JPSIM Journal of Pakistan Society of Internal Medicine

Original Article

Muscular Involvement in Dengue Fever: Clinical Spectrum and Pathophysiological Mechanisms

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Abstract

Objective: To determine the prevalence and clinical characteristics of muscular involvement in dengue infection, including myalgia, myositis, rhabdomyolysis, and hypokalaemic paralysis, by evaluating clinical presentations and laboratory parameters—particularly creatine phosphokinase (CPK) levels—in patients presenting to the outpatient department and those admitted to the dengue ward.

Methods: We conducted a prospective descriptive study including 75 patients with confirmed dengue fever. Demographic, clinical, and biochemical data were collected. Muscular involvement was classified as myalgia, myositis, rhabdomyolysis, or hypokalemic paralysis. Creatine phosphokinase (CPK) levels and other laboratory parameters were recorded. Associations were assessed using chi-square/Fisher's exact tests, Mann–Whitney U test, and odds ratios with 95% confidence intervals.

Results: The mean age of participants was 36.8 ± 16.5 years; 70.7% were male. Elevated CPK was observed in 48.0% of patients. Rhabdomyolysis occurred exclusively in those with elevated CPK (22.2% vs. 0.0%; Fisher's exact $p = 0.0018$; OR = 22.3, 95% CI 1.23–404.2). Muscle weakness was significantly more common in patients with elevated CPK (44.4% vs. 5.1%; $\chi^2 = 13.78$, $p < 0.001$; OR = 14.8, 95% CI 3.09–70.95). No significant association was found between CPK status and self-reported muscle pain ($p = 0.968$). No participants exhibited electrolyte imbalance.

Conclusion: Muscular complications, including rhabdomyolysis and weakness, are significantly associated with elevated CPK in dengue fever. Routine CPK monitoring may help in early detection of severe muscular involvement. Larger, multicenter studies are warranted.

Keywords: Dengue Fever; Myositis; Rhabdomyolysis; Creatinine Phosphokinase.

How to cite this:

Munir A, Zeb S, Majid A, Hafsa. Muscular Involvement in Dengue Fever: Clinical Spectrum and Pathophysiological Mechanisms. J Pak Soc Intern Med. 2026;7(3): 257-261

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Received: 23-02-2026 **Revised:** 03-06-2026 **Accepted:** 12-08-2026 **DOI:** https://doi.org/10.70302/jpsim.v7i3.2648

Introduction

Dengue fever is caused by the dengue virus (DENV), which has four serotypes (DENV1, DENV2, DENV3, and DENV4). The virus is transmitted through the bite of female Aedes aegypti mosquitoes. Transmission occurs when an infected mosquito bites a new host after feeding on the blood of an infected individual. Dengue fever can affect individuals of all ages and can be life-threatening if it progresses to severe dengue. Symptoms include fever, flu-like symptoms, eye pain, dengue haemorrhagic fever, circulatory failure leading to shock, thrombocytopenia (low platelet count), and anaemia (low red blood cell count).[1]

A study estimates that approximately 3.9 billion people are at risk of contracting dengue. While 128 countries are vulnerable, the majority of the susceptible population (70%) resides in Asia.[2] In Pakistan, between 1 January and 27 September 2022, the National Institute of Health-Islamabad recorded a total of 25,932 confirmed dengue cases and 62 deaths across the country. As of 22 September, data on the distribution of cases by province were available for 83% (21,777 cases) of the total. Among these, 32% (6,888 cases) were reported in Sindh, 29% (6,255 cases) in Punjab (including Islamabad Capital Territory), 25% (5,506 cases) in Khyber Pakhtunkhwa, and 14% (3,128 cases) in Balochistan.[3]

Myalgia, or muscle pain, is a common early symptom of dengue fever, typically affecting the back and proximal limb muscles, and is experienced by up to 93% of patients.[4] A large study in Peru, Bolivia, Ecuador, and Paraguay found that 90.1% of 1716 confirmed dengue cases had myalgia.[5] Among 334 laboratory-positive US residents who travelled to endemic areas, only 30% reported myalgia.[6]

Myositis refers to the inflammation of skeletal muscles and is clinically characterized by motor weakness in all four limbs. Though limited studies are available that address the prevalence of myositis in dengue patients, one study puts this value at 4%. Dengue-associated myositis can vary in severity, from mild muscle weakness to severe cases leading to quadriplegia and respiratory failure, with some cases resulting in death. Concomitant myocarditis has also been reported. [7,8]

Rhabdomyolysis, a condition where skeletal muscle breaks down, releasing creatine phosphokinase (CPK) into the bloodstream, has been observed in some dengue patients, although it is rare. Despite the global impact of dengue, few clinical studies and case reports address rhabdomyolysis in dengue infections. CPK levels are not routinely tested unless there is a strong clinical suspicion. Studies have shown that rhabdomyolysis is associated with acute kidney injury (AKI) in 15.6% to 35.8% of cases, and it is an independent risk factor for AKI.[9]

In patients with dengue, myositis and rhabdomyolysis may be present concurrently. In a case report, a 21-year-old patient presented with severe myalgia, bilateral upper and lower limb weakness, and a raised CPK; MRI confirmed myositis and myonecrosis; nerve conduction studies showed bilateral lower limb and axillary sensory motor neuropathy. Conservative management, including IV fluids, analgesics, plasmapheresis, and antibiotics, resulted in uneventful recovery.[10]

Hypokalemic paralysis, another potential complication of dengue fever, can present with acute severe flaccid paralysis of both lower and upper limbs. Hypokalemic paralysis in dengue is attributed to a combination of transient intracellular potassium shift, renal potassium wasting and reversible tubular dysfunction.[11] An important differential to consider is Guillain-Barré syndrome, as both present with acute flaccid paralysis and hyporeflexia, but the hypokalemic paralysis responds rapidly to potassium supplements while GBS requires IV immunoglobulins. Studies have shown that up to 70 % of dengue patients have hypokalemia to some extent only a few progress into overt paralysis. [12]

While myalgia is common, its correlation with objective markers of muscle damage like CPK is poorly understood. Furthermore, the prevalence of severe complications like rhabdomyolysis in a systematic cohort, and their predictive factors, remain undefined. This study aims to quantitatively define the spectrum of muscular involvement in dengue and its correlation with CPK levels.

Objective: To determine the prevalence and clinical characteristics of muscular involvement in dengue infection, including myalgia, myositis, rhabdomyolysis, and hypokalaemic paralysis, by evaluating clinical presentations and laboratory parameters—particularly creatine phosphokinase (CPK) levels—in patients presenting to the outpatient department and those admitted to the dengue ward.

Methods

This prospective descriptive study was conducted in the Dengue Unit, Lady Reading Teaching Hospital, Peshawar, over a period of six months following approval of the synopsis. The sample size of 75 was calculated using the OpenEpi sample size calculator, based on a 95% confidence level, 5% margin of error, and an assumed population proportion of 4%.[6] Patients were enrolled through consecutive non-probability sampling.

Patients with a confirmed diagnosis of dengue fever, established by NS1 antigen or IgM serology, were included. Both male and female patients aged between 12 and 60 years, presenting within the first seven days of symptom onset, were eligible. Patients with pre-existing neuromuscular disorders such as myasthenia gravis, those with chronic diseases that could independently cause muscle weakness or pain such as chronic kidney disease or hypothyroidism, and those taking medications affecting muscle or potassium metabolism, including statins, corticosteroids, or diuretics, were excluded. Patients with other identified causes of hypokalaemia, such as diarrhoea, vomiting, or diuretic use, as well as those unwilling to provide informed consent, were also excluded.

Data were collected using a structured proforma, which included demographic information such as age, gender, and dengue status, along with detailed questions exploring muscular involvement in dengue fever. Written informed consent was obtained from all participants. The study was conducted after approval from the Institutional Review Board (IRB) of LRH, and permission was obtained from the head of the department prior to data collection. Confidentiality of participant data was ensured, with

storage on a password-protected computer. Clinical assessment included documentation of muscle pain severity, muscle weakness (graded using the Medical Research Council scale), and laboratory investigations. Rhabdomyolysis was diagnosed in patients with CPK >5× the upper limit of normal with compatible clinical features. Electrolyte levels, renal function, and other relevant laboratory parameters were measured. Data were analyzed using SPSS version 25. Continuous variables were expressed as mean ± SD or median (IQR), and categorical variables as frequencies and percentages. Associations were examined using chi-square or Fisher's exact test for categorical data and Mann–Whitney U test for non-normally distributed continuous variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported where appropriate. A two-sided $p < 0.05$ was considered statistically significant.

Results

A total of 75 participants were included in the study, with a mean age of 36.8 years (SD = 16.5), and a median of 35.0 years (IQR 22.5–48.5). Among the study cases, 70.7% were male (Figure 1)

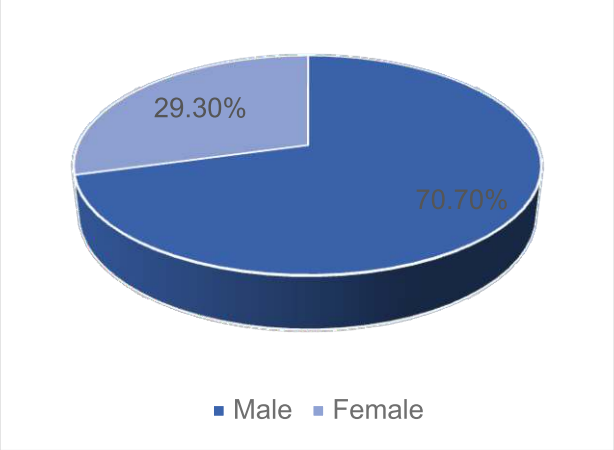

Figure 1: *Gender based distribution of study cases.*

Overall, 36 participants (48.0%) demonstrated elevated creatine phosphokinase (CPK) levels, while 39 (52.0%) had normal values. Electrolyte disturbances were not observed in any participant (0/75, 100%). Most participants reported mild muscle pain (n = 70, 93.3%), with a minority reporting moderate (n = 4, 5.3%) or severe pain (n = 1, 1.3%). Muscle weakness was documented in 18 participants (24.0%) and was absent in 57 (76.0%). Rhabdomyolysis was diagnosed in 8 participants (10.7%), while the remaining 67 (89.3%) did not meet diagnostic criteria. Paracetamol (acetaminophen) was the sole analgesic prescribed, administered to all participants requiring pain management (n = 75, 100%). Clinical characteristics are summarized in Table 2.

Rhabdomyolysis occurred exclusively among participants with elevated CPK (22.2% vs. 0.0%). Fisher's exact test confirmed a significant association ($p = 0.0018$; OR = 22.3, 95% CI 1.23–404.2). Muscle weakness was significantly more frequent in patients with elevated CPK (44.4% vs. 5.1%; $\chi^2 = 13.78$, $p < 0.001$; OR = 14.8, 95% CI 3.09–70.95). There was no association between CPK status and self-reported muscle pain ($p = 0.968$). Median CPK values were markedly higher among participants with rhabdomyolysis compared with those without (1155 vs. 130 U/L; Mann–Whitney U = 536.0, $p < 0.001$). No significant difference in age was observed between participants with elevated versus normal CPK ($p = 0.783$).

Table 1: *Baseline Demographic and clinical characteristics of the study cases*

Variable		n (%)
Age groups	<18 Years	11 (14.7)
	19 to 40 Years	34 (45.3)
	>40 Years	30 (40.0)
Gender	Male	53 (70.7)
	Female	22(29.3)
Elevated CPK		36 (48.0)
Normal CPK		39 (52.0)
Rhabdomyolysis	Yes	8 (10.7)
	No	67 (89.3)
Muscle weakness	Yes	18 (24.0)
	No	57 (76.0)
Electrolyte imbalance — Yes		0 (0.0)
Muscle pain — Mild	Mild	70 (93.3)
	Moderate	4 (5.3)
	Severe	1 (1.3)
Analgesia: Paracetamol		75 (100)

Discussion

Out of all the patients, with a positive serological diagnosis of dengue, nearly half had an increased CPK levels, while none had electrolyte imbalance. Rhabdomyolysis was identified in nearly 10% of the patients, and it was significantly associated with CPK. Muscle weakness was identified in nearly one-forth of the participants, and it was also significantly associated with CPK.

Myalgia is defined by pain, tenderness, and slight muscle swelling, with diffuse myalgia being a notable symptom in the early stages of dengue fever. In a comprehensive study involving 1716 confirmed dengue cases , 90.1% reported myalgia,[5] while another study found that 30% of 334 laboratory-positive US residents exhibited this symptom post-international travel,[6] with a higher prevalence in adults compared to pediatric patients.[13] In our study 93.2% of the patients reported mild while only 5.3% moderate and 1.3% severe myalgia. The precise mechanism underlying myalgia in dengue remains unclear, though it may be attributed to widespread viral infiltration of muscle tissues during viremia accompanied by subsequent inflammatory responses.

Myositis is characterized by inflammation of skeletal muscle, leading to pronounced motor weakness across all four limbs. In a cohort of 40 pediatric patients with benign acute myositis, 50% tested positive for the dengue virus, with 45% exhibiting significantly elevated CPK levels exceeding 1000 IU/L. 14 The severity of dengue-associated myositis spans from mild, self-resolving weakness to severe manifestations,including quadriplegia and respiratory failure, with concurrent myocarditis also reported and fatalities occurring in severe instances.[15,16]

Very few cases of rhabdomyolysis in dengue patients have been reported in the medical literature, Sargeant et al. reports a case in which a patient presented with acute febrile illness was admitted to the hospital, serological tests confirmed dengue infection. He was managed conservatively and on day 6 was subsequently discharged, on day 8 he suddenly developed heamaturia, he was found to have myoglobinuria and significantly raised CPK levels, confirming a diagnosis of rhabdomyolysis. He was managed with aggressive hydration and monitoring of urine output and renal functions; resulting in an uneventful recovery and was subsequently discharged.[17] Acharya et al. described another case in which a patient presented with fever, muscle pain and tenderness along with painful limb movements. The very next day he developed acute flaccid quadriparesis gradually involving the pharyngeal and respiratory muscles. Further investigations revealed deranged renal functions, raised serum and urine myoglobin confirming the diagnosis of rhabdomyolysis, IgM by ELISA was strongly positive for dengue.[18]

The above cases highlight the importance of recognizing the complications of dengue fever, with rhabdomyolysis being a rare but fatal one. We recommend observation and counselling of at risk patients, as muscle weakness, tenderness, painful movements or passing red colored urine may herald a possible outcome of rhabdomyolysis. CPK levels are crucial in such settings as they are significantly elevated in these patients.

Although none of our patients had electrolyte imbalance, hypokalaemia have been found in many patients with dengue elsewhere, rarely associated with acute flaccid paralysis, Hira et al. in a study in India reports that out of 88 patients admitted to dengue ward, 12 had neuromuscular weakness and 10 had some degree of hypokalemia, including 2 with severe (< 2.50 mEq/L).[19] Kayal et al. in a study in northeast India assessed 56 patients who presented with acute flaccid paralysis and hypokalemia, only 1 had confirmed dengue infection. In the above cases of hypokalemic paralysis, nearly all responded significantly to potassium supplementation, with the weakness resolving within 24 hrs.[20]

Our study has limitations. The main interest of this study is the involvement of skeletal muscle. We did not include the possible effects of dengue on smooth and cardiac muscles, including myocarditis and autonomic dysfunction, and these should be evaluated in future studies. Our study was conducted at a single center with a modest sample size, which may limit generalizability. The cross-sectional design precludes causal inference. The findings provide important preliminary evidence and highlight the need for larger multicenter studies.

Conclusion

In conclusion, muscular complications, including rhabdomyolysis and weakness, are associated with elevated CPK in dengue fever. Routine CPK monitoring should be considered in patients with dengue, particularly those presenting with muscle weakness, to facilitate early recognition and management of severe muscular involvement.

Ethical Approval: The IRB/EC approved this study via letter no. 46/LRH/MTI dated January 17, 2025.

Conflict of Interest: None

Funding Source: None

Authors' Contribution

AM: Conception.

SZ: Design of the work.

AMa, H: Data acquisition, analysis, or interpretation.

AM, AMa, H: Draft the work.

SZ: Review critically for important intellectual content.

All authors approve the version to be published.

All authors agree to be accountable for all aspects of the work.

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