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Predicting outcomes in undifferentiated prolonged fever presenting to the emergency department: A prospective study from North India

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Abstract:

OBJECTIVES: Undifferentiated prolonged fever presenting to the emergency department (ED) poses significant diagnostic and prognostic challenges, particularly in low- and middle-income countries. We aimed to describe the clinical spectrum and in-hospital outcomes of adults presenting to the ED with undifferentiated prolonged fever and to identify the baseline predictors of mortality.

METHODS: In this prospective observational study, consecutive patients aged ≥ 13 years who fulfilled Durack and Street's criteria for fever of unknown origin were enrolled between March 2022 and September 2024 at the ED of a tertiary care center in North India. Patients with immunosuppressive states or nosocomial fever were excluded. All patients underwent a standardized diagnostic evaluation guided by potentially diagnostic clues. Baseline demographic, clinical, and laboratory variables recorded at ED presentation, including complete blood count-derived inflammatory indices, were evaluated as potential predictors of in-hospital mortality using receiver operating characteristic (ROC) analysis and multivariable logistic regression.

RESULTS: A total of 100 patients were enrolled (mean age: 39 years; 57% male), with a median fever duration of 45 days (interquartile range: 30–90). Infections were the most common etiology (37%), with tuberculosis predominating, followed by malignancies (21%), predominantly advanced hematological malignancies, and noninfectious inflammatory diseases (19%), which frequently presented with multisystem involvement, most commonly systemic lupus erythematosus and Still's disease. Despite extensive evaluation, 19 patients (19%) remained undiagnosed. Overall, 25 patients (25%) died during hospitalization, with the highest mortality observed among undiagnosed cases (8/19, 42%). In the univariate analysis, neutrophil percentage, neutrophil-to-lymphocyte ratio (NLR), aspartate transaminase, and lactate dehydrogenase levels were significantly higher in the mortality group, whereas total protein and albumin levels were significantly lower. ROC analysis demonstrated modest discriminatory ability for NLR (area under the curve: 0.651). In multivariable analysis, admission NLR emerged as the only independent baseline predictor of in-hospital mortality (odds ratio: 1.089 per one-unit increase; 95% confidence interval: 1.006–1.178; $P = 0.034$).

CONCLUSION: Undifferentiated prolonged fever presenting to the ED is associated with substantial in-hospital mortality and diagnostic uncertainty. Admission NLR was independently associated with mortality, but discrimination was modest; it may have adjunctive value for early risk stratification pending external validation.

Keywords:

Emergency department, fever of unknown origin, in-hospital mortality, neutrophil-to-lymphocyte ratio, prognosis, undifferentiated prolonged fever

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Box-ED Section**What is already known on the study topic?**

- Fever of unknown origin (FUO) has traditionally been studied in inpatient wards or outpatient clinic settings, with emphasis on etiological classification and diagnostic yield
- Classical FUO is often considered a relatively benign condition, with favorable outcomes and frequent spontaneous resolution in undiagnosed cases.

What is the conflict on the issue? What is its importance for the readers?

- Patients with undifferentiated prolonged fever frequently present to the emergency department (ED), yet their clinical spectrum, outcomes, and prognostic factors remain poorly characterized
- It is unclear whether ED presentations of undifferentiated prolonged fever follow the benign course described in the classical FUO series or represent a high-risk population requiring early risk stratification.

How is this study structured?

- This was a single-center, prospective, observational cohort study of 100 consecutive patients aged ≥ 13 years presenting to a tertiary care ED with undifferentiated prolonged fever.

What does this study tell us?

- Undifferentiated prolonged fever presenting to the ED is associated with substantial in-hospital mortality and frequent diagnostic uncertainty
- Baseline neutrophil-to-lymphocyte ratio is independently associated with mortality, although its discriminatory performance is modest and its role is adjunctive rather than standalone.

emergency department (ED), often with acute systemic illness, organ dysfunction, or sepsis-like features, and without prior definitive diagnostic evaluation. In this setting, ED physicians must balance early resuscitation, risk stratification, and disposition decisions under significant time and resource constraints, often before the etiology of fever is established. Despite these challenges, undifferentiated prolonged fever presenting to the ED remains poorly characterized. In resource-constrained settings, where the ED frequently serves as the primary point of care, delayed referral pathways and limited access to advanced diagnostics may further influence disease severity and prognosis at presentation.

Classically, FUO has been considered a relatively benign condition with a good prognosis, including spontaneous resolution of fever in a substantial proportion of undiagnosed cases without specific therapy.^[6] Limited available evidence, however, suggests that ED presentations of FUO may not follow this benign course. A retrospective Australian study conducted over two decades ago reported that although such presentations were relatively uncommon, they were associated with disproportionately high rates of bacteremia and poor clinical outcomes.^[7] However, prospective data evaluating the outcomes among patients presenting to the ED with undifferentiated prolonged fever are lacking.

To address this gap, we conducted a prospective observational study to evaluate the baseline predictors of in-hospital mortality among adult patients presenting to the ED with undifferentiated prolonged fever. We hypothesized that baseline laboratory markers reflecting systemic inflammatory burden – particularly complete blood count-derived indices – would be independently associated with in-hospital mortality. As a secondary objective, we aimed to describe the clinical spectrum and etiological distribution of undifferentiated prolonged fever in this ED cohort at a large tertiary care center in North India.

Methods**Study design and setting**

This prospective observational study was conducted from March 2022 to September 2024 in the Acute Care and Emergency Medicine (ACEM) Unit of the Department of Internal Medicine at the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. PGIMER, Chandigarh is a large tertiary care academic referral center serving patients from multiple states in North India. The ACEM unit manages a high volume of emergency admissions and includes emergency rooms, observation units, and a high-dependency unit providing care for critically ill medical patients. The study was approved by the

Introduction

Undifferentiated prolonged fever remains one of the most challenging clinical presentations in acute and emergency care. Traditionally described within the framework of fever of unknown origin (FUO), it is defined as a fever $\geq 38.3^{\circ}\text{C}$ lasting at least 3 weeks without a diagnosis despite structured evaluation.^[1-3] It encompasses a broad and evolving spectrum of infections, noninfectious inflammatory diseases (NIIDs), malignancies, and miscellaneous conditions, influenced by regional epidemiology, host immune status, and the availability of diagnostic resources.^[1-5]

Most existing FUO literature originates from inpatient wards or outpatient clinics, where evaluation is sequential, and patients are relatively stable.^[1-5] However, a clinically significant subset of patients with undifferentiated prolonged fever first present to the

Institutional Ethics Committee of PGIMER, Chandigarh (INT/IEC/2022/00648, dated March 16, 2022). Written informed consent was obtained from all participants or their legally authorized representatives. This study was designed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Study population

Consecutive patients aged ≥ 13 years admitted to the ACEM unit with undifferentiated prolonged fever who fulfilled Durack and Street's criteria for classic FEO were prospectively assessed for eligibility. Classic FEO was defined as fever $\geq 38.3^{\circ}\text{C}$ on multiple occasions for at least 3 weeks, with no established diagnosis after three outpatient visits or 3 days of inpatient evaluation.^[3] Patients with known immunosuppressive states (including human immunodeficiency virus [HIV] infection, posttransplant status, or chemotherapy-induced neutropenia) and those with nosocomial FEO were excluded.

Diagnostic evaluation and patient management

All enrolled patients were evaluated using a standardized diagnostic protocol for FEO guided by potentially diagnostic clues, defined as localizing clinical features or laboratory abnormalities suggestive of a specific etiology.^[2,5] Baseline evaluation included detailed clinical assessment and laboratory investigations, including complete blood count (with peripheral smear), biochemical profile, coagulation parameters, blood and other body fluid cultures, urinalysis, C-reactive protein, HIV testing, chest radiography, and ultrasonography of the abdomen.

Cross-sectional imaging with contrast-enhanced computed tomography (CT) and ^{18}F -fluorodeoxyglucose positron emission tomography combined with CT (FDG-PET/CT) was performed when clinically indicated. Image-guided biopsies and bone marrow examinations were undertaken based on clinical or radiological findings. Final diagnoses were established using the standard diagnostic criteria and guideline-recommended definitions.

Following enrollment, patients were admitted to the observation unit or high-dependency unit, depending on clinical severity and bed availability. Patients were followed throughout hospitalization until discharge, death, or leaving against medical advice.

Outcomes

In-hospital outcomes – including discharge, death, or leaving against medical advice – were recorded. Baseline demographic, clinical, and laboratory variables recorded at ED presentation were evaluated as potential predictors of in-hospital mortality, with particular emphasis

on complete blood count-derived inflammatory indices, including the neutrophil-to-lymphocyte ratio (NLR; neutrophil count/lymphocyte count), monocyte–lymphocyte ratio (monocyte count/lymphocyte count), platelet–lymphocyte ratio (platelet count/lymphocyte count), systemic inflammatory response index (neutrophil count $\times$ monocyte count/lymphocyte count), and systemic immune–inflammation index (platelet count $\times$ neutrophil count/lymphocyte count). Patients who left against medical advice were excluded from the analyses of mortality predictors.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software version 25.0 (IBM Corp., Armonk, NY, USA). The categorical variables were summarized as frequencies and percentages, and continuous variables were expressed as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR), depending on whether the data were normally distributed. Normality of continuous variables was assessed using the Shapiro–Wilk test. Group comparisons were performed using the chi-square test for categorical variables and the Mann–Whitney *U*-test or Student's *t*-test for continuous variables, depending on data distribution.

Variables demonstrating significant association on univariate analysis were evaluated for their discriminatory ability for in-hospital mortality using receiver operating characteristic (ROC) curve analysis with the calculation of the area under the curve (AUC). Variables demonstrating fair discriminatory ability and considered clinically relevant were entered into multivariable logistic regression to identify the independent predictors of mortality. The number of predictors included in the model was limited to minimize overfitting, given the limited number of mortality events. Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test. Multicollinearity among candidate predictors was evaluated using correlation matrices.

A two-sided $P < 0.05$ was considered statistically significant. As this was a prospective cohort study, all consecutive eligible patients presenting during the study period were enrolled; a formal *a priori* sample size calculation was not performed.

Results

Baseline characteristics

During the study period, 103 consecutive patients fulfilled criteria for FEO. Three patients were excluded due to underlying HIV infection, and 100 patients were included in the final analysis [Figure 1]. The

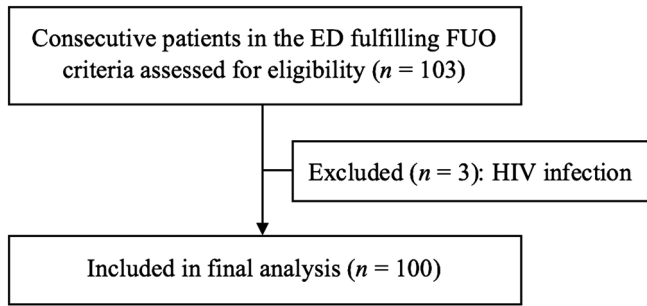


Figure 1: Flow diagram of eligibility assessment and inclusion. ED: Emergency department, FUO: Fever of unknown origin, HIV: Human immunodeficiency virus

mean age was 38.8 ± 17.6 years, and 57 were male. The median duration of fever at ED presentation was 45 days (IQR: 30–90), and 77 patients had a documented temperature $\geq 39^\circ\text{C}$ at ED admission. The common presenting symptoms included weight loss (71%), cough (49%), dyspnea (33%), and abdominal pain (17%). On examination, hepatosplenomegaly was present in 60% of patients, lymphadenopathy in 36%, and skin rash in 18%.

Diagnostic investigations

Whole-body imaging was performed in 46 patients (contrast-enhanced CT in 38, FDG-PET/CT in 19, and both in 11), yielding potentially diagnostic clues in 36 patients (78.3%). Imaging-guided tissue sampling was undertaken in 29 patients and established the final diagnosis in 21 (72.4%). Bone marrow examination was performed in 26 patients and contributed to the final diagnosis in 14 (53.8%). Blood cultures were obtained at admission in all patients and were diagnostically contributory in four cases.

Etiological spectrum

The etiological distribution is summarized in Table 1. Infections were the most common cause ($n = 37$).

Tuberculosis was the single most frequent diagnosis ($n = 15$), including disseminated ($n = 10$) and extrapulmonary disease ($n = 5$). Diagnosis was established by acid-fast bacilli staining ($n = 6$), GeneXpert ($n = 2$), histopathology ($n = 2$), or characteristic clinicoradiological features ($n = 5$). Thirteen patients improved on antituberculous therapy; two died due to advanced disease.

Tropical infections ($n = 9$) included enteric fever ($n = 3$), scrub typhus ($n = 2$), malaria ($n = 1$), dengue ($n = 1$), and undifferentiated tropical fevers ($n = 2$). Malaria was diagnosed on repeat peripheral smear examination. Other tropical infections (except undifferentiated cases) were serologically confirmed. Thrombocytopenia and hepatosplenic involvement were common, and all patients improved.

Table 1: Etiological spectrum of undifferentiated prolonged fever ($n=100$)

Etiology	n (%)
Infections	37 (37)
Tuberculosis	15 (15)
Infective endocarditis	3 (3)
Complicated UTI	3 (3)
Enteric fever	3 (3)
Nonresolving pneumonia	2 (2)
Scrub typhus	2 (2)
Undifferentiated tropical febrile illnesses	2 (2)
Disseminated histoplasmosis	1 (1)
Malaria	1 (1)
Dengue	1 (1)
Visceral leishmaniasis	1 (1)
<i>Klebsiella pneumoniae</i> bacteremia	1 (1)
Infected pancreatic collection	1 (1)
Esophageal candidiasis	1 (1)
Malignancy	21 (21)
Non-Hodgkin lymphoma	8 (8)
Hodgkin lymphoma	5 (5)
Acute leukemia	5 (5)
Myeloproliferative neoplasm	1 (1)
Angiosarcoma of the liver	1 (1)
Metastatic squamous cell carcinoma	1 (1)
Noninfectious inflammatory diseases	19 (19)
Systemic lupus erythematosus	8 (8)
Still's disease	5 (5)
Dermatomyositis	2 (2)
ANCA-associated vasculitis	1 (1)
Pauci-immune renal-limited glomerulonephritis	1 (1)
Sarcoidosis	1 (1)
Silicosis with pulmonary alveolar proteinosis	1 (1)
Miscellaneous	4 (4)
Hemophagocytic lymphohistiocytosis	3 (3)
Thrombotic microangiopathy	1 (1)
Unknown	19 (19)

ANCA: Antineutrophil cytoplasmic antibody, UTI: Urinary tract infection

Three patients with complicated urinary tract infections presented with acute kidney injury. Diagnosis was established based on repeat urinalysis and CT imaging; one had *Escherichia coli* growth on repeat cultures. One patient died due to sepsis and multiorgan failure.

Two patients had nonresolving pneumonia with multiorgan dysfunction. Diagnosis was established through repeated respiratory sampling and thoracic CT. One patient with dual *E. coli*–*Aspergillus* infection died due to progressive respiratory failure with multiorgan dysfunction.

Infective endocarditis was culture-proven ($n = 2$; *Streptococcus* species and *Pseudomonas aeruginosa* complicating a coronary stent pseudoaneurysm). One patient had *Klebsiella pneumoniae* bacteremia without an identifiable primary focus and died due to septic

shock. Additional infectious causes included esophageal candidiasis diagnosed on endoscopy ($n = 1$) and an infected pancreatic collection identified on whole-body imaging ($n = 1$). Visceral leishmaniasis ($n = 1$) was diagnosed by rK39 serology and polymerase chain reaction and successfully treated with amphotericin B. Progressive disseminated histoplasmosis ($n = 1$) was confirmed on lymph node biopsy; this patient died due to advanced disease.

Malignancy ($n = 21$) included 19 hematological and 2 solid-organ cancers. Lymphoid malignancies predominated ($n = 13$), including non-Hodgkin lymphoma ($n = 8$; diffuse large B-cell, $n = 5$; angioimmunoblastic T-cell, $n = 2$; anaplastic large cell, $n = 1$) and Hodgkin lymphoma ($n = 5$). All lymphomas were Stage IV at presentation. Acute leukemia ($n = 5$) and myeloproliferative neoplasm ($n = 1$; primary myelofibrosis) required bone marrow examination for the diagnosis due to absent peripheral blasts and noncontributory initial imaging. Solid tumors included hepatic angiosarcoma ($n = 1$) and metastatic squamous cell carcinoma ($n = 1$), diagnosed by liver and retroperitoneal biopsies, respectively. Three patients with malignancy (two with acute leukemia and one with Hodgkin lymphoma) died due to advanced or progressive disease.

Among noninfectious inflammatory diseases ($n = 19$), systemic lupus erythematosus (SLE; $n = 8$) was the most common diagnosis and uniformly presented with multisystem involvement. Three patients with SLE died (two due to multiorgan dysfunction and one due to superadded fungal sepsis). Patients with Still's disease ($n = 5$) presented with neutrophilic leukocytosis, marked hyperferritinaemia (>2000 ng/mL), and serositis. As diagnosis required exclusion of alternative causes, extensive evaluation was performed, including CT ($n = 5$), FDG-PET/CT ($n = 2$), bone marrow examination ($n = 4$), and skin biopsy ($n = 2$). One patient with Still's disease died due to a progressive hyperinflammatory state.

Two patients with anti-melanoma differentiation-associated gene 5 (MDA5) dermatomyositis developed rapidly progressive interstitial lung disease and died of respiratory failure. Both cases of vasculitis responded to immunosuppressive therapy. Sarcoidosis was confirmed by endobronchial ultrasound-guided biopsy. Silicosis-associated pulmonary alveolar proteinosis was confirmed by open lung biopsy, and the patient died of progressive respiratory failure.

Miscellaneous causes included hemophagocytic lymphohistiocytosis (HLH) without identifiable triggers ($n = 3$) and thrombotic microangiopathy ($n = 1$). HLH was diagnosed using HLH-2004 criteria; one patient died due to progressive hyperinflammatory

syndrome. Thrombotic microangiopathy was diagnosed based on schistocytes on repeat peripheral smear and resolved with therapeutic plasma exchange.

Despite extensive evaluation, no definitive etiology was identified in 19 patients. Among these, only four underwent whole-body imaging, which did not yield potentially diagnostic clues. Eight of the 19 undiagnosed patients died, predominantly due to progressive multiorgan dysfunction.

Outcomes

The median time from ED admission to definitive diagnosis was 6.5 days (IQR 3–15). Twenty-six patients required intensive care unit admission, of whom 15 required mechanical ventilatory support. The median hospital stay was 10 days (IQR: 5–16), shorter in the undiagnosed group (7 days, IQR: 3.5–12) than in diagnosed cases (11 days, IQR: 6–18).

Overall, 25 patients (25%) died during hospitalization, and five left against medical advice. Mortality was higher among undiagnosed cases (8/19, 42%) compared with those with established diagnoses (17/81, 21%).

Predictors of in-hospital mortality

In the univariate analysis, neutrophil percentage, NLR, aspartate transaminase (AST), and lactate dehydrogenase (LDH) levels were significantly higher in the mortality group, whereas total protein and albumin levels were significantly lower [Table 2]. ROC analysis demonstrated modest discriminatory ability for LDH (AUC: 0.727; 95% confidence interval [CI]: 0.595–0.860; $P = 0.002$), AST (AUC: 0.677; 95% CI: 0.523–0.830; $P = 0.018$), NLR (AUC: 0.651; 95% CI: 0.506–0.796; $P = 0.043$), and neutrophil percentage (AUC: 0.648; 95% CI: 0.506–0.790; $P = 0.048$). Albumin and total protein showed inverse, nonsignificant discrimination.

Multivariable logistic regression analysis, including NLR, albumin, and LDH, showed that admission NLR remained the only independent predictor of in-hospital mortality (odds ratio: 1.089 per one-unit increase; 95% CI: 1.006–1.178; $P = 0.034$), whereas albumin and LDH did not retain statistical significance [Table 3]. The model demonstrated acceptable calibration (Hosmer–Lemeshow $P = 0.272$) with modest explanatory power (Nagelkerke $R^2 = 0.213$). In an alternative model that included AST in place of albumin, NLR remained the only independent predictor, whereas AST and LDH did not retain statistical significance.

Discussion

This prospective study demonstrates that undifferentiated prolonged fever presenting to the ED represents a

Table 2: Univariate analysis of baseline predictors of in-hospital mortality

Parameter (s)	All (n=100)	Survivors (n=70)	Died (n=25)	P
Age (years)	38.8±17.7	37.2±17.2	40.1±17.0	0.469
Male gender	57 (57)	41 (58.6)	12 (48.0)	0.361
Duration of fever (days)	45 (30–90)	30 (30–63)	60 (30–90)	0.105
Maximum temperature (°C)	39.2±0.7	39.2±0.7	39.2±0.8	0.62
Weight loss	71 (71)	52 (74.3)	15 (60)	0.179
Hemoglobin (g/dL)	8.3±2.3	8.3±2.1	8.1±2.5	0.744
TLC (per mm ³)	8900 (4425–15,600)	8700 (4400–15,700)	9300 (4300–15,500)	0.899
Platelets (per mm ³)	215,000 (95,000–369,000)	154,500 (72,000–254,750)	103,000 (25,000–220,000)	0.058
Differential count				
Neutrophil (%)	75.9 (57.6–84.0)	72.4 (50.6–83.1)	80.0 (65.6–86.4)	0.04
Lymphocyte (%)	12.3 (8.1–23.0)	13.2 (9.3–24.0)	10.8 (7.1–19.8)	0.059
Monocyte (%)	7.7 (4.5–12.1)	7.9 (5.0–11.8)	5.5 (3.5–13.1)	0.256
NLR	6.0 (2.1–10.1)	5.0 (1.8–8.6)	7.8 (3.5–12.7)	0.036
MLR	0.5 (0.3–1.0)	0.5 (0.3–0.8)	0.4 (0.3–1.1)	0.732
PLR	115.1 (62.2–246.9)	114.4 (65.2–255.1)	132.0 (49.5–262.8)	0.939
SIRI	4486.2 (972.0–8645.2)	4486.2 (647.3–8600.8)	3822.9 (1279.3–7496.2)	0.859
SII	779,937.1 (125,641.1–1,963,842.1)	779,937.1 (111,578.1–2,048,255.8)	715,858.8 (159,994.5–1,746,044.5)	0.716
Serum bilirubin (mg/dL)	0.7 (0.5–1.5)	0.7 (0.5–1.3)	0.9 (0.5–2.1)	0.537
AST (U/L)	39.8 (27.0–87.8)	36.5 (24.9–65.0)	81.5 (34.4–155.6)	0.015
ALT (U/L)	27.7 (14.8–61.9)	23.85 (14.2–56.0)	40.7 (13.6–76.1)	0.321
ALP (U/L)	168.0 (115.5–271)	168.0 (115–260)	191.5 (108.8–321)	0.789
LDH (U/L)	396 (247–759)	351 (229–564)	666 (464–1811)	0.002
Total protein (g/dL)	6.2±1.1	6.4±1.0	5.6±1.3	0.004
Albumin (g/dL)	2.7±0.6	2.8±0.6	2.4±0.6	0.028
CRP (mg/L)	107 (51–163)	95 (36–168)	112.5 (62.5–152.8)	0.697
Ferritin (ng/mL) (n=60)	1894 (813–3950)	1689 (723–5577)	2000 (1650–3136)	0.409
Fibrinogen (g/L) (n=47)	3.7 (2.5–4.7)	4.0 (3.0–4.9)	2.5 (1.2–3.2)	0.084

Values are given as *n* (%), mean±SD, or median (IQR). ALP: Alkaline phosphatase, ALT: Alanine transaminase, AST: Aspartate transaminase, CRP: C-reactive protein, IQR: Interquartile range, LDH: Lactate dehydrogenase, MLR: Monocyte lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet lymphocyte ratio, SD: Standard deviation, SII: Systemic immune-inflammation index, SIRI: Systemic inflammatory response index, TLC: Total leukocyte count

Table 3: Multivariate analysis of baseline predictors of in-hospital mortality

Parameters	OR (95% CI)	P
NLR	1.089 (1.006–1.178)	0.034
Albumin	0.423 (0.163–1.095)	0.076
LDH	1.001 (1.000–1.001)	0.076

NLR: Neutrophil-to-lymphocyte ratio, LDH: Lactate dehydrogenase, OR: Odds ratio, CI: Confidence interval

high-risk clinical entity. In contrast to traditional FUO cohorts – often derived from ward- or clinic settings – our ED cohort was characterized by acute multisystem illness, advanced disease at presentation, and high in-hospital mortality. A substantial proportion of patients remained without a definitive diagnosis despite extensive evaluation. Admission NLR was independently associated with in-hospital mortality; however, its discriminatory performance was modest.

Although infections remained the most common etiological category, their relative contribution differed from many classical FUO series from low- and middle-income countries, where indolent infections, particularly tuberculosis, often predominate.^[1,4,5,8] While tuberculosis remained frequent in our cohort,

its proportional dominance was attenuated, with a broader spectrum of acute bacterial and endemic infections becoming more prevalent. This pattern suggests presentation during a more dynamic and clinically unstable phase of infectious illness in the ED, in which classical diagnostic features may be incomplete or evolving.^[9] Similarly, malignant and NIID etiologies frequently presented with advanced or rapidly progressive multisystem involvement mimicking sepsis.^[8,10] Together, these overlapping infectious, inflammatory, and malignant phenotypes underscore the diagnostic complexity of undifferentiated prolonged fever in the ED.

Notably, nearly one-fifth of patients remained undiagnosed, and this group experienced the highest mortality. This likely reflects both early disease evolution and the practical constraints inherent to ED-based care. Advanced diagnostic modalities such as FDG-PET/CT and image-guided biopsies, while valuable in classical FUO algorithms, may not be immediately feasible in unstable patients or within the time-limited ED environment.^[1,2,4] Consequently, undifferentiated prolonged fever presenting to the

ED cannot be approached using the serial, stepwise diagnostic pathways designed for stable inpatient or outpatient populations.^[1,2,5,11] Instead, ED evaluation must prioritize simultaneous physiological stabilization and early source localization, with expedited imaging and targeted tissue sampling when feasible, alongside careful reassessment to avoid diagnostic anchoring.

Classical FUO series have largely emphasized etiological classification and diagnostic yield, with limited focus on short-term outcomes. In many such cohorts, not only do diagnosed cases have a favorable prognosis, but undiagnosed cases often experience spontaneous resolution of fever.^[4,6,12] In contrast, our findings highlight that FUO presenting to the ED is associated with substantial mortality. This divergence underscores the importance of recognizing ED presentations of prolonged fever as a prognostically distinct entity, in which early outcome assessment may be as critical as etiological diagnosis. As emphasized by Durack and Street, FUO must be interpreted within its clinical context, as prognosis, diagnostic priorities, and urgency vary across patient groups.^[3] Consistent with this principle, the outcomes observed in our emergency department cohort underscore the need for early risk stratification before etiological clarity is achieved.

In this context, admission NLR was independently associated with in-hospital mortality. Prior emergency and critical care studies have consistently demonstrated associations between elevated NLR and adverse outcomes across heterogeneous conditions, including severe infections, inflammatory disease flares, and malignancy-associated hyperinflammatory states.^[13-20] Notably, reported “high-risk” thresholds vary considerably, underscoring the context-dependent nature of NLR rather than a universal cut-off. Accordingly, NLR was analyzed as a continuous variable in our cohort. Although the per-unit effect size was modest, increasing NLR values were associated with higher odds of mortality. NLR may reflect the degree of early systemic inflammatory response at ED presentation. Given its availability and low cost, it may have adjunctive value in early ED assessment of undifferentiated prolonged fever, supporting closer monitoring and expedited diagnostic evaluation. However, its modest discriminatory performance indicates that it should not be used as a standalone prognostic tool. These findings are hypothesis-generating and warrant validation in larger, multicenter cohorts before routine clinical application.

Limitations

This study has limitations. First, it was conducted at a single tertiary-care referral ED, which may limit the generalizability to other emergency care settings with differing patient acuity, referral patterns, and

resource availability. Second, advanced investigations, such as FDG-PET/CT, image-guided tissue sampling, and metagenomic testing, could not be performed uniformly across all patients due to clinical instability or logistical constraints inherent to emergency care, potentially reducing the etiological yield, particularly in undiagnosed cases. Third, postdischarge follow-up was limited, and some diagnoses may have been established after hospitalization. Fourth, the sample size was determined by patient accrual over the study period and may have limited statistical power to detect the smaller associations. Given the limited number of mortality events, the number of variables included in multivariable modeling was restricted to minimize overfitting. Only admission clinical and laboratory parameters were analyzed, consistent with the primary objective of evaluating early predictors of outcome. Time-dependent factors such as disease progression, treatment escalation, intensive care interventions, and mechanical ventilation were not incorporated into the regression models; therefore, residual confounding by underlying disease severity cannot be entirely excluded, as is common in observational prognostic studies conducted in acute care settings.

Conclusion

Undifferentiated prolonged fever presenting to the ED represents a high-risk clinical entity distinct from classical FUO, characterized by diagnostic uncertainty and substantial in-hospital mortality, and requiring early prognostication. Admission NLR was independently associated with in-hospital mortality; however, its discriminatory performance was modest. As a readily available and inexpensive marker, NLR may have adjunctive value in early ED evaluation, but it should not be considered a standalone prognostic tool. These findings warrant validation in larger, multicenter cohorts before routine clinical implementation.

Author contributions

AKP: Conceptualization (lead); Methodology (lead); Formal analysis (lead); Writing - original draft (supporting), Writing - review and editing (lead)

VK: Data curation (lead); Writing - original draft (lead)

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RK: Data curation (supporting); Writing - review and editing (supporting)

DPD: Data curation (supporting); Writing - review and editing (supporting)

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Conflicts of interest

None Declared.

Ethical approval

The Institutional Ethics Committee of Postgraduate Institute of Medical Education and Research, Chandigarh (India) approved the study (No.: INT/IEC/2022/00648, date March 16, 2022).

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