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Inflammatory markers as a prognostic tool in acute undifferentiated febrile illness: Study from eastern Nepal

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ABSTRACT

Background & objectives: Infectious diseases are the leading causes of morbidity and death in India. Aim of this study was to asses prognosis of disease on value of inflammatory markers in patients with an acute undifferentiated febrile illness (AUFI). **Methods:** All patients aged 18 years or older who report with an AUFI and have no clear source of infection after the initial clinical assessment. The patients underwent tests for Total Leukocyte Count (TLC), C-Reactive Protein (CRP), and Lactate Dehydrogenase (LDH) on the first day of admission. These tests were then repeated every third day of sickness until discharge. **Results:** 42% cases were in 26 – 35 yr age group with mean age of study population was 29.23 ± 8.04yr and male: female ratio of 1:2.54. 120 (60%) were positive for dengue, 50 (25%) for malaria, for enteric fever 30 (15%). In our study dengue was significantly associated with levels of CRP, LDH, and TLC, whereas malaria and enteric fever were not associated with TLC levels. **Conclusions:** Our study shows higher values of inflammatory markers are early prognostic markers for the AUFI.

Key words: AUFI, prognostic tool, clinical evaluation, discharge

INTRODUCTION

An acute undifferentiated febrile illness (AUFI) refers to a fever lasting less than 14 days, with no identifiable cause related to a single organ or system.[1] India is mostly afflicted by infectious illnesses, which are the primary factors contributing to illness and mortality. There is a scarcity of field studies on the causes and outcomes of fever in India, and the ability to monitor and track it is hindered by the low availability of healthcare services.

In cases of AUFI, the symptoms are not specific, and in the absence of good diagnostic tools, it is necessary to administer broad empirical treatment to prevent fatalities. Early prognostication is of utmost importance. The indiscriminate utilization of antimicrobial agents not only results in a heightened financial load on healthcare expenses but also contributes to the escalation of drug resistance, medication interactions, and adverse drug responses among these individuals. In several regions of underdeveloped nations, where there is a scarcity of

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diagnostic resources, the causes of Acute Undifferentiated Febrile Illness (AUFI) remain mostly unidentified.

Physicians frequently make presumptive diagnoses of patients based on clinical characteristics and assumptions about the presence of circulating infections. Early prognosis is crucial for enhancing patient outcomes and determining the appropriate course of treatment. Aim of this study was to asses prognosis of disease on value of inflammatory markers in patients with AUFI.

MATERIALS AND METHODS

The study was carried out in the Department of Ophthalmology, Ram Kumar Mahabir Prasad Kedia Eye Hospital, Birgunj. A total of 200 patients, of various genders and ages 18 and above, were enrolled in the study. All patients who are 18 years of age or older and come with an Acute Unexplained Fever of Infection (AUFI) without any clear source of infection after the initial clinical assessment.

Excluded from the study were patients with cancer, autoimmune diseases, individuals on immunosuppressive medications, individuals who tested positive for Covid-19, and individuals under the age of 18. A complete history was gathered from the patient who met the established criteria.

Diagnosis involved the observation of clinical features, as well as the performance of quick antigen tests and peripheral smear examinations to detect parasites such as malaria. Blood cultures were also conducted, whenever possible. The patients underwent testing for Total Leukocyte Count (TLC), C-Reactive Protein (CRP), and Lactate Dehydrogenase (LDH) on the first day of admission. These tests were then repeated every third day throughout the duration of their illness until discharge. The statistical analysis was conducted using the Epi info program developed by the Centers for Disease Control and Prevention (CDC) in the United States.

RESULTS

200 patients, who exhibited fever as their primary symptom and had no other identifiable sources of infection, were subjected to blood sample collection. The specimens obtained and analyzed in the microbiology laboratory. The highest proportion of instances, accounting for 42%, occurred in the age range of 26 to 35 years, while the lowest proportion, just 4%, occurred in the age group of 46 to 55 years. The average age of the study population was 29.23 ± 8.04 years, with a male-to-female ratio of 1:2.54.

**Table 1. Pattern of Etiological classification of AUFI among study subjects**

Diagnosis	Number	Percentage
Dengue	120	60.00%
Malaria	50	25.00%
Enteric fever	30	15.00%

According to the Etiological categorization of Acute Undifferentiated Febrile Illness (AUFI), 120 cases (60%) tested positive for dengue, 50 cases (25%) tested positive for malaria, and 30 cases (15%) tested positive for enteric fever. (Table 1)

Figure 1. Length of hospital stay (in days)
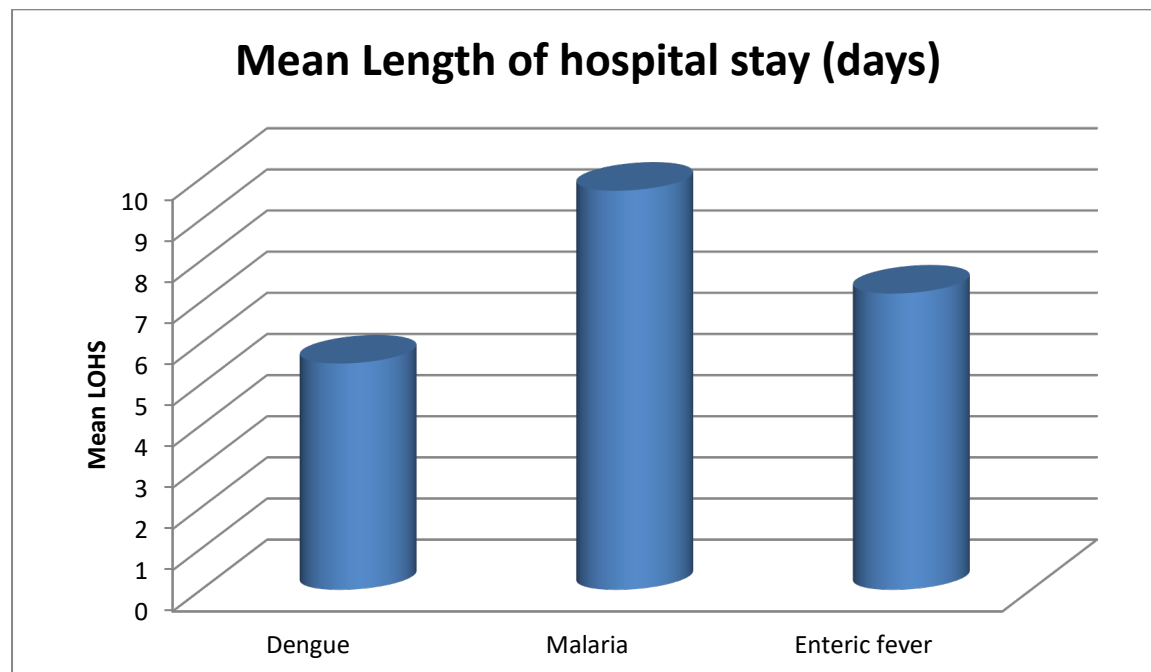
The longest duration of hospitalization was observed in cases of malaria, with an average of 9.7 ± 2.1 days. This was followed by enteric fever, which had an average hospital stay of 7.2 ± 1.5 days. On the other hand, the shortest duration of hospitalization, averaging 5.5 ± 3.2 days, was observed in cases of dengue. Out of the total number of dengue patients, 11 experienced sequelae whereas the remaining cases were minor. In some cases, patients were treated with supportive measures and were discharged after 3-5 days of being admitted, without any additional laboratory studies being conducted. (Figure 1)

Table 2: Analysis of lab parameters for dengue

Lab test	Dengue				P value
	Day 1(116)	Day 3 (116)	Day 5 (78)	Day 7 (11)	
TLC	4.65 ± 2.2	4.76 ± 2.02	5.5 ± 1.9	5.95 ± 2.3	0.010*
CRP	19.93± 20.12	11.1 ± 8.9	7.39 ± 6.2	5.22 ± 3.27	0.0001*
LDH	662.29 ± 352.85	572.83 ± 270.82	516.14 ± 248.73	479.2 ± 420.55	0.005*

Our investigation found a strong association between dengue and levels of

C-reactive protein (CRP), lactate dehydrogenase (LDH), and total leukocyte count (TLC) ($p<0.05$). (Table 2)

Table 3: Analysis of lab parameters for malaria

Lab test	Malaria						P value
	Day 1 (36)	Day 3 (32)	Day 5 (30)	Day 7 (28)	Day 9 (20)	Day 11 (10)	
TLC	5.4 ± 2.2	5.8 ± 1.2	6.4 ± 1.8	6.34 ± 1.4	6.5 ± 1.1	6.56±1.6	0.057
CRP	21.4 ± 12.3	13.6 ± 9.5	10.4 ± 6.5	8.5 ± 5.5	6.5 ±5.2	5.5 ± 4.5	0.0001*
LDH	682.34 ± 124.5	634 ± 325.2	540.25 ± 225.4	480.47 ± 213.2	440.3 ± 179.5	410.6 ± 162.5	0.003*

In our study, we found a significant correlation between malaria and levels of C-reactive protein (CRP) and lactate dehydrogenase (LDH) ($p<0.05$). However, we did not observe any association between malaria and total leukocyte count (TLC). (Table 3)

Table 4: Analysis of lab parameters for Enteric fever

Lab test	Enteric fever					P value
	Day 1 (32)	Day 3 (30)	Day 5 (28)	Day 7 (25)	Day (9) 7	
TLC	6.8 ± 4.4	6.47 ± 4.2	5.98± 4.8	5.5 ± 3.5	4.9 ± 3.1	0.703
CRP	34.2 ± 15.5	26.5 ± 18.4	18.5 ± 15.8	16.8 ± 11.5	12.2 ± 8.2	0.0001*
LDH	789 ± 166.2	689.5 ± 156.2	624.5 ± 112.6	486.2 ± 102.5	440.8 ± 88.6	0.0001*

Our investigation found a strong correlation between enteric fever and levels of CRP and LDH ($p<0.05$), while no correlation was observed with TLC ($p>0.05$). (Table 4)

DISCUSSION

Our study found that the highest proportion of instances, 42%, occurred in the age range of 26-35 years, while the lowest proportion, 4%, occurred in the age group of 46-55 years. The average age of the study population was 29.23 ± 8.04 years. The majority of cases were of males, with a male-to-female ratio of 2.54:1.

In a study conducted by Yogendra Pandurang Shelke et al. (2020) titled "Spectrum of Infections in Acute Febrile Illness in Central India," it was discovered that out of a total of 270 patients, 138 (51.11%) were male and 132 (48.88%) were female. The predominant age group was 15-25 years, accounting for 25.95% of the participants. This was followed by 16.29% of individuals in the 36-45 years age group, with a mean age of 34.56 ± 19.57 years, which was higher than the average age in our study.[2]

According to our study, out of the cases of Acute Undifferentiated Febrile Illness (AUFI), 120 (60%) were found to be positive for dengue, 50 (25%) for malaria, and 30 (15%) for enteric fever, based on their etiological classification.

In their study titled "Spectrum of Infections in Acute Febrile Illness in Central India," Yogendra Pandurang Shelke et al. (2020)[2] discovered that out of a total of 270 patients, 127 (47%) were diagnosed with scrub typhus, 33 (12%) had malaria, 47 (17.40%) had dengue, 12 (4%) had enteric fever, 5 (2%) had leptospirosis, 18 (6.66%) remained undiagnosed, and 28 (10.37%) had other infections such as viral, urinary tract infection, upper and lower respiratory tract infection, and acute gastroenteritis.

In addition, Kinley Wangdi et al. (2019)[3] identified dengue as a prevalent infection, whereas Kundavaram Paul Prabhakar Abhilash et al. (2016)[4] identified scrub typhus as the most common infection.

The study revealed that malaria had the longest duration of hospital stay, with an average of 9.7 ± 2.1 days, followed by enteric fever with an average of 7.2 ± 1.5 days. On the other hand, dengue had the shortest duration of hospital stay, with an average of 5.5 ± 3.2 days. In a study conducted by Yogendra Pandurang Shelke et al. (2020)[2], it was discovered that the average length of hospital stay for all patients with Acute Unexplained Fever of Intermediate duration (AUFI) was 5.34 ± 3.42 days.

The study found a significant association between dengue and levels of C-reactive protein (CRP), lactate dehydrogenase (LDH), and total leukocyte count (TLC) (p<0.05). Eleven individuals exhibited lucopenia on day 1, along with difficulties and an extended duration of hospitalization. Patients with a longer hospital stay demonstrated higher levels of CRP and LDH. The leukopenia and all other elevated levels returned to normal in subsequent measurements, indicating recovery. In a similar vein, Amogh Ananda Rao et al. (2020)[5] discovered that the length of hospitalization varied between two and seven days. Remarkably, there was a notable inverse relationship between the proportion of lymphocytes in the differential leukocyte count upon admission and the length of hospitalization (p=0.028).

In our study, we found a significant correlation between malaria and levels of C-reactive protein (CRP) and lactate dehydrogenase (LDH) (p<0.05). However, we did not observe any association between malaria and total leukocyte count (TLC). Patients with longer hospital stays exhibited elevated levels of CRP and LDH on the first day.

All other high numbers returned to normal in a sequential manner, indicating recovery. In a similar vein, Mohammed Abdulhafeez Hassan et al. (2021)[6] observed a substantial reduction in the total leukocyte count (TLC). Rudrajit Paul et al. (2012)[7] discovered that malaria patients had elevated mean CRP levels (31.29 ± 20.4 mg/L), which were positively associated with the length of hospitalization (P < 0.05).

CONCLUSION

Our work demonstrates that elevated levels of inflammatory markers serve as early prognostic indicators for the Acute Uncomplicated Fever of Inflammatory origin (AUFI). Assessing inflammatory markers is necessary to determine the prognosis of AUFI. Plans are underway to perform extensive studies.

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AUTHORS' CONTRIBUTION

All the authors have contributed equally.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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