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Evaluation of Renal Functions in Tropical Acute Febrile Illness

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Abstract

***Introduction:** India is endemic for dengue, malaria, typhoid and scrub typhus infections. Acute kidney injury (AKI) is one of the most challenging problems faced by clinicians in tropical acute febrile illness. Due to emerging and re-emerging diseases, population growth, urbanisation, migration, international travel, pandemics, and global warming, the incidence of tropical acute febrile illness is continuously increasing. The spectrum of tropical acute febrile illness is also changing. While some infections like malaria are contained because of effective implementation of national programmes, various febrile illnesses like scrub typhus and dengue have shown a resurgence. There is a scarcity of literature available from developing countries like India. This study was planned to know the spectrum of tropical acute febrile illness and its association with AKI.*

***Methods:** The present study is a prospective observational study conducted on 100 adult patients of tropical acute febrile illness who reported to the medicine department at Pt. B.D. Sharma PGIMS Rohtak, Haryana. A detailed history and clinical examination was done in all subjects included in the study. Patients who fulfilled case definition criteria were evaluated for AKI as per definitions of KDIGO classification on day of admission and then subsequently on day 3, 7, and 14 with laboratory investigations, i.e., serum creatinine, blood urea, urine output, and eGFR.*

***Results:** The most common tropical acute febrile illness (TAFI) diagnosed in the current study was dengue in 43% cases. The spectrum of TAFI was dengue (43%), followed by malaria (23%), scrub typhus (19%), enteric fever (9%), and mixed pattern (6%). The febrile illnesses causing AKI in decreasing trend in present study was malaria (40.6%), scrub typhus (31.2%), dengue (12.5%), mixed disease pattern (9.4%) and enteric fever (6.3%). The proportion of AKI was highest among the subgroup with malaria (56.5%), followed by scrub typhus (52.63%), mixed infections (50%), enteric fever (22.22%), and dengue fever (9.30%). Among the subtypes of malaria, 64.7% of Plasmodium vivax cases and 50% of falciparum cases had AKI; but none of the mixed cases had AKI. In the present study; none of the patients with Dengue, enteric fever, or mixed disease pattern had undergone dialysis. Only one patient of Scrub Typhus with AKI underwent dialysis. 38.46% cases required dialysis of malaria subgroup. Total cases of AKI were 32, out of these 18.75% were dialysed and in-hospital mortality was none.*

***Conclusion:** In the present study, the proportion of AKI in tropical fever was 32%. Serum blood urea, serum creatinine, urine output, eGFR and hospital stay were statistically significantly different between AKI and non AKI. The most common cause of AKI in TAFI was malaria followed by scrub typhus and mixed infection. Long-term studies are needed to know the exact spectrum of AKI in TAFI, so that an effective strategy can be implemented to prevent this recoverable complication.*

***Key words:** Tropical acute febrile illness (TAFI), acute kidney injury (AKI).*

Introduction

Infectious diseases are a major cause of acute kidney injury (AKI) in tropical countries during the monsoon season. Tropical acute febrile illness (TAFI) is defined as all acute febrile syndromes with oral temperature over 37.5° c within the last 24 hours and less than 2 weeks with nonspecific symptoms like fever, generalised body pain, loose stools, vomiting, swelling of legs, generalised swelling of body, decreased urine output, breathlessness, cough, chest pain, altered sensorium, headache, and nonspecific signs like tachycardia, myalgia, conjunctival congestion, rashes, joint pains, etc.[1-3]. Epidemics of acute febrile illness have been causing major concerns in India. Every year during and after the rainy season an epidemic of acute febrile illness is witnessed in Northern India, but the relative contribution of various aetiological agents remains unknown[4-6].

Acute kidney injury in tropical fever is characterised by abrupt deterioration in kidney function which clinically manifests as acute increase in nitrogen waste products, measured by blood urea nitrogen and serum creatinine levels with or without reduced urine output over the course of hours to weeks. Renal abnormalities in tropical infections range from asymptomatic urinary abnormalities to severe forms of AKI necessitating emergent renal replacement therapy. These can be either related to direct involvement of the kidneys and urinary tract via tubulointerstitial toxicity and injury to glomerular endothelium or indirect consequence of systemic effects of infection, i.e.,

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haemolysis, rhabdomyolysis, hypovolaemic shock, septic shock, and immune complex deposition in glomeruli[7]. Direct invasion of the tubules in the kidney and resultant tubulointerstitial inflammation leading to AKI has been demonstrated in patients infected with leptospirosis and scrub typhus. *Plasmodium falciparum* has been shown to affect the glomerular endothelium through cytoadherence of infected red blood cells in circulation. In addition, the kidneys are susceptible to damage by various other mechanisms. Glomerular damage secondary to immune-complex deposition or activation of complement can also occur in some infections, e.g., mesangiocapillary glomerulonephritis seen in quartan malaria.

There is a paucity of data in the northern part of India on the spectrum and renal involvement in patients of tropical fever. In a recent study from a tertiary care hospital in North India, dengue (71.2%) was the most common cause of tropical acute febrile illness, followed by malaria, enteric fever, scrub typhus, and mixed infection[8]. Due to emerging and re-emerging diseases, population growth, urbanisation, migration, international travel, pandemics and global warming, the incidence of tropical acute febrile illness is continuously increasing. The spectrum of tropical acute febrile illness (TAFI) is changing and various febrile illnesses such as scrub typhus and dengue have shown resurgence. Some infections like malaria are contained because of effective implementation of national programme. Moreover, as already stated the spectrum of tropical acute febrile illness is different from developed countries.

Material and methods

The present study was a prospective observational study conducted on 100 adult patients aged more than 18 years of tropical acute febrile illness who reported between October 2017 and October 2018 to the medicine department at Pt. B.D. Sharma, PGIMS Rohtak, Haryana. All the patients were admitted with fever of less than 2 weeks duration with signs and symptoms suggestive of tropical acute febrile illness like generalised body pain, nausea, and vomiting, loose stools, myalgia, joint pain, conjunctival congestion, pedal oedema, generalised swelling of body, cough with expectoration, chest pain, shortness of breath, headache, and altered sensorium were screened. Patients aged less than 18 years or more than 75 years, patients having nosocomial infections, chronic infections, fever due to noninfectious aetiologies were excluded from the study. Patients of chronic kidney disease, acute kidney injury secondary to noninfectious aetiologies, urosepsis, lower respiratory tract infections, haematological malignancies, immunocompromised or immunosuppressed individuals, and pregnant females were also excluded from the study.

All patients were evaluated by a set of routine blood and urine investigations, peripheral blood smears for malaria, chest radiograph, abdominal ultrasonogram, blood cultures, IgM typhidot test for enteric fever, leptospiral IgM ELISA (PAN Bio Ltd, Brisbane, Australia), dengue IgM (PAN Bio Ltd, Brisbane, Australia) and arterial blood gas. KDIGO guidelines were used for AKI diagnosis and classification[9]. The tropical acute febrile illness was considered in patients who had clinical and laboratory diagnostic features suggestive of malaria, dengue, scrub typhus, leptospirosis, and enteric fever. The patients positive for more than one tropical infection by specific investigation were considered as having mixed infections. All patients were evaluated for AKI on day of admission and then subsequently on day 3, 7 and 14 with laboratory investigations, i.e., serum creatinine, blood urea, urine output, and eGFR.

Statistical analysis

AKI was considered as explanatory variable. Descriptive analysis was carried-out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Categorical outcomes were compared between study groups using Chi square test/student's t test. The trend of laboratory values from admission to final follow-up, at different time intervals was assessed by comparing the mean values, using one-way repeated measures ANOVA. Data were analysed and statistically evaluated using SPSS 22.0 software.

Results

The present study included 100 adult patients of tropical acute febrile illness. The mean age was 34.9 ± 13.01 years. The spectrum of TAFI was dengue (43%) followed by malaria (23%), scrub typhus (19%), enteric fever (9%) and mixed pattern (6%) (Table I). Among the study population, 32% people developed AKI. Out of which 7% had AKI stage I, 16% had AKI stage II and remaining 9% had AKI stage III (Table II). Patients of tropical acute febrile illness showed increasing trend of blood urea and serum creatinine up to 7 days and then it started decreasing after treatment. eGFR also showed similar trends (Table III).

Out of 32 patients with AKI, 13 patients had AKI due to malaria (40.6%), followed by 10 due to scrub typhus (31.3%), 4 due to dengue (12.5%), 3 due to mixed pattern disease (9.4%), and 2 due to enteric fever (6.2%). The proportion of AKI was highest among people with malaria – 13 cases (56.5%), followed by scrub typhus – 10 cases (52.63%), and 3 cases of mixed infections (50%). Among people with Dengue fever, 9.30% had AKI and 22.22% of enteric fever patients had AKI. Among the subtypes of

malaria, 64.7% of *Plasmodium vivax* cases and 50% of falciparum cases had AKI but none of the mixed cases had AKI (Table I). Dialysis was required in one patient of scrub typhus and 5 patients of malaria with AKI. None of the patients with dengue, enteric fever, or mixed disease pattern needed dialysis (Table II).

Table I: Causes of acute kidney injury in tropical acute febrile illness (N = 100).

Diagnosis	Total n - 100	AKI	
		AKI n - 32	No AKI n - 68
Dengue	43	4 (9.302%)	39 (90.69%)
Scrub typhus	19	10 (52.63%)	9 (47.36%)
Malaria	23	13 (56.5%)	10(43.5%)
• Malaria (vivax)	17	11 (64.70%)	6 (35.29%)
• Malaria (falciparum)	4	2 (50%)	2 (50%)
• Malaria (vivax + falciparum)	2	0 (0%)	2 (100%)
Enteric Fever	9	2 (22.22%)	7 (77.77%)
Mixed Pattern Disease	6	3 (50 %)	3 (50 %)
• Scrub typhus with enteric fever	2	0 (0%)	2 (100%)
• Dengue with malaria (vivax))	1	1 (100%)	0 (0%)
Enteric Fever with malaria (vivax)	1	1 (100%)	0 (0%)
• Scrub typhus with leptospirosis	2	1 (50%)	1 (50%)

Table II: Distribution of patients in relation to diagnosis and AKI staging (N = 32).

Diagnosis	AKI stage			Dialysis required	
	I	II	III	Yes	No
Malaria (N = 13)	3	5	5	5	8
Scrub typhus (N = 10)	3	5	2	1	9
Enteric fever (N = 2)	0	1	1	0	2
Dengue (N = 4)	0	3	1	0	4
Mixed disease pattern (N = 3)	1	2	0	0	3
Total (N = 32)	7	16	9	6	26

Amongst the AKI patients, complications in the form of thrombocytopenia were present in 19 patients, anuria in 3 patients, and ARDS in 2 patients. The mean duration of hospital stay in patients with AKI was 10.75 ± 5.58 days as compared to 6.88 ± 0.76 days in patients without AKI and this difference was statistically significant (p value < 0.001). Age, diagnosis, SpO_2, temperature, haemoglobin, total leucocyte count, neutrophils, lymphocytes, absolute platelet count, blood urea, serum creatinine, corrected serum calcium, serum uric acid, serum albumin, urine output, eGFR, and hospital stay were statistically significantly different between AKI and non AKI (p value < 0.05) (TableIV). Hence, these factors can be the influencing factors in occurrence of AKI among patients presenting with TAFI.

Table III: Comparison of haematological and renal parameters in tropical acute febrile illness patients on follow-up (100).

Parameter	Baseline	Day 3 follow-up	Day 7 follow-up	Day 14 follow-up	P* value
Haemoglobin (g/dl)	13.48 ± 2.25	13.42 ± 2	12.98 ± 1.7	12.74 ± 1.41	> 0.05
Total leucocyte count	6528 ± 3789.33	6591 ± 2178.83	6254 ± 1569.05	6498 ± 1096	*> 0.05*
Absolute platelet count	68910 ± 58408.19	100580 ± 44514.25	158990 ± 32417.57	267200 ± 46233.49	< 0.001
Blood urea (mg/dl)	45.59 ± 57.84	42.49 ± 42.55	30.37 ± 25	19.42 ± 14.3	< 0.001
Serum creatinine (mg/dl)	1.52 ± 1.38	1.45 ± 1.26	1.07 ± 0.89	0.89 ± 0.55	< 0.001
Corrected serum calcium (mg/dl)	9.49 ± 0.53	9.34 ± 0.36	9.26 ± 0.33	9.27 ± 0.26	> 0.05
Serum phosphate (mg/dl)	3.4 ± 0.38	3.4 ± 0.42	3.49 ± 0.41	3.4 ± 0.38	> 0.05
Serum uric acid (mg/dl)	3.4 ± 1.09	3.52 ± 1.14	3.39 ± 0.75	2.84 ± 0.71	> 0.05
Serum protein (g/dl)	7.59 ± 0.29	7.57 ± 0.25	7.55 ± 0.25	7.48 ± 0.32	> 0.05
Serum albumin (g/dl)	3.41 ± 0.24	3.51 ± 0.22	3.69 ± 0.17	3.59 ± 0.21	> 0.05
Serum sodium (meq/l)	141.35 ± 2.99	141.45 ± 2.14	139.22 ± 2.84	140.79 ± 3.39	> 0.05
Serum potassium (meq/l)	3.53 ± 0.31	3.71 ± 0.34	3.81 ± 0.37	3.79 ± 0.31	> 0.05
Urine output (ml)	1236.3 ± 443.89	1328.8 ± 425.58	1501.5 ± 335.48	1784.5 ± 307.95	< 0.001
eGFR (ml/min/ 1.73m^2)	83.66 ± 43.22	87.53 ± 43.64	105.94 ± 43.61	111.94 ± 40.22	< 0.001

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Discussion

India is an endemic country for dengue, malaria, typhoid, and scrub typhus. Tropical acute febrile illness accounts for the majority of hospitalisation in India. There are only limited studies from north India about the spectrum and renal involvement in tropical illnesses. This study was conducted to know the relative contribution of the aetiological agents in an outbreak of acute febrile illness and subsequently their effect on the renal parameters.

The spectrum of TAFI in the present study in decreasing trend was dengue (43%), followed by malaria (23%), scrub typhus (19%), enteric fever (9%), and mixed pattern (6%). The most common cause of tropical acute febrile illness

Table IV: Predictive factors associated with AKI (N = 100).

Parameter	AKI		*P value
	Present (N = 32)	Absent (N = 68)	
	Mean ± SD	Mean ± SD	
Age (Years)	39.88 ± 13.67	32.56 ± 12.09	< 0.01
Gender			#P value
Male	23 (71.87%)	45 (66.17%)	> 0.05
Female	9 (28.12%)	23 (33.82%)	
Diagnosis			#P value
Dengue	4 (9.3%)	39 (90.7%)	< 0.001
Scrub typhus	10 (52.6%)	9 (47.4%)	
Malaria	13 (56.5%)	10 (43.5%)	
Enteric fever	2 (22.2%)	7 (77.8%)	
Mixed disease pattern	3 (50%)	3 (50%)	
Physical examination parameters			
Systolic BP (mmHg)	114.88 ± 7.92	113.85 ± 5.01	> 0.05
Diastolic BP (mmHg)	71.94 ± 6.53	68.74 ± 7.25	> 0.05
Pulse rate (per min)	84.56 ± 10.05	84.06 ± 8.62	> 0.05
SpO_2 (%)	96.03 ± 2.1	97.47 ± 1.2	< 0.001
Temperature (° F)	103.22 ± 0.83	102.32 ± 1.1	< 0.001
Biochemical parameters			
Haemoglobin (g/dl)	12.57 ± 2.8	13.91 ± 1.81	> 0.05
Total leucocytes count (per mm^3)	9615.63 ± 5322.75	5075 ± 1188.42	> 0.05
Neutrophils (per mm^3)	76.47 ± 10.85	60.93 ± 7.62	< 0.001
Lymphocytes (per mm^3)	19.47 ± 10.16	34.1 ± 7.18	< 0.001
Absolute platelets count (per mm^3)	94444.44 ± 59298.68	61852.94 ± 56484.38	< 0.05
Blood urea (mg/dl)	109.97 ± 66.11	15.29 ± 3.17	< 0.001
Blood sugar (mg/dl)	97.56 ± 11.6	99.22 ± 8.23	> 0.05
Serum creatinine (mg/dl)	2.99 ± 1.67	0.83 ± 0.11	< 0.001
Corrected serum calcium (mg/dl)	9.65 ± 0.63	9.41 ± 0.47	< 0.05
Serum phosphate (mg/dl)	3.31 ± 0.43	3.44 ± 0.35	> 0.05
Serum uric acid (mg/dl)	3.73 ± 1.67	3.24 ± 0.62	< 0.05
Serum protein (g/dl)	7.52 ± 0.31	7.62 ± 0.27	> 0.05
Serum albumin (g/dl)	3.49 ± 0.29	3.37 ± 0.2	< 0.05
Serum sodium (meq/l)	141.41 ± 3.71	141.32 ± 2.61	> 0.05
Serum potassium (meq/l)	3.46 ± 0.5	3.56 ± 0.16	> 0.05
Urine output (ml)	732.19 ± 354.5	1473.53 ± 233.48	< 0.001
eGFR (ml/min/1.73 m^2)	32.05 ± 23.31	107.94 ± 25.27	< 0.001
Hospital stay (days)	10.75 ± 5.58	6.88 ± 0.76	< 0.001

**Student's t- test, #Chi square test*

was dengue which was consistent with various other studies conducted attributable to climatic change, rainy season, distinct geography, and resurgence of dengue[8,10,11]. Falciparum malaria was seen in only 4% cases in the present study and this showed a decreasing trend as observed in recent studies as most patients do not report to tertiary care setting and complicated malaria is not so common because of use of antimalarial drug at periphery[12,13].

Table V: Comparison of present study with various other studies.

Study	Basu *et al*[2]	Nair *et al*[14]	Atkar *et al*[15]	Present study
Most common cause of TAFI	Scrub typhus (51.2%)	Malaria (48.17%)	Malaria (31.43%)	Dengue (43%)
Proportion of AKI in TAFI	41.1%	54%	27.86%	32%
Most common cause of AKI in TAFI	Scrub typhus	Leptospirosis	*P. falciparum*	*P. vivax*
Proportion of AKI among malaria patients	57.35%	34.95%	27.87%	56.52%
Proportion of AKI among dengue patients	35.7%	69.4%	27.03%	10.26%
Proportion of AKI among scrub typhus patients	42.6%	40%	25%	52.63%
Proportion of AKI among enteric fever patients	6.3%	42.9%	9.68%	22.22%
Proportion of AKI among leptospirosis patients	50%	98.7%	41.67%	0%

The incidence of AKI in acute tropical febrile illness in the present study was 32%, which was different as compared to the other studies due to reporting of different proportion of critically ill patients of TAFI in the tertiary care centre[2,12-14].

The proportion of AKI among malaria patients was 56.52%. Similar findings were reported by Basu *et al* in their study which was conducted in southern India[2]. However, our findings were contradictory to other studies[12-16]. Aktar *et al* found only 27% malaria patients developed AKI[13]. This difference could be due to geographical variations among different study populations. The spectrum of malarial sub-types in decreasing trend in present study was vivax (73.9%), falciparum (17.4%) and mixed (8.7%). Results were similar to the study conducted by Trivedi *et al*, which concluded that *Plasmodium vivax* was the major parasite type (52.54%), followed by *P. falciparum* (33.75%), and mixed malarial infections (13.69%)[17]. Among the sub-types of malaria, 64.7% of *Plasmodium vivax* cases and 50% of falciparum cases developed AKI but none of the mixed cases developed AKI. AKI develops in falciparum malaria because of the unique properties of the parasite which produces haemorrhagic changes leading to renal ischaemia and rarely rhabdomyolysis. While global incidence of malaria has fallen in the last decade, it continues to be an important cause of mortality and morbidity in acutely ill febrile patients. In the present study, all complications of malaria have been reported in vivax. *P. vivax* malaria is now increasingly

associated with severe disease and high case fatality due to more pronounced inflammatory response and higher cytokine production. A recent retrospective study also concluded that anaemia, hepato-renal dysfunctions were equally frequent in vivax malaria and it can no longer be considered as benign infection[18]. The present study showed that the proportion of AKI in scrub typhus was 52.63% and in a previous study conducted by Aggarwal *et al*, the proportion of AKI in scrub typhus was 40%[19]. In southern, India the studies conducted by Basu *et al*, Nair *et al*, and Aktar *et al*, the proportion of AKI in scrub typhus were 42.6%, 40% and 25% respectively which were lower than the proportion of AKI in scrub typhus in the present study due to more critically ill patients of scrub typhus reporting to our institute which is a tertiary care centre[2,12,13]. AKI was less among dengue patients due to timely diagnosis, fluid management, and ICU care. A few studies have reported very high incidence of dengue-associated AKI[12,20].

In the present study, none of the patients with dengue, enteric fever, or mixed disease pattern had undergone dialysis. Total cases of AKI were 32, out of these 18.75% were dialysed and in-hospital mortality was none. Nair *et al*, in his study found that 10.2% of AKI patients underwent dialysis and in-hospital mortality was 3% among all patients[12]. In another study conducted in southern India, it was found that 19.21% of AKI patients required dialysis[2].

The mean duration of hospital stay was statistically significant in patients with AKI (10.75 ± 5.58 days) as compared to in patients without AKI (6.88 ± 0.76 days). Khalil *et al* demonstrated that patients with AKI had longer duration of hospital stay than patients without AKI[21]. The positive predictors of AKI from this study were comparable to the studies conducted by Saravu *et al*, Basu *et al*, and Nair *et al*[2,12,14].

Conclusion

From this present study it can be concluded that the most common cause of TAFI was dengue followed by malaria, scrub typhus, enteric fever and mixed disease pattern. The spectrum of AKI in TAFI in decreasing trend in the present study was malaria, scrub typhus, dengue, mixed disease pattern, and enteric fever. Long-term studies are needed to know the exact spectrum of AKI in TAFI, so that an effective strategy can be implemented to prevent this recoverable complication. It is necessary to increase public awareness, provide clinical education and training about tropical illnesses, and form specialised renal teams to treat severe AKI patients.

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