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ORIGINAL RESEARCH ARTICLE

RELATIONSHIP OF OUTCOMES BETWEEN DIFFERENT ETIOLOGIES AND SEVERITY GROUPS OF PATIENTS PRESENTING WITH ACUTE FEBRILE ILLNESS WITH TRANSAMINITIS

Sunil Kumar Patel[1,*], Shital Adhikari[1], Madhur Dev Bhattarai[1], Basanta Gauli[1],Sailesh Gurung[1], Pratik Wagley[1], Niraj Puri[1], Anjana Lamichhane[1]

[1]Pulmonary and Critical Care Unit, Department of Medicine, Chitwan Medical College and Teaching Hospital, Bharatpur, Nepal

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***Correspondence to:** Sunil Kumar Patel, Pulmonary and Critical Care Unit, Department of Medicine, Chitwan Medical College and Teaching Hospital, Bharatpur, Nepal.*

Email: sunil_ptl6@yahoo.com

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ABSTRACT

Background: Acute febrile illness (AFI) is defined as a fever lasting less than 14 days with no evidence of organ-specific symptoms or signs of infection. Our aim was to determine the most common etiology of AFI with transaminitis and to find the relationship between clinical and laboratory investigation profile, as well as outcomes of illness.

Methods: This is a hospital based prospective study conducted in Chitwan Medical College and Teaching Hospital (CMC-TH) from 17 April 2021 to 18 October 2021. All patients >15 years of age admitted with acute febrile illness and elevated transaminases under Pulmonary and Critical Care Medicine (PCCM) Unit of CMCTH were enrolled consecutively.

Results: The mean age of the patients (n=103) was 45.1 ± 16.8 years. There were almost equal proportion of males and females. The most common presenting symptom (besides fever) was headache, followed by myalgia, with a median duration of 5 days. Scrub typhus was the commonest diagnosis (60, 58.3%). A diagnosis of Acute Undifferentiated Febrile Illness (AUFI) was given in (39, 37.9%) patients. The three transaminitis severity groups (mild, moderate and severe) were not significantly different by age, gender and comorbidity status. Acute kidney injury and multi-organ dysfunction syndrome (MODS) were significantly associated with severe transaminitis (P<0.05). The mortality rate was also higher in the severe transaminitis group.

Conclusions: Scrub typhus has emerged as the most common cause of Acute Febrile Illness with transaminitis requiring hospital admission in this part of the country. Scrub typhus should be suspected in all patients who report with AFI with transaminitis in endemic areas.

INTRODUCTION

Fever is a typical complaint among patients presenting to the emergency department. It accounts for 15% of complaints among the elderly and 5% among adults.[1]Acute febrile illness (AFI) is defined as a fever lasting less than 14 days with no evidence of organ-specific symptoms or signs of infection, such as abscess, pneumonia, or acute pyelonephritis.[2] In the developing world, malaria, dengue, enteric fever, rickettsial illness, leptospirosis are the common causative agents for AFI.[3] AFI with transaminitis is one of the common presentations among patients. It covers a wide range of causes, from infectious to non-infectious illness.[4]Hepatitis A through E are well-known hepatotropic viruses that can infect the liver and cause hepatic damage. Dengue fever, malaria, enteric fever, scrub typhus, leptospirosis, and Japanese encephalitis (JE) are examples of systemic infections by non-hepatotropic viruses, protozoa, and bacteria that can induce hepatic injury either directly or indirectly through toxins and cytokines.[5,6] AFI and transaminitis combination might present diagnostic issues, especially in the tropics, where viral hepatitis, malaria, and dengue fever are very common. However, few studies have found a link between liver function abnormalities and these infections. Season and geography have a significant impact on the proportion of these fevers in hospitalized patients.[7]

Our aim is to determine the most common etiology of AFI with transaminitis in a tertiary care hospital in central part of Nepal, and to find the relationship between clinical and laboratory investigation profile, as well as patient outcomes.

METHODS

This was a hospital based prospective study conducted in Chitwan Medical College and Teaching Hospital (CMC-TH) of Nepal from 17 April 2021 to 18 October 2021.

Patients with acute febrile illness and elevated transaminases admitted under PCCM Unit of (CMC-TH) were eligible for enrollment. Elevation of serum transaminases is defined as level above upper limit of normal (in women, >32 IU/L for Aspartate aminotransferases (AST) and > 33 IU/L for Alanine aminotransferases (ALT), in men, the ULN is > 40 IU/L for AST, > 41 IU/L for ALT).[8] Furthermore transaminitis (elevated ALT

&AST) was classified into 3 categories based on the magnitude of enzyme level alteration, 1. Mild< 5 times upper reference limit (URL), Moderate 5-10 times URL, Severe > 10 times URL. Multi-organ dysfunction syndrome (MODS) was defined as ≥2 organ system failures, acute kidney injury (AKI) as per the latest Acute Kidney Injury Network (AKIN) classification guidelines and acute respiratory distress syndrome (ARDS) as per Berlin definition 2012, acute non cardiogenic pulmonary edema with bilateral alveolar or interstitial infiltrates on a chest radiograph and a PaO2/FiO2 of less than 200 mmHg.

Patients were excluded from the study if they had RT-PCR positive for SARS CoV2, hospitalized or had surgery in the previous two weeks or if they had a medical condition that puts them at higher risk for recurrent fever or infections (such as Human Immunodeficiency Virus, primary immunodeficiency, cancer, autoimmune disorders, congenital lung or heart disease, immunosuppressive medications, indwelling hardware [shunt/ prosthesis/catheters]).

Age, gender, presenting symptoms and duration, concomitant comorbidities, and baseline organ failure were all documented in the patient demographics. Complete blood counts, electrolytes, renal and liver function tests, and specific investigations for various etiologies such as thick and thin blood films, rapid diagnostic card test (RDT) for *Plasmodiumvivax* and *Plasmodium falciparum*, blood cultures, urine cultures, IgM Enzyme Linked Immuno Sorbent Assay (ELISA) for scrub typhus and leptospirosis, NS1 antigen and or ELISA IgM for dengue, IgM for herpes simplex virus (HSV) and JE virus, polymerase chain reaction (PCR) for HSV, JE and tuberculosis, cerebrospinal fluid (CSF) examination, were recorded based on clinical indications. Electrocardiography (ECG), echocardiography (ECHO), and cardiac enzymes were performed on clinical judgment.

Data was analyzed using SPSS version 20. Standard descriptive statistics was used to describe the data. Continuous variables were expressed as mean ± SD or median (range) whereas categorical variables were expressed as frequency (percentage). Fisher's exact test was used to find association between etiology groups (scrub typhus, AUFI and others) and severity of transaminitis (mild, moderate and severe group) with patient clinical characteristics (age, gender, comorbidity status and presenting syndrome) and outcomes (requirement of MV and ICU, hospital stay and mortality rate). A P-value <0.05 was considered statistically significant.

RESULTS

Out of total 115 patients, 12 patients were excluded from the analysis because they didn't meet the criteria for AFI (5 cases of pneumonia, 4 cases of meningoencephalitis, 2 cases of urinary tract infection and 1 case of Hepatitis A). The mean age of the patients (n=103) was 45.1 ± 16.8 years. In this study male 55 (53.4%) were slightly predominant than female 48 (46.6%) (Table 1). The age histogram of the patients is shown in Figure 1.

Table 1: Patient characteristics (n = 103)

Characteristics	Frequency (%)
Age (years), Median ± SD	45.1 ± 16.8 (Range: 14 – 83)
Gender, n (%)	
Male	55 (53.4)
Female	48 (46.6)
Personal history, n (%)	
Smoking	18 (17.5)
Alcohol	24 (23.3)
Comorbidity present, n (%)	19 (18.4)
Comorbidity, n (%)	
Hypertension	9 (8.7)
Diabetes Mellitus	5 (4.8)
Asthma/COPD	4 (3.9)
Presenting symptoms#, n (%)	
Headache	32 (31.1)
Myalgia	29 (28.2)
Cough	23 (22.3)
SOB	22 (21.4)
Nausea/Vomiting	18 (17.5)
Diarrhoea	13 (12.6)
Hemoptysis	1 (1.0)
Seizures	1 (1.0)
Duration of symptoms, (days) IQR	5 (1 - 14)
Final Diagnosis, n (%)	
Scrub Typhus	60 (58.3)
AUFI	39 (37.9)
Dengue	2 (1.8)
Leishmaniasis	1 (1.0)
Enteric fever	1 (1.0)
Severity of transaminitis, n (%)	
Mild	65 (63.1)
Moderate	29 (28.2)
Severe	9 (8.7)

 # Symptoms besides fever, SD= Standard Deviation, IQR= Inter-Quartile Range, COPD = Chronic Obstructive Pulmonary Disease, SOB= Shortness of Breath

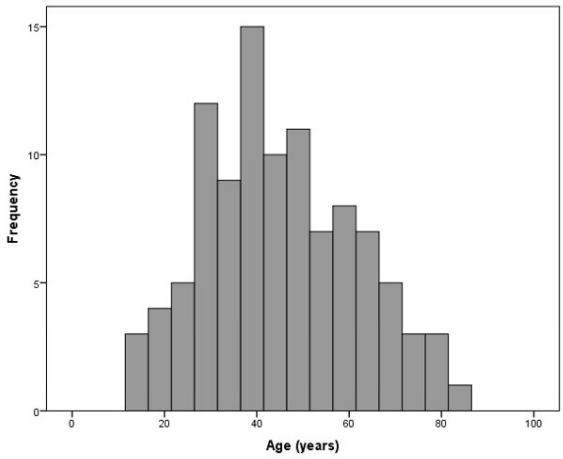

Figure 1: Age histogram of the patients with AFI with transaminitis (n = 103)

There were almost equal proportion of males and females. At least one comorbidity was present in 19 (18.4%) patients. The most common presenting symptom (besides fever) was headache, followed by myalgia, with a median duration of 5 days. Scrub typhus was the frequent-most diagnosis (60, 58.3%). A diagnosis of Acute Undifferentiated Febrile Illness (AUFI) was given in 39 (37.9%) patients. Based on the pre-defined criteria of transaminitis, almost two-thirds (63.1%) of the patients had mild transaminitis. Only 9(8.7%) had severe transaminitis. The frequently performed tests in patients in the study are shown in Table 2.

There were no significant differences in the age, gender, comorbidity and presenting syndrome distribution between the different etiological groups Table 3.

Table 2: Frequently performed tests in patients with AFI with transaminitis

Tests	Frequency, n (%)
IgM ELISA for Scrub Typhus	94 (91.3)
IgM for Dengue	54 (52.4)
IgM for Leptospirosis	33 (32.0)
Serology for malarial antigen	27 (26.2)
Blood C/S	27 (26.2)
Urine C/S	24 (23.3)
HBsAg	24 (23.3)
rK-39, CSF examination[!]	1 (1.0)

! Tests that were performed the lowest, C/S = Culture/Sensitivity, HBsAg = Hepatitis B Surface Antigen, CSF= Cerebrospinal Fluid

Table 3: Clinical characteristics and outcome of the patients (n = 103) categorized according to etiology

Characteristics	Scrub typhus (n = 60)	AUFI (n = 39)	Others[#] (n = 4)	p-value
Age (years), median (IQR)	41.5 (14 – 79)	48 (16 – 83)	44 (14 – 83)	0.29
Male gender, n (%)	31 (51.7)	21 (53.8)	3 (75.0)	0.73
Comorbidity present, n(%)	13 (24.5)	6 (19.4)	0 (0.0)	0.90
Presenting syndrome				
Thrombocytopenia	44 (74.6)	30 (76.9)	4 (100.0)	
ARDS	4 (6.7)	1 (2.5)	-	
AKI	8 (13.3)	4 (10.2)	-	0.77
Encephalopathy	1 (1.7)	-	-	
MODS	17 (28.3)	5 (12.8)	-	
Pleural effusion	1 (1.7)	1 (2.5)	-	
MV requirement	4 (6.7)	2 (5.1)	0 (0.0)	0.34
ICU requirement	36 (61.0)	12 (30.8)	2 (50.0)	0.008
Hospital stay (days)	7 (1 – 15)	6 (1 – 14)	8 (4 – 8)	0.22
Mortality rate	2 (3.3)	1 (2.6)	0 (0.0)	0.18

Others include enteric fever, dengue and leishmaniasis, MV=Mechanical Ventilation, AKI= Acute Kidney Injury

Severe transaminitis was associated with scrub typhus group, though statistically insignificant. Among various patient outcome variables, the proportion of patients requiring ICU admission was significantly higher (P = 0.008) in the scrub typhus compared to the other groups. Requirement of mechanical ventilation, hospital stay and mortality rates between the groups were not significantly different. The three transaminitis severity groups were not significantly different by age, gender, comorbidity status and etiology groups (Table 4).

Table 4: Clinical characteristics based on severity of transaminitis

Characteristics	Transaminitis severity			p-value
	Mild (n = 65)	Moderate (n = 29)	Severe (n = 9)	
Age (years)	46 (17 – 79)	38 (14 – 83)	50 (20 – 61)	0.14
Male gender, n (%)	36 (55.4)	15 (51.7)	4 (44.4)	0.87
Comorbidity present, n (%)	13 (24.1)	4 (16.0)	2 (25.0)	0.72
Presenting syndrome				
Thrombocytopenia	52 (80.0)	20 (71.4)	6 (66.7)	0.12
ARDS	1 (1.5)	2 (6.9)	2 (22.2)	0.08
AKI	7 (10.8)	2 (6.9)	3 (33.3)	0.01
Encephalopathy	0 (0.0)	1 (3.4)	0 (0.0)	0.9
MODS	10 (15.4)	8 (27.6)	4 (44.4)	0.02
MV requirement	3 (4.6)	2 (6.9)	1 (11.1)	0.07
ICU requirement	27 (41.5)	17 (58.6)	6 (66.7)	0.20
Hospital stay (days)	6 (1 – 13)	7 (2 – 14)	4 (1-15)	0.05
Mortality rate	0 (0.0)	1 (3.4)	2 (22.2)	0.03

AKI and MODS were significantly associated with severe transaminitis (P<0.05). The mortality rate was also higher in the severe transaminitis group Severity of transaminitis was not statistically associated with the clinical diagnosis. However, a larger proportion of patients with scrub typhus had severe transaminitis (13.3%) compared to other AUFI (2.6%) Table 5.

Table 5: Abbreviated table

Characteristics	Transaminitis severity			P-value
	Mild	Moderate	Severe	
Scrub typhus (n = 60)	34 (56.7)	18 (30.0)	8 (13.3)	0.223
AUFI (n = 39)	27 (69.2)	11 (28.2)	1 (2.6)	
Other etiology groups (n=4)	4 (100.0)	0 (0.0)	0 (0.0)	

DISCUSSION

The main aim of our study was to describe the etiology of AFI with transaminitis and find out the relationship between severities of transaminitis with clinical parameters. In our study, the etiology of AFI was identified in 64 (62.1%) of the patients. The rates of determining the etiology in AFI has varied from 40 – 73.3%.[9,10]A slightly better diagnosis was observed in our study, which may in part be due to our study cohort who comprised of subjects with advanced illness requiring ICU care but more importantly due to the wider diagnostic methods employed such as molecular diagnostic methods for viruses, ELISA for scrub typhus combined with RDTs for dengue, malaria, and typhoid. Despite extensive investigation with all serological testing, 37.9% of the patients in our study had an unknown cause. Though these tests are of little utility early in the course of AUFI, but they can be helpful in determining the etiology during outbreaks and for patients who present after several days of onset of illness.

Thrombocytopenia was the commonest finding among the patients (75.7%), with no significant differences between the different etiologies. Twenty two (21.3%) patients developed MODS, out of which 17 patients were of scrub typhus. The spectrums of severe multiorgan manifestations include jaundice, acute renal failure (ARF), ARDS, septic shock and disseminated intravascular coagulation (DIC) among many others.[11]Requirement of intensive care unit (ICU) admission and mechanical ventilation were observed to be more common with scrub typhus compared to others.

In addition, the scrub typhus group had a substantially greater incidence of MODS (Odds Ratio{OR}: 3.5, p<0.001), ARDS (OR: 17.1), thrombocytopenia (OR: 2.8), and transaminitis (OR: 2.8) than the non-scrub typhus group (OR: 2.7).[12]Similarly, increased transaminases and thrombocytopenia were seen in 87% and 79% of scrub typhus patients, respectively. In a large retrospective research by Varghese et al. MODS was found in 34% of the cases and central nervous system dysfunction, renal failure, and shock requiring vasoactive drugs were determined to be independent predictors of mortality in multivariate analysis.

Scrub typhus is an under studied tropical disease and a leading cause of undifferentiated treatable fever in Asia.[13,14]Scrub typhus has been regarded as a serious public health problem in Asia-Pacific area, causing illness in about 1 million people each year.[15]It is also an emerging public health problem in Nepal with several outbreaks since 2015. The prevalence of scrub typhus varies from 0%–8% to 60% in different countries.[16]Our study reports a prevalence of 58.3% for scrub typhus among patients with AFI, comparable to other studies such as those by Chrispal A et al (47.5%), Sedhain et al (35.9%), Munilakshmi et al 21 (41.7%), and Narvencar et al 18 (34%). The positivity was found to be higher in reports by Thapa S et al 524 (29.2%), Leelarasamee et al 85 (7.5%), and Khan et al 19%. (19.4%). This discrepancy could be due non-specific presentation of the disease, sample size, geographic location, and diagnostic method used. Because we included only patients with AFI with transaminitis, our reported prevalence could have been higher as scrub typhus frequently causes hepatic derangements.

The most consistent laboratory finding in scrub typhus has been transaminitis, with a variable reporting of its occurrence (66.7% to >90%).[17,18]In our study, the distribution of transaminitis (mild, moderate and severe) was not significantly different between the etiology groups. In scrub typhus there were mild to moderate elevation of transaminases (AST or ALT < 5 times upper limit of normal value). The extent of raised liver transaminases in scrub typhus is unknown and just a few studies have addressed this issue in the literature. However, severe transaminitis was more frequently observed in scrub typhus (13.3%) compared to other groups. In scrub typhus hepatitis, there was no significant variation in the magnitude of AST/ALT levels between severe and non-severe cases. This finding was supported by a report study conducted by KIM et al in 2010.[19]Furthermore, it was seen that patients with AKI, MODS, and mortality were more likely to have severe transaminitis. This possibly reveals the role of transaminase elevation as a prognostic factor for patients with AFI.

Hepatic involvement is most likely due to the organism's predilection for the liver sinusoidal epithelial cell, which causes sinusoidal infiltration, hepatocellular cholestasis, pericholangitis, and perivascular lesions in the portal area.[20]According to a recent study, infection of dendritic cells and activated inflammatory monocytes suggests a potential route for *Orientia tsutsugamushi* dissemination from the first eschar.[21] *O. tsutsugamushi*, on the other hand, as an obligate intracellular pathogen has been seen in infected hepatocytes.[22] According to Watanabe et al rickettsiae may have a direct hepatocellular cytopathic effect, rather than indirect immunoreactions.[23]These findings suggested that the immunological response of the host, rickettsial burden, and virulence may all have a role in hepatic dysfunction.

There are some limitations of the paper. First, this was single center study, it may not accurately reflect the true prevalence of AFI with transaminitis in the community at large. Second

limitation is related to epidemiology of tropical infections. These infections occur in outbreaks, thus their prevalence may vary from year to year. To identify the changing trends in epidemiology and antimicrobial susceptibility, periodic updates including follow-up investigations are required.

CONCLUSION

Our study showed Scrub typhus has emerged as the most common cause of AFI with transaminitis requiring hospital admission in this part of the country. Scrub typhus should be suspected in all patients who report with AFI with transaminitis in endemic areas and have any of the symptoms listed above.

CONFLICT OF INTEREST: None

FINANCIAL DISCLOSURE: None

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