

Clinical and Biochemical Profile of Patients Admitted with Fever and Multiple Organ Dysfunction Syndrome of Unknown Etiology: A Prospective Observational Study from a Tertiary Care Centre in Eastern Uttar Pradesh

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Abstract

Background: Fever with multiple organ dysfunction syndrome (MODS) in which no cause is evident after initial evaluation is common in tropical India and carries high morbidity and mortality. Regional data on its clinical and biochemical profile are limited.

Aim: To describe the clinical and biochemical profile, final diagnoses and in-hospital outcome of adults admitted with fever and MODS of unknown etiology.

Materials and Methods: A prospective observational study was conducted over one year in the Department of General Medicine, BRD Medical College, Gorakhpur. Consecutive adults with fever ($\geq 38^{\circ}\text{C}$) and dysfunction of two or more organ systems, without an established cause after initial workup, were enrolled. Clinical features, hematological, hepatic, renal and inflammatory parameters (day 1 and day 3), final diagnosis and

outcome were recorded. Chi-square or Fisher's exact test was applied; $p < 0.05$ was considered significant.

Results: Of 72 patients, 39 (54.2%) were male and 41– 60 years was the commonest age group (37.5%). Jaundice (51.4%), headache (33.3%) and abdominal pain (30.6%) were the commonest symptoms. Acute kidney injury (84.7%), hypoalbuminemia (79.2%), elevated LDH (79.2%), hyperbilirubinemia (75.0%), thrombocytopenia (59.7%) and raised procalcitonin (59.7%) were the leading derangements. Sepsis of unidentified cause (41.7%) and pyrexia of unknown etiology (30.6%) together formed 72.2% of final diagnoses. Nine patients (12.5%) died. Jaundice, dyspnea, altered sensorium and seizures were more frequent among non-survivors, without statistical significance.

Conclusion: Fever with MODS of unknown etiology is dominated by renal, hepatic and hematological dysfunction, and most cases remain etiologically unresolved. Early biochemical profiling, serial monitoring and syndromic management are essential.

Keywords: Acute kidney injury, Procalcitonin, Sepsis, Pyrexia of unknown origin, Thrombocytopenia, Jwara (fever).

Introduction

Fever is among the commonest reasons for hospital admission in tropical countries. When it is accompanied by dysfunction of two or more organ systems and no cause is evident after initial evaluation, it becomes a diagnostic and therapeutic emergency^{1,2}. Such patients present with an evolving mix of jaundice, oliguria, breathlessness, hypotension and altered sensorium, and the clinician must treat before the etiology is known.

The basis of multiple organ dysfunction syndrome (MODS) in febrile illness is a dysregulated host response. Pro-inflammatory cytokines, endothelial activation, microvascular thrombosis and mitochondrial dysfunction together impair tissue perfusion and oxygen use³. Routine laboratory tests reflect this process: raised C-reactive protein (CRP), leukocytosis or leukopenia, transaminase and bilirubin elevation, rising urea and creatinine, and coagulation abnormalities. Serum lactate, procalcitonin and ferritin add information on severity, although none is specific for etiology^{4,5}.

In India, the spectrum of acute febrile illness with MODS is shaped by local epidemiology. Studies from Karnataka and Mumbai identified dengue, leptospirosis, malaria and hepatitis E as leading causes, with mortality ranging from under 5% to 50% depending on the agent^{6,7}. Studies from eastern India highlight tuberculosis and hematological malignancy as important

causes of prolonged fever⁸. Despite extensive workup, about one-third of febrile MODS patients remain without a confirmed diagnosis⁶. Data from eastern Uttar Pradesh, a region with a large rural population and a high burden of tropical infections, are scarce.

In Ayurveda, fever is described as Jwara and is regarded as the foremost among diseases. Sannipataja Jwara (fever with vitiation of all three Dosha) is described with multisystem features and a guarded prognosis, a picture that parallels severe febrile illness with MODS⁹. A clear modern clinical and biochemical profile of this condition may help practitioners of both systems recognise severity early and plan integrative supportive care.

The present study was therefore undertaken to assess the clinical presentation, organ involvement, biochemical markers, final diagnoses and in-hospital outcome of adults admitted with fever and MODS of unknown etiology at a tertiary care centre in eastern Uttar Pradesh.

Aim and objectives: The aim was to assess the clinical and biochemical profile of patients admitted with fever with MODS of unknown etiology. The objectives were (i) to evaluate the clinical presentation and organ involvement, (ii) to analyse biochemical markers of organ dysfunction, and (iii) to determine outcomes and clinical features associated with mortality.

Materials and Methods

Study design and setting: This was a prospective observational study conducted in the Department of General Medicine, BRD Medical College, Gorakhpur, Uttar Pradesh. The institution is a tertiary referral centre serving a predominantly rural population of eastern Uttar Pradesh and adjoining areas. The study ran for one year, to capture seasonal variation in febrile illness.

Ethics: The study was approved by the Institutional Human Ethics Committee (IHEC) of BRD Medical

College, Gorakhpur, and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from each patient or legally authorised representative using an information sheet in English and Hindi. Patient identifiers were removed before analysis.

Inclusion criteria: (i) Age 18 years or above; (ii) axillary temperature $\geq 38^{\circ}\text{C}$ (100.4°F) at presentation or within 24 hours before admission; (iii) MODS, defined as dysfunction of two or more organ systems (respiratory, renal, hepatic, cardiovascular, neurological or hematological); (iv) etiology unknown after initial evaluation, including complete blood count, renal and liver function tests, chest radiograph and relevant cultures; and (v) written informed consent.

Exclusion criteria: (i) Refusal of consent; (ii) pregnancy; and (iii) pre-existing chronic organ dysfunction unrelated to the acute illness, such as chronic kidney disease, chronic liver disease or chronic heart failure.

Sampling: Consecutive sampling was used. All eligible patients admitted during the study period were enrolled, giving a final sample of 72 patients.

Definitions: Acute kidney injury (AKI) was defined by the Acute Kidney Injury Network (AKIN) criteria. Acute hepatitis was defined as a rise in serum transaminases above twice the upper limit of normal. Acute respiratory distress syndrome was defined by acute onset, bilateral infiltrates on chest radiograph and $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg. Pneumonia was defined by fever, respiratory symptoms and radiographic consolidation, and meningitis by fever, altered mental status and abnormal cerebrospinal fluid. Laboratory abnormalities (thrombocytopenia, anemia, hyperbilirubinemia, hypoalbuminemia, raised CRP, ferritin, procalcitonin

and LDH, acidosis, hyponatremia, hyperkalemia and hypertriglyceridemia) were classified against the reference ranges of the institutional laboratory.

Data collection: A structured case report form recorded demographic details, presenting symptoms, duration of fever, vital signs and organ-specific dysfunction. Laboratory data included hemoglobin, total leukocyte count (TLC), platelet count, serum bilirubin, total protein, albumin, aspartate aminotransferase (SGOT/AST), alanine aminotransferase (SGPT/ALT), alkaline phosphatase (ALP), urea and creatinine on day 1 and day 3 of admission. CRP, ferritin, LDH, triglycerides, procalcitonin, arterial blood gas and serum electrolytes were recorded at admission. Microbiological cultures, serology (dengue, scrub typhus, leptospirosis and others as indicated), PCR and imaging were documented as performed. Treatment was decided by the treating physician and was not influenced by the investigators. Outcome was recorded as discharged or expired.

Statistical analysis: Data were analysed with SPSS version 26 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as frequency and percentage. Continuous variables were tested for normality and expressed as mean $\pm$ standard deviation (SD) and median (interquartile range, IQR). Clinical features were compared between survivors and non-survivors using the Chi-square test or Fisher's exact test, as appropriate. A p-value < 0.05 was considered statistically significant.

Observations and Results

Demographic profile: Seventy-two patients were enrolled. Males slightly outnumbered females (54.2% vs 45.8%). The commonest age group was 41–60 years (37.5%), followed by 21–40 years (33.3%) (Table 1).

Table 1: Demographic profile of study participants (n=72)

Variable	Category	n	%
Gender	Male	39	54.2
	Female	33	45.8
Age group	18–20 years	6	8.3
	21–40 years	24	33.3
	41–60 years	27	37.5
	≥61 years	15	20.8

Final diagnosis: Sepsis of unidentified cause (41.7%) and pyrexia of unknown etiology (PUE, 30.6%) together accounted for 52 patients (72.2%). A specific diagnosis was reached in 20 patients (27.8%), most often pneumonia and tubercular meningitis (Table 2).

Table 2: Distribution of final diagnosis (n=72)

Diagnosis	n	%
Sepsis of unidentified cause	30	41.7
Pyrexia of unknown etiology	22	30.6
Pneumonia	8	11.1
Tubercular meningitis	6	8.3
Cellulitis	2	2.8
Liver abscess	2	2.8
Dengue	1	1.4
Viral meningitis	1	1.4

Clinical symptoms: Jaundice was the commonest symptom (51.4%), followed by headache, abdominal pain and dyspnea. Seizures were the least frequent (15.3%) (Table 3).

Table 3: Clinical symptoms at presentation (n=72)

Symptom	n	%
Jaundice	37	51.4

Symptom	n	%
Headache	24	33.3
Pain abdomen	22	30.6
Dyspnea	21	29.2
Vomiting	19	26.4
Altered sensorium	18	25.0
Seizure	11	15.3

Hematological and biochemical abnormalities: AKI was the commonest organ dysfunction (84.7%), with severe AKI in 25.0%. Hypoalbuminemia and elevated LDH (79.2% each) and hyperbilirubinemia (75.0%) were the next most frequent (Table 4).

Table 4: Hematological and biochemical abnormalities (n=72)

Abnormality	n	%
Acute kidney injury	61	84.7
Severe acute kidney injury	18	25.0
Hypoalbuminemia	57	79.2
Elevated LDH	57	79.2
Hyperbilirubinemia	54	75.0
Thrombocytopenia	43	59.7
Severe thrombocytopenia	14	19.4
High procalcitonin	43	59.7
Leukocytosis	42	58.3
High ferritin	42	58.3
High CRP	41	56.9
Anemia	31	43.1
Acidosis	28	38.9
Severe acidosis	9	12.5

Abnormality	n	%
Hyponatremia	27	37.5
Hypertriglyceridemia	23	31.9
Hyperkalemia	19	26.4

Serial laboratory parameters: Mean TLC, bilirubin, transaminases, urea and creatinine were raised on day 1 and fell slightly by day 3, while mean platelet count rose. Hemoglobin and albumin declined marginally (Table 5).

Table 5: Hematological, hepatic and renal parameters on day 1 and day 3 (n=72)

Parameter	Day 1 mean ± SD	Day 1 median (IQR)	Day 3 mean ± SD	Day 3 median (IQR)
Hemoglobin (g/dL)	11.19 ± 2.43	11.30 (9.60–12.90)	10.74 ± 2.31	10.90 (9.10–12.50)
TLC (/mm ³)	15,164.58 ± 10,469.84	12,100 (7,825–18,950)	13,982.64 ± 9,658.27	11,650 (7,600–17,100)
Platelet count (/mm ³)	141,027.78 ± 101,933.64	124,500 (92,750–206,000)	158,416.67 ± 112,548.92	139,000 (102,000–225,000)
Serum bilirubin (mg/dL)	3.26 ± 2.44	2.69 (1.95–3.61)	2.98 ± 2.16	2.40 (1.70–3.30)
Total protein (g/dL)	5.92 ± 1.02	5.95 (5.30–6.60)	5.78 ± 0.96	5.80 (5.20–6.30)
Albumin (g/dL)	2.94 ± 0.73	2.90 (2.40–3.40)	2.88 ± 0.69	2.80 (2.30–3.30)
SGOT/AST (IU/L)	146.58 ± 180.42	82.50 (42.00–178.50)	132.44 ± 164.38	75.00 (39.00–160.00)
SGPT/ALT (IU/L)	118.63 ± 142.84	65.50 (31.00–142.00)	106.71 ± 130.65	58.00 (28.00–126.00)
ALP (IU/L)	198.83 ± 112.44	176.00 (118.00–252.00)	187.52 ± 106.37	165.00 (110.00–238.00)

Parameter	Day 1 mean ± SD	Day 1 median (IQR)	Day 3 mean ± SD	Day 3 median (IQR)
Urea (mg/dL)	78.42 ± 46.63	69.50 (42.00–103.00)	70.58 ± 41.92	63.00 (38.00–92.00)
Creatinine (mg/dL)	2.42 ± 1.46	2.10 (1.68–2.84)	2.18 ± 1.31	1.90 (1.50–2.60)

Inflammatory and tissue injury markers: Median procalcitonin was 2.71 ng/mL with a wide range (0.02–101 ng/mL). Median ferritin was 643.93 ng/mL (Table 6).

Table 6: Inflammatory and tissue injury markers at admission (n=72)

Marker	Mean ± SD	Median (IQR)	Range
CRP (mg/L)	35.88 ± 22.92	32.57 (16.22–55.60)	2.1–96.4
Ferritin (ng/mL)	994.95 ± 746.45	643.93 (306.48–1,907.00)	29.9–2,001
LDH (IU/L)	548.64 ± 401.33	382.50 (276.75–756.25)	110–2,100
Triglycerides (mg/dL)	186.42 ± 92.84	168.00 (124.00–238.00)	58–498
Procalcitonin (ng/mL)	9.94 ± 20.01	2.71 (0.51–5.61)	0.02–101

Outcome: Sixty-three patients (87.5%) were discharged and nine (12.5%) died. Jaundice, dyspnea, altered sensorium and seizures were more frequent among non-survivors, but no symptom showed a statistically significant association with mortality (Table 7).

Table 7: Clinical symptoms in survivors and non-survivors

Symptom	Discharged (n=63) n (%)	Expired (n=9) n (%)	p-value*
Jaundice	31 (49.2)	6 (66.7)	0.48
Dyspnea	17 (27.0)	4 (44.4)	0.431
Altered sensorium	14 (22.2)	4 (44.4)	0.208
Seizure	9 (14.3)	2 (22.2)	0.617
Pain abdomen	20 (31.7)	2 (22.2)	0.71
Vomiting	17 (27.0)	2 (22.2)	1.00
Headache	22 (34.9)	2 (22.2)	0.703

*Fisher's exact test.

Discussion

This study shows that adults admitted with fever and MODS of unknown etiology in eastern Uttar Pradesh present with predominantly renal, hepatic and hematological dysfunction, that nearly three-quarters remain without a specific diagnosis, and that in-hospital mortality was 12.5%.

Demographic profile: The modest male predominance (54.2%) agrees with Muthaiah et al. (61.3% male) and Salagre et al. (67.8% male)^{6,7}. Greater outdoor and occupational exposure and delayed health-seeking among men may explain this pattern. Most of our patients were 41–60 years old, whereas Salagre et al. found that patients under 35 years dominated dengue, leptospirosis and malaria groups⁷. Our cohort had established MODS rather than uncomplicated febrile illness, which may favour older patients with less physiological reserve.

Diagnostic spectrum

Sepsis of unidentified cause and PUE together formed 72.2% of final diagnoses. This is far higher than the undiagnosed proportion in classical fever of unknown origin (FUO) series: 8.5% (Colpan et al.), 6.1% (Jin-ling et al.), 20.1% (Shi et al.), 17.1% (Bosilkovski et al.), 29.2% (Yan et al.) and 11.4% (Xie et al.) (10–13,15,16). Even Muthaiah et al., who studied febrile MODS, left 34.7% undiagnosed⁶. Classical FUO allows stepwise evaluation over weeks. Patients with MODS need immediate empirical therapy and organ support, and prior antibiotic use, culture-negative sepsis and late referral reduce diagnostic yield.

Dengue accounted for only 1.4% of our cases, compared with 29.3% in Mysuru, where leptospirosis was also common (22.7%)⁶. This underlines how strongly local epidemiology and season shape the etiological mix. Tubercular meningitis (8.3%) was less frequent than the tuberculosis burden of 32–50% of infectious causes reported in FUO series^{10,11,12,14}. It remains important because central nervous system tuberculosis can present with fever, altered sensorium and seizures, and our findings support early tuberculosis-directed evaluation in febrile patients with neurological signs⁸.

Clinical profile

Jaundice (51.4%) was the leading symptom and was far commoner than the 20.7% icterus reported in complicated monsoon fevers⁸. Altered sensorium was also more frequent (25.0% vs 8.8%), while headache, vomiting and abdominal pain were less common⁷. Patients who reach MODS thus show fewer constitutional symptoms and more organ-specific signs.

Hepatic and renal dysfunction

Biochemical hepatic involvement exceeded clinical jaundice: hyperbilirubinemia was present in 75.0% and

hypoalbuminemia in 79.2%. This compares with abnormal liver function in 68% in the Mysuru cohort and hepatic derangement in 66.5% of dengue cases in Mumbai^{6,7}. AKI (84.7%) was the single commonest organ dysfunction and exceeded the 45.9% renal failure seen in leptospirosis⁷. Hypoperfusion, sepsis-associated microcirculatory injury, dehydration and pre-referral nephrotoxic exposure are likely contributors. The gap between symptoms and laboratory findings shows that bedside assessment alone underestimates organ injury.

Hematological findings: Thrombocytopenia (59.7%), anemia (43.1%) and leukocytosis (58.3%) were frequent, comparable to the 78.7% hematological derangement in the Mysuru cohort⁶. Thrombocytopenia occurred despite dengue being rare, which suggests platelet consumption from sepsis, endothelial injury and microvascular activation rather than a virus-specific effect.

Inflammatory markers: Elevated LDH (79.2%), procalcitonin (59.7%), ferritin (58.3%) and CRP (56.9%) were common. In classical FUO, Xie et al. used these markers to separate infectious, inflammatory and neoplastic causes¹⁶, and Yan et al. combined clinical and laboratory indicators in a machine learning model to predict etiology¹⁵. In our MODS cohort, the markers were broadly raised across diagnostic groups, so they are better read as indicators of inflammatory burden and severity than of etiology. The combination of high ferritin, LDH and triglycerides with cytopenias also warrants screening for secondary hemophagocytic lymphohistiocytosis in selected patients.

Serial monitoring

Mean TLC, bilirubin, transaminases, urea and creatinine fell and mean platelet count rose between day 1 and day 3. This suggests early response to supportive care in many patients, although values remained abnormal.

Repeat testing on day 3 is a simple way to identify patients who are not improving.

Outcome

Mortality of 12.5% was lower than the 28% reported by Muthaiah et al. and between the 3.8–5.6% of dengue and malaria and the 32.6–50% of leptospirosis and hepatitis E reported by Salagre et al.^{6,7}. It closely matched the 12.7% in the FUO series of Colpan et al. (10) and, as expected, exceeded the mortality in pediatric FUO¹⁷. The lower rate may reflect differences in etiological mix and early supportive care. Non-survivors more often had jaundice (66.7% vs 49.2%), dyspnea (44.4% vs 27.0%), altered sensorium (44.4% vs 22.2%) and seizures (22.2% vs 14.3%). These differences were not significant, likely because only nine patients died, but they agree with the finding that central nervous system involvement and the number of failing organs predict death⁶.

Ayurvedic perspective: The classical description of Sannipataja Jwara, with involvement of all three Dosha, drowsiness, fainting, delirium, dyspnoea, haemoptysis, rashes with blackish and reddish patches, reduced elimination of urine and faeces and a poor prognosis, closely resembles the multisystem picture seen in this cohort⁹. The present profile can help Kayachikitsa (internal medicine) practitioners recognise when fever has progressed to organ dysfunction that needs urgent referral and critical care. It also provides baseline data for future integrative studies of adjuvant Ayurvedic therapy in the recovery phase of severe febrile illness.

Limitations

This was a single-centre study with a modest sample of 72 patients and only nine deaths, which limited statistical power. Advanced diagnostics were not uniformly available, which contributed to the large undiagnosed group. Severity scores, treatment-related

predictors and post-discharge follow-up were not analysed.

Conclusion

Fever with MODS of unknown etiology in this eastern Uttar Pradesh cohort was marked by acute kidney injury, hepatic dysfunction, hypoalbuminemia, thrombocytopenia and raised inflammatory markers, with in-hospital mortality of 12.5%. Nearly three-quarters of patients remained without a specific diagnosis, reflecting how rapidly organ dysfunction outpaces etiological confirmation. Laboratory evidence of organ injury was more common than clinical signs, so early and serial biochemical profiling should accompany bedside assessment. Jaundice, dyspnea, altered sensorium and seizures should prompt closer monitoring and early escalation of care. Larger multicentre studies with severity scores, expanded diagnostics and integrative approaches are needed to define prognostic markers and improve outcomes.

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Declarations

Ethical approval: Institutional Human Ethics Committee, BRD Medical College, Gorakhpur. Written informed consent was obtained from all participants.

Author contributions: AP conceived the study, collected and analysed data, and drafted the manuscript. MM supervised the study, interpreted data and critically revised the manuscript. Both authors approved the final version.

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