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Original Research Article

A Clinical Study of Acute Kidney Injury in Patients with Acute Febrile Illness with Thrombocytopenia

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Abstract

Background: Infectious diseases significantly contribute to morbidity and mortality in our country, with tuberculosis, falciparum malaria, and leptospirosis being common causes of death. This study aims to investigate the causes, clinical features, and associated organ dysfunction in patients with acute febrile illnesses and acute renal failure.

Methods: This cross-sectional study was conducted in the Department of General Medicine, Government Medical College, and Hospital, Wanaparthy, Telangana State. Patients over 18 years old with an acute febrile illness and a platelet count below 150,000/mm^3, who have acute kidney injury due to Dengue, Malaria, Leptospira infection, Rickettsial fever, Typhoid, or Chikungunya, confirmed by laboratory tests. AKI was diagnosed based on the recent KDIGO AKI Guidelines.

Results: A variety of AFI diagnoses were identified, with Dengue being the most frequent, followed by Malaria, Scrub Typhus, Leptospirosis, and unspecified causes. The majority of patients (64.0%) presented with mild thrombocytopenia. A significant proportion also had moderate (18.0%) and severe thrombocytopenia (18.0%). Dengue appeared to be associated with a higher risk of moderate and severe thrombocytopenia compared to other diagnoses. A significant proportion of patients (50.0%) developed AKI during their AFI illness. Dengue and Leptospirosis were associated with a higher prevalence of AKI compared to other diagnoses. The severity of AKI also differed based on the diagnosis. Dengue and Leptospirosis had a wider range of AKI stages, while Scrub Typhus and Malaria had mostly less severe stages.

Conclusion: This study highlights the complex clinical picture associated with AFI and thrombocytopenia. While Dengue appears to be the most common diagnosis, other infectious agents can also contribute. The presence of thrombocytopenia is a frequent finding, with Dengue potentially leading to more severe cases. The study also emphasizes the significant risk of AKI in this patient population, particularly with Dengue and Leptospirosis.

Keywords: Acute Febrile Illness, Thrombocytopenia, Acute Kidney Injury, Tropical Illness.

Introduction

Acute kidney injury (AKI), a sudden and often reversible decline in kidney function, poses a significant global health challenge. It can lead to long-term complications and even death, particularly in hospitalized patients [1, 2]. In tropical and subtropical regions, a specific challenge arises when AKI occurs in patients with acute febrile illness (AFI) accompanied by thrombocytopenia (low platelet count). This syndrome, often referred to as Dengue hemorrhagic fever (DHF) but encompassing other infectious diseases like malaria, leptospirosis, and scrub typhus, presents a complex clinical picture with a high risk of AKI [3]. Despite the established association, the underlying mechanisms linking AFI, thrombocytopenia, and AKI remain incompletely understood [4]. Several potential factors might contribute, including hypovolemia severe febrile illness can lead to dehydration and decreased blood volume, reducing blood flow to

the kidneys and compromising their ability to filter waste products from the blood. Infectious agents might directly invade and damage the kidney cells, leading to impaired function and decreased urine output [5]. Inflammation associated with the infection can cause leakage of fluids and proteins from blood vessels into surrounding tissues, potentially affecting kidney function, and leading to a buildup of waste products in the bloodstream. The body's immune response to the infection can sometimes lead to an overreaction, damaging healthy tissues like the kidneys in a process known as immune-mediated injury. Early identification and management of AKI in patients with AFI and thrombocytopenia are crucial for improving patient outcomes. However, diagnosing AKI in this context can be challenging. Traditional markers of kidney function, such as serum creatinine levels, may not always reflect the true extent of the injury, especially in the early stages [6]. Additionally, these patients often present with other symptoms like fever, rash, and muscle aches, which can mask the signs of AKI. Therefore, a clear understanding of the risk factors, clinical presentation, and optimal management strategies for AKI in this patient population is critical. This comprehensive clinical study aims to determine the spectrum of acute kidney injury in acute febrile illness with Thrombocytopenia.

Material and Methods

This cross-sectional study was conducted in the Department of General Medicine, Government Medical College, and Hospital, Wanaparthy, Telangana State. Institutional Ethical approval was obtained for the study. Written consent was obtained from all the participants of the study after explaining the nature of the study in the vernacular language and the expected outcomes.

Inclusion Criteria

1. Patients over 18 years old with an acute febrile illness and a platelet count below 150,000/mm^3, who have acute kidney injury due to Dengue, Malaria, Leptospira infection, Rickettsial fever, Typhoid, or Chikungunya, confirmed by laboratory tests.
2. Males and females
3. Willing to participate in the study voluntarily

Exclusion Criteria

1. Patients under 18 years old
2. Pregnant women
3. Snake bite cases
4. Bacterial sepsis with clinical and radiological signs of pyelonephritis, pneumonia, meningitis, gastroenteritis, acute viral hepatitis, or intra-abdominal abscess
5. Immunocompromised individuals
6. Patients with inherited thrombocytopenia or chronic liver disease

Acute kidney injury (AKI) is common, harmful, and potentially treatable, with even minor reductions in kidney function leading to poor outcomes. Early detection and treatment are crucial for improving prognosis. According to the recent KDIGO AKI Guidelines [7]

AKI is defined by any of the following criteria:

1. Increase in serum creatinine (SCr) by ≥0.3 mg/dl (≥26.5 µmol/l) within 48 hours; or
2. Increase in SCr to ≥1.5 times the baseline level within the previous 7 days: or
3. Urine volume <0.5 ml/kg/h for 6 hours.

During the study period, we examined the total number of hospitalized patients with acute febrile illness and thrombocytopenia to correlate the development and spectrum of acute kidney injury (AKI) among them and measure its outcomes. For cases without known baseline creatinine levels, we assumed a baseline of 0.8. We monitored the reduction of creatinine during the hospital stay until discharge to identify AKI cases. Outcomes were measured by eGFR using the MDRD formula at discharge and classified into three groups:

1. Complete recovery: >60 ml/min
2. Partial recovery: 15-60 ml/min
3. No recovery: <15 ml/min
4. Death

Statistical analysis: All the available data was uploaded to an MS Excel spreadsheet and analyzed by SPSS version 21 in Windows format. The continuous variables were represented as mean, standard deviation, and percentages. The categorical variables were calculated by chi-square test for differences between groups and the values were considered as significant if the p values (<0.05).

Results

A total of 50 cases of acute febrile illness with thrombocytopenia were reported and included in our study. Most of the patients were males 35(70%) and 15(30%) were females. The male to female ratio was 2.1: 1. The common age group involved was 18 – 30 years and 26% of the cases in the study were between age group 31 – 45 years. Table 1 summarizes the diagnoses and clinical presentations of 50 patients. A high proportion of patients (92%) presented with fever, making it the most common clinical presentation across all diagnoses. Dengue fever was the most frequent diagnosis (15 patients), followed by malaria (11 patients), Scrub Typhus (7 patients), Leptospirosis (4 patients), and unspecified causes (13 patients). All patients with Dengue (100%) reported fever, with a significant proportion also experiencing

headache (80%). Bleeding tendencies (20%) and arthralgia (20%) were less frequent but still present in some cases. Similar to Dengue, all patients with Malaria reported fever (100%). However, headache (36.4%) and arthralgia (18.1%) were less common compared to Dengue. Bleeding tendencies were rare (9.0%) in this group. Fever was again the most common presentation (100%) in both Scrub Typhus and Leptospirosis. However, headache, arthralgia, and bleeding tendencies were less frequent compared to Dengue and Malaria. A significant proportion (84.6%) of patients in the unspecified category still presented with fever.

Table 1 shows the diagnosis and clinical presentation of 50 cases of acute febrile illness with thrombocytopenia included in the study

Diagnosis	Frequency	Clinical Presentation			
		Fever	Headache	Arthralgia	Bleeding tendencies
Dengue	15	15 (100%)	12(80%)	3(20%)	3(20%)
Malaria	11	11(100%)	4(36.4%)	2(18.1%)	1(9.0%)
Scrub Typhus	7	7(100%)	4(5.7%)	2(2.8%)	1(1.4%)
Leptospirosis	4	2(50%)	2(50%)	1(25%)	1(25%)
Unspecified	13	11(84.6%)	4(30.8%)	3(23.0%)	1(7.7%)
Total	50	46(92%)	26(42%)	11(22%)	7(14%)

Table 2 shows the relationship between the severity of thrombocytopenia and the diagnosis among the 50 patients with acute febrile illness (AFI) included in the study. Mild Thrombocytopenia: Platelet counts between 100,000 and 140,000 platelets per microliter (μL) of blood. Moderate Thrombocytopenia: Platelet counts between 50,000 and 99,000 platelets per microliter (μL) of blood. Severe Thrombocytopenia: Platelet counts less than 50,000 platelets per microliter (μL) of blood. The majority of patients (64.0%) presented with mild thrombocytopenia. Moderate thrombocytopenia was observed in 18.0% of patients, and severe thrombocytopenia was present in another 18.0%. A significant proportion of Dengue patients (53.3%) had mild thrombocytopenia. However, a substantial number also had moderate (20.0%) and severe (26.7%) thrombocytopenia. Most Malaria cases (72.7%) presented with mild thrombocytopenia. The prevalence of moderate (18.1%) and severe (9.0%) thrombocytopenia was lower compared to Dengue. The majority of Scrub Typhus patients (85.7%) had mild thrombocytopenia, with only one case (14.3%) showing moderate thrombocytopenia. No patients in this group had severe thrombocytopenia. The distribution of thrombocytopenia severity in Leptospirosis was more balanced, with half the patients (50.0%) having mild thrombocytopenia, one case (25.0%) with moderate thrombocytopenia, and another case (25.0%) with severe thrombocytopenia.

Table 2: Showing the severity of thrombocytopenia and diagnosis of the cases included in the study

Diagnosis	Frequency	Grade of thrombocytopenia		
		Mild	Moderate	Severe
Dengue	15	8 (53.3%)	3(20.0%)	4(26.7%)
Malaria	11	8(72.7%)	2(18.1%)	1(9.0%)
Scrub Typhus	7	6(85.7%)	1(14.3%)	0(00.0%)
Leptospirosis	4	2(50.0%)	1(25.0%)	1(25.0%)
Unspecified	13	8(46.1%)	2(7.7%)	3(2.3%)
Total	50	32(64.0%)	9(18.0%)	9(18.0%)

Table 3 analyses the presence of various signs and symptoms among the 50 patients with acute febrile illness (AFI) and thrombocytopenia included in the study. Organomegaly (enlarged organs) was the most frequent sign, identified in 32.0% of patients across all diagnoses. Pallor (pale appearance) and lymphadenopathy (swollen lymph nodes) were less common, seen in 10.0% and 6.0% of patients, respectively. Icterus (jaundice, yellowing of skin) was the least frequent sign, observed in only 20.0% of patients. While some signs like organomegaly (26.7%) were present in a significant proportion of Dengue patients, other signs like pallor (6.7%) and lymphadenopathy (absent) were less frequent. Icterus was observed in a small number of cases (13.3%). Similar to Dengue, organomegaly (45.4%) was the most common sign of Malaria. Icterus (18.1%) was also present in some cases, while pallor (9.1%) and lymphadenopathy (absent) were less frequent. Organomegaly (42.8%) was again the most prominent sign of Scrub Typhus. Icterus (28.6%) was observed in a higher proportion compared to Dengue and Malaria. Pallor (14.3%) and lymphadenopathy (14.3%) were present in some patients. All four signs were observed in Leptospirosis patients, with half

(50.0%) having pallor and icterus, and a quarter (25.0%) each experiencing lymphadenopathy and organomegaly. The pattern of signs in unspecified cases was similar to the overall trend, with organomegaly (23.1%) being the most frequent and other signs being less common.

Table 3: Showing the signs and symptoms of the 50 cases of acute febrile illness with thrombocytopenia

Diagnosis	Frequency	Signs and symptoms			
		Pallor	Icterus	Lymph oade nopathy	Organomegaly
Dengue	15	1(6.7%)	2(13.3%)	0(00.0%)	4(26.7%)
Malaria	11	1(3.6%)	2(18.1%)	0(00.0%)	5(45.4%)
Scrub Typhus	7	1(14.3%)	2(28.6%)	1(14.3%)	3(42.8%)
Leptospirosis	4	1(50.0%)	2(50.0%)	1(25.0%)	1(25.0%)
Unspecified	13	1(7.7%)	2(15.4%)	1(7.7%)	3(23.11%)
Total	50	5(10.0%)	10(20.0%)	3(6.0%)	16(32.0%)

Table 4 explores the prevalence and severity of acute kidney injury (AKI). Acute Kidney Injury (AKI) diagnosis was according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. A significant proportion of patients (50.0%) developed AKI during their AFI illness. Dengue showed the highest prevalence of AKI (66.7%) among all diagnoses. The majority of AKI cases in Dengue were classified as Stage 1 (60%) with some Stage 2 (30%) and Stage 3 (10%). Malaria had a lower AKI prevalence (36.4%) compared to Dengue. Most cases were Stage 1 (75%) with some Stage 2 (25%). No Stage 3 AKI was observed in Malaria. The prevalence of AKI in Scrub Typhus was lower (42.8%) compared to Dengue and Malaria. All cases were Stage 1, indicating the least severe form of AKI. Leptospirosis had a high AKI prevalence (75%) similar to Dengue. However, the distribution was different, with more Stage 2 (50%) cases and fewer Stage 1 (33.3%) cases compared to Dengue. No Stage 3 AKI was seen in Leptospirosis. A moderate proportion (38.5%) of unspecified cases developed AKI. All these cases were classified as Stage 1, suggesting a less severe form of kidney injury.

Table 4: Showing the Acute Kidney injury of the 50 cases of acute febrile illness with thrombocytopenia

Diagnosis	Frequency	Total No of AKI	Stage of AKI		
			Stage 1	Stage 2	Stage 3
Dengue	15	10(66.7%)	6	3	1
Malaria	11	4(36.4%)	3	1	0
Scrub Typhus	7	3(4.3%)	3	0	0
Leptospirosis	4	3(75%)	2	1	0
Unspecified	13	5(38.5%)	5	0	0
Total	50	25(50.0%)	19	5	1

We calculated the estimated glomerular filtration rate (eGFR) at discharge as a prognostic indicator for the potential development of chronic kidney disease in the future. Discharge creatinine levels were utilized for eGFR calculation. Among the 25 patients with acute kidney injury (AKI), 19 showed eGFR >90 mL/min/1.73 m², indicating nearly complete recovery, while 5 had eGFR >60 mL/min/1.73 m², signifying partial recovery. One patient exhibited eGFR <15 mL/min/1.73 m² and unfortunately succumbed. The management of acute febrile illness with thrombocytopenia cases was monitored until discharge from admission.

Discussion

The current study aimed to investigate the causes, clinical features, and associated organ dysfunction in patients with acute febrile illnesses accompanied by acute renal failure. Most of the patients were male, comprising 70% (35 patients), while females made up 30% (15 patients), resulting in a male-to-female ratio of 2.1:1. The most commonly affected age group was 18-30 years, with 26% of the cases falling between 31-45 years. The average age of the patients was 44.5 years. In a similar study conducted in South India, the mean age of the patients for scrub typhus was 45.5 years, malaria was 35.8 years and dengue was 28.6 years. [8] In tropical countries, infectious diseases are a significant cause of acute renal failure. Common infections leading to acute renal failure include leptospirosis, falciparum malaria, and sepsis. Evaluating the causes of acute renal failure is challenging due to inadequate diagnostic facilities. Acute renal failure in the context of infectious diseases indicates severe illness. [9] Early detection and aggressive management can improve patient survival. In our study of 50 patients, we identified 25 (50%)cases of acute renal failure caused by infectious diseases, with leptospirosis and

falciparum malaria being significant contributors. In 26% of the patients, the specific organism could not be identified due to the lack of advanced diagnostic facilities, and these cases were classified as unspecified. [10]

In a study conducted by Leelarasamee et al. [11] on acute febrile illnesses, the etiologies remained unknown in a majority of cases (61.3%), compared to 26% of unspecified fevers in our study. The same study identified dengue in 5.7% of cases, scrub typhus in 7.5%, and leptospirosis in 1.1%, whereas our study found these rates to be 30%, 14.0%, and 8.0%, respectively [11]. Similarly, Chrispal et al. [12] conducted a study in South India, where a clear diagnosis was not achieved in 8% of cases, and 7.3% were categorized as unspecified fever. In their study, patients with acute febrile illness were diagnosed with scrub typhus (47.5%), malaria (17.1%), enteric fever (8%), leptospirosis (3%), rickettsiosis (1.8%), and Hantavirus (0.3%). Studies suggest that most patients are asymptomatic, with thrombocytopenia often diagnosed incidentally, and only a small proportion exhibiting bleeding tendencies [13, 14]. Our study yielded similar results. Approximately 20% of dengue and 25% of leptospirosis cases presented with bleeding manifestations, though this finding was not statistically significant. Bleeding tendencies were even lower in other diagnoses.

In this study, the proportion of AKI cases was higher than in most studies, such as those by Bhandary et al [15] and Basu et al. [16]. This discrepancy may be attributed to the AKI criteria used; the RIFLE criteria, for instance, categorize more patients with AKI than the WHO 2006 criteria, as shown by Thanachartwet V. et al. [17]. The 50% AKI rate in our study likely reflects the greater sensitivity of the KDIGO criteria. Aggressive treatment was necessary for patients with AKI, as it significantly predicted impending death, similar to findings by Saravu et al. [18] and Waikar SS et al. [19]. In this study, the most common cause of AKI, particularly in stage 1, was dengue, and RRT was promptly initiated. However, Basu G. et al. [16] reported scrub typhus followed by falciparum malaria as the common cause of AKI. The proportion of malaria patients with AKI, severe AKI, RRT initiation, and in-hospital mortality differed from studies by Bhandary et al [15], Basu et al. [16] Saravu et al. [18] Kute et al. [20] and Gupta et al. [21]. The higher proportion of AKI stage 1 patients may represent typically asymptomatic and undiagnosed cases, better detected using the more sensitive KDIGO criteria. In this study, AKI stage 3 was associated with the highest in-hospital mortality.

Conclusion

This study highlights the complex clinical picture associated with AFI and thrombocytopenia. While Dengue appears to be the most common diagnosis, other infectious agents can also contribute. The presence of thrombocytopenia is a frequent finding, with Dengue potentially leading to more severe cases. The study also emphasizes the significant risk of AKI in this patient population, particularly with Dengue and Leptospirosis. These findings highlight the importance of considering AFI and thrombocytopenia as potential risk factors for AKI. Further research is needed to explore the underlying mechanisms of AKI in this context and develop strategies for early detection, prevention, and management.

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