The discovered relationship between retro-orbital pain, skin rash and mild bleeding with dengue is consistent with the literature (29, 30). Previous studies that combined retro-orbital

pain with headache found no link (19), whereas studies that investigated retro-orbital pain independently found an association similar to our study (31). On the other hand, when compared to malarial cases, dengue cases were attributed with mild bleeding. Other research findings, including a surveillance study of the 2011 dengue outbreak in Manderla, Kenya, found these to be directly correlated with dengue (30, 32, 33).

Our survey found no significant difference in the incidence of dengue and malaria fatigue. The exact mechanism by which dengue and malaria cause fatigue is unknown. It is possible that the complicated immunological response elicited by infection causes an inordinate amount of inflammatory cytokines during the acute phase, and that the interaction of these cytokines with the neurohormonal, musculoskeletal, and immune systems contributes to fatigue. These associations might be influenced by host genetic factors, illness, personality traits, and susceptibility to psychological trauma (34).

Arthralgia was found comparatively in fewer malaria patients than in the dengue infection group, however myalgia was equally common in both the participants. In the comparative study, Verma et al discovered that arthralgia was present in the dengue group, whereas no patients suffering from malaria complained of arthralgia (35). According to Chan et al., the study results revealed a significant association between DENV 3 and muscle aches (36). Correspondingly, Hasley et al (2012) discovered that DENV 3-infected patients had prevalent myalgia and arthralgia symptoms (37). As a result, it has been hypothesized that DENV 3 has an increased preference and binding affinity for receptors in the musculoskeletal, narrowing it down even farther that variants I targets muscles and genotype III targets joints (38).

In the current study, thrombocytopenia was more common in malaria infected patients than in dengue patients. Both infections are characterized by a low platelet count. As previously reported, the extent of thrombocytopenia did not vary by malaria species. Platelet counts seem to fall very soon during the clinical course of malaria infection and stay low for around a week. Even if the infection is not managed, the count appear to rise slowly after the first week (39). When seeking a dengue diagnosis, physicians frequently wait for a 2nd platelet count at least 24 hours after the initial to see whether the counts decline as a lead to a dengue diagnosis, which therefore delays screening for alternative diseases such as malaria (40). Malaria and dengue fever are mosquito-borne infections that are rapidly spreading and present serious health concerns. Because the symptoms of these two infections are very similar, they are frequently misdiagnosed.

In a study conducted in southern India, the arguments for malaria attack were normal WBC, moderate to severe thrombocytopenia, and splenomegaly, whereas criteria for DF were normal to low WBC, moderate to severe thrombocytopenia, and rare splenomegaly (41).

Malaria and dengue fever are mosquito-borne infections that are rapidly spreading and present serious health concerns. Because the symptoms of these two infections are very similar, they are frequently misdiagnosed (42). As a result, this study may aid in distinguishing between two infections to the point where mortality may be reduced.

CONCLUSION

It is therefore concluded that simple clinical and laboratory data can be used to distinguish dengue from malarial infections. Further research is needed to validate these results across different geographical regions and periods of time. If the concepts conduct effectively in these settings over time, they might be used to establish clinical diagnostic algorithms.

Conflicts of Interest: The authors reflect no conflict of interest.

REFERENCES

1. Pal M. Dengue fever: An emerging and re-emerging viral disease of major public health importance. *Madridge J Immunol*. 2018;2(1):51-2.

2. Mordecai EA, Ryan SJ, Caldwell JM, Shah MM, LaBeaud AD. Climate change could shift disease burden from malaria to arboviruses in Africa. *The Lancet Planetary Health*. 2020;4(9):e416-e23.
3. Epelboin L, Hanf M, Dussart P, Ouar-Epelboin S, Djossou F, Nacher M, et al. Is dengue and malaria co-infection more severe than single infections? A retrospective matched-pair study in French Guiana. *Malaria journal*. 2012;11(1):1-8.
4. Khan NU, Danish L, Khan HU, Shah M, Ismail M, Ali I, et al. Prevalence of dengue virus serotypes in the 2017 outbreak in Peshawar, KP, Pakistan. *Journal of Clinical Laboratory Analysis*. 2020;34(9):e23371.
5. Idrees S, Ashfaq UA. A brief review on dengue molecular virology, diagnosis, treatment and prevalence in Pakistan. *Genetic Vaccines and Therapy*. 2012;10(1):1-10.
6. Jahan F. Dengue fever (DF) in Pakistan. *Asia pacific family medicine*. 2011;10(1):1-4.
7. Drumond BP, Mondini A, Schmidt DJ, Bronzoni RVdM, Bosch I, Nogueira ML. Circulation of different lineages of Dengue virus 2, genotype American/Asian in Brazil: dynamics and molecular and phylogenetic characterization. *PLoS one*. 2013;8(3):e59422.
8. Halsey ES, Williams M, Laguna-Torres VA, Vilcarromero S, Ocaña V, Kochel TJ, et al. Occurrence and correlates of symptom persistence following acute dengue fever in Peru. *The American journal of tropical medicine and hygiene*. 2014;90(3):449.
9. Bedane AS, Tanto TK, Asena TF. Malaria distribution in Kucha district of Gamo Gofa Zone, Ethiopia: a time series approach. *American Journal of Theoretical and Applied Statistics*. 2016;5(2):70-9.
10. Hay SI, Guerra CA, Tatem AJ, Noor AM, Snow RW. The global distribution and population at risk of malaria: past, present, and future. *The Lancet infectious diseases*. 2004;4(6):327-36.
11. Talapko J, Škrlec I, Alebić T, Jukić M, Včev A. Malaria: the past and the present. *Microorganisms*. 2019;7(6):179.
12. Ketema T, Bacha K, Birhanu T, Petros B. Chloroquine-resistant Plasmodium vivax malaria in Serbo town, Jimma zone, south-west Ethiopia. *Malaria journal*. 2009;8(1):1-8.
13. French L, Gray T, Natarajan P. Malaria: prevention and treatment. *InnovAIT*. 2014;7(4):224-32.
14. White N, Pukrittayakamee S, Hien T, Faiz M, Mokuolu O, Dondorp A. Erratum: Malaria (The Lancet (2014) 383 (723-735)). *The Lancet*. 2014;383(9918).
15. WHO. WORLD MALARIA REPORT. WHO REPORT. 2015.
16. Kleinschmidt I, Schwabe C, Benavente L, Torrez M, Ridl FC, Segura JL, et al. Marked increase in child survival after four years of intensive malaria control. *The American journal of tropical medicine and hygiene*. 2009;80(6):882.
17. Shu P-Y, Yang C-F, Kao J-F, Su C-L, Chang S-F, Lin C-C, et al. Application of the dengue virus NS1 antigen rapid test for on-site detection of imported dengue cases at airports. *Clinical and Vaccine Immunology*. 2009;16(4):589-91.
18. Zainah S, Wahab AA, Mariam M, Fauziah M, Khairul A, Roslina I, et al. Performance of a commercial rapid dengue NS1 antigen immunochromatography test with reference to dengue NS1 antigen-capture ELISA. *Journal of virological methods*. 2009;155(2):157-60.
19. Potts JA, Rothman AL. Clinical and laboratory features that distinguish dengue from other febrile illnesses in endemic populations. *Tropical Medicine & International Health*. 2008;13(11):1328-40.
20. Khan E, Khat M, Khan N, Nasir A, Ayub S, Hasan R. Demographic and clinical features of dengue fever in Pakistan from 2003–2007: a retrospective cross-sectional study. *PLoS one*. 2010;5(9):e12505.
21. Suwanbamrung C. Developing the active larval indices surveillance system for dengue solution in low and high dengue risk primary care units, Southern Thailand. *Journal of Health Research*. 2018;32(6):408-20.
22. Anker M, Arima Y. Male–female differences in the number of reported incident dengue fever cases in six Asian countries. *Western Pacific surveillance and response journal: WPSAR*. 2011;2(2):17.
23. Thai KT, Phuong HL, Nga TTT, Giao PT, Van Nam N, Binh TQ, et al. Clinical, epidemiological and virological features of Dengue virus infections in Vietnamese patients presenting to primary care facilities with acute undifferentiated fever. *Journal of Infection*. 2010;60(3):229-37.
24. Hasan SR, Riaz M, Jafri FA. Characteristics and outcome of dengue infection; clinical perspective from a secondary care hospital of Karachi. *Pakistan journal of medical sciences*. 2013;29(1):115.
25. Gurumurthy R, Gayathri K, Seethamma R, Bhargav P. Clinical spectrum and course of dengue fever during pregnancy: Institutional

- experience from south india. IOSR Journal of Dental and Medical Sciences. 2014.
26. Banzai S, Ayoola E, Sammani EE, Rahim S, Subramaniam P, Gadour M, et al. The clinical pattern and complications of severe malaria in the Gizan region of Saudi Arabia. *Annals of Saudi medicine*. 1999;19(4):378-80.
27. Tangpukdee N, Charunwatthana P, Boonnak K, Krudsood S, Kano S, Wilairatana P, et al. Mimicking platelet indices in patients with malaria and dengue hemorrhagic fever: characteristics and clinical applications. *Tropical Medicine and Health*. 2022;50(1):1-10.
28. Khan NA, Azhar EI, El-Fiky S, Madani HH, Abuljadial MA, Ashshi AM, et al. Clinical profile and outcome of hospitalized patients during first outbreak of dengue in Makkah, Saudi Arabia. *Acta tropica*. 2008;105(1):39-44.
29. Kularatne S, Gawarammana I, Kumarasiri P. Epidemiology, clinical features, laboratory investigations and early diagnosis of dengue fever in adults: a descriptive study in Sri Lanka. *Southeast Asian Journal of Tropical Medicine and Public Health*. 2005;36(3):686.
30. Guo C, Zhou Z, Wen Z, Liu Y, Zeng C, Xiao D, et al. Global epidemiology of dengue outbreaks in 1990–2015: a systematic review and meta-analysis. *Frontiers in cellular and infection microbiology*. 2017;7:317.
31. Ramos MM, Tomashek KM, Arguello DF, Luxemburger C, Quiñones L, Lang J, et al. Early clinical features of dengue infection in Puerto Rico. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 2009;103(9):878-84.
32. Obonyo M, Fidhow A, Ofula V. Investigation of laboratory confirmed Dengue outbreak in North-eastern Kenya, 2011. *PLoS one*. 2018;13(6):e0198556.
33. Ramos-De La Medina A, Remes-Troche JM, González-Medina MF, Cerón T, Zamudio C, Díaz-Vega A. Abdominal and gastrointestinal symptoms of Dengue fever. Analysis of a cohort of 8559 patients. *Gastroenterología y hepatología*. 2011;34(4):243-7.
34. Sigera PC, Rajapakse S, Weeratunga P, De Silva NL, Gomes L, Malavige GN, et al. Dengue and post-infection fatigue: findings from a prospective cohort—the Colombo Dengue Study. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 2021;115(6):669-76.
35. Verma RK, Giri R, Singh N, Gupta C, Jain A. A study on clinical presentation and outcome of concurrent malaria and dengue infection from a malaria endemic zone of North India. *J Med Sci Clin Res*. 2016;4(12):15116-27.
36. Chan K-S, Chang J-S, Chang K, Lin C-C, Huang J-H, Lin W-R, et al. Effect of serotypes on clinical manifestations of dengue fever in adults. *J Microbiol Immunol Infect*. 2009;42(6):471-8.
37. Halsey ES, Marks MA, Gotuzzo E, Fiestas V, Suarez L, Vargas J, et al. Correlation of serotype-specific dengue virus infection with clinical manifestations. *PLoS neglected tropical diseases*. 2012;6(5):e1638.
38. Suppiah J, Ching S-M, Amin-Nordin S, Mat-Nor L-A, Ahmad-Najimudin N-A, Low GK-K, et al. Clinical manifestations of dengue in relation to dengue serotype and genotype in Malaysia: A retrospective observational study. *PLoS neglected tropical diseases*. 2018;12(9):e0006817.
39. Lacerda MVG, Mourão MPG, Coelho HCC, Santos JB. Thrombocytopenia in malaria: who cares? *Memórias do Instituto Oswaldo Cruz*. 2011;106:52-63.
40. Karunaratna S, Ranaweera D, Vitharana H, Ranaweera P, Mendis K, Fernando D. Thrombocytopenia in malaria: A red-herring for dengue, delaying the diagnosis of imported malaria. *Journal of Global Infectious Diseases*. 2021;13(4):172.
41. Chrispal A, Boorugu H, Gopinath KG, Chandy S, Prakash JAJ, Thomas EM, et al. Acute undifferentiated febrile illness in adult hospitalized patients: the disease spectrum and diagnostic predictors—an experience from a tertiary care hospital in South India. *Tropical doctor*. 2010;40(4):230-4.
42. Bin Asad MHH, Nazir H, Khalid S, Bibi S, Afzal K, Al-Kharaman YM, et al. Erupt of malaria, dengue and chikungunya in Pakistan: Recent insights about prevalence, diagnosis and treatment. *Pakistan Journal of Pharmaceutical Sciences*. 2019;32(4).