E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/16.02.212

Research Article

A Clinico-Epidemiological Profile and Etiological Spectrum of Fever of Unknown Origin in Children Age 1-17 Years: A Prospective Observational Study from a Tertiary Care Centre in North India

Dr. Anshu Vyas[1], Dr. Rinku Saini[2], Dr. Lovesh Saini[3], Dr. Yashvi Gehlot[4], Dr. Priti Saini[5]
[1]Post Graduate Student, Department of Pediatric Medicine, SMS Medical College & Attached Group of Hospitals, Jaipur
[2]Professor, Department of Pediatric Medicine, SMS Medical College & Attached Group of Hospitals, Jaipur
[3]Associate Professor, Department of Preventive & Social Medicine, SMS Medical College & Attached Group of Hospitals, Jaipur
[4]Senior Demonstrator, Department of Pathology, SMS Medical College & Attached Group of Hospitals, Jaipur
[5]Professor, Department of Pathology, SMS Medical College & Attached Group of Hospitals, Jaipur
Corresponding Author: Dr Priti Saini
Professor, Department of Pathology, SMS Medical College & Attached Group of Hospitals, Jaipur
Email: drpritirps@gmail.com
Address: 502, Sunshine Kalyan, Sikar Road, Jaipur, Pin 302039
Received: 11.06.2026 Revised: 20.07.2026 Accepted: 06.08.2026

ABSTRACT
Background: Fever of unknown origin (FUO) remains a major diagnostic challenge in paediatric practice because of its diverse etiologies and variable clinical manifestations. Contemporary prospective data from North-Western India are limited.
Objectives: To evaluate the clinico-epidemiological profile and etiological spectrum of fever of unknown origin among children age 1–17 years admitted to a tertiary care centre.
Methods: A hospital-based prospective observational study was conducted in the Department of Paediatric Medicine, Sir Padampat Institute of Neonatology and Paediatric Health, SMS Medical College, Jaipur, from June 2024 to May 2025. Eighty children fulfilling the predefined criteria for fever of unknown origin were enrolled. Demographic characteristics, clinical features, laboratory investigations, imaging findings, and final diagnoses were recorded using a standardized protocol. Statistical analysis was performed using SPSS version 26.0.
Results: The mean age of participants was 6.93 ± 5.15 years, with children age 1–5 years accounting for 53.75% of cases. Males predominated (61.25%). The mean duration of fever was 33.05 ± 13.6 days. Poor activity and appetite (81.25%) and weight loss (51.25%) were the most frequent presenting features. Anaemia was the commonest haematological abnormality (66.25%). Infectious diseases represented the predominant etiological group (83.75%), followed by malignancies (8.75%), undiagnosed cases (5.0%), and connective tissue diseases (2.5%). Tuberculosis (47.5%) and brucellosis (25.0%) were the leading final diagnoses. Thrombocytopenia, leukopenia, neutropenia, and pancytopenia showed significant associations with malignant disorders.
Conclusions: Infectious diseases, particularly tuberculosis, remain the principal cause of paediatric fever of unknown origin in this region. A structured, stepwise diagnostic approach supported by targeted laboratory investigations facilitates early diagnosis and appropriate management while reducing unnecessary investigations and empirical antimicrobial therapy.

Keywords: Fever of unknown origin; Children; Tuberculosis; Brucellosis; Pediatric infection; Clinico-epidemiological study.

INTRODUCTION

Fever is one of the most frequent reasons for paediatric outpatient visits and hospital admissions. Although most febrile illnesses in children are self-limiting and resolve within a few days, prolonged fever without an identifiable cause remains a significant diagnostic challenge. Fever of unknown origin (FUO) represents a heterogeneous clinical entity encompassing infectious, inflammatory,

autoimmune, malignant, and miscellaneous disorders. Delayed diagnosis may result in prolonged hospitalization, inappropriate antimicrobial therapy, increased healthcare costs, and considerable anxiety for both caregivers and clinicians (1,2).

The concept of FUO has evolved considerably since it was first described by Petersdorf and Beeson in 1961 as documented fever of at least 38.3°C lasting for three weeks without a definitive diagnosis despite one week of inpatient evaluation (2). With advances in diagnostic technology and changing healthcare practices, this classical definition has been modified, particularly for paediatric patients. Current paediatric studies generally define FUO as unexplained fever persisting for two weeks or longer despite an appropriate history, physical examination, and initial diagnostic evaluation (3,4). This revised definition reflects the shorter duration of common viral illnesses in children and facilitates earlier identification of serious underlying diseases.

The etiological spectrum of paediatric FUO varies considerably across different geographic regions, socioeconomic conditions, and healthcare systems. Infectious diseases continue to represent the leading cause in most developing countries, whereas autoimmune disorders, connective tissue diseases, malignancies, and undiagnosed conditions contribute a greater proportion of cases in developed nations (5,6). Improvements in vaccination coverage, public health measures, microbiological techniques, molecular diagnostics, and advanced imaging have altered the epidemiological profile of FUO over recent decades. Nevertheless, a substantial proportion of children remain undiagnosed even after comprehensive evaluation, emphasizing the complexity of this clinical condition (6,7).

Diagnosis of FUO requires a meticulous and systematic approach. A comprehensive clinical history and repeated physical examination remain the cornerstone of evaluation, often providing important diagnostic clues that guide further investigations. Baseline laboratory tests, microbiological cultures, serological investigations, imaging studies, and invasive procedures should be performed selectively according to clinical suspicion rather than indiscriminately. Such an evidence-based approach not only improves diagnostic yield but also minimizes unnecessary investigations, reduces healthcare expenditure, and prevents inappropriate empirical treatment (4,7,8).

The epidemiology of paediatric FUO differs significantly between countries and even among different regions within the same country. In India, infectious diseases such as tuberculosis, enteric fever, scrub typhus, brucellosis, urinary tract infection, and other endemic infections continue to account for the majority of cases because of regional disease prevalence, environmental exposure, and socioeconomic factors (5,8). However, increasing recognition of autoimmune diseases, haematological malignancies, and inflammatory disorders has broadened the differential diagnosis, requiring clinicians to adopt a multidisciplinary diagnostic strategy.

Despite several published studies, prospective data describing the clinico-epidemiological profile and etiological spectrum of paediatric FUO from North-Western India, particularly Rajasthan, remain limited. Regional differences in infectious disease prevalence, healthcare accessibility, nutritional status, and diagnostic facilities necessitate contemporary local evidence to guide clinical decision-making. Understanding the current distribution of etiological factors and associated clinical characteristics may facilitate earlier diagnosis, optimize resource utilization, and improve patient outcomes.

Therefore, the present prospective observational study was undertaken to evaluate the clinico-epidemiological profile, laboratory characteristics, and etiological spectrum of fever of unknown origin among children age 1–17 years admitted to a tertiary care centre in Rajasthan. The findings are expected to contribute contemporary regional evidence regarding paediatric FUO and assist clinicians in developing a rational, stepwise diagnostic approach for children presenting with prolonged unexplained fever.

MATERIALS AND METHODS

Study Design and Setting

This hospital-based prospective observational study was conducted in the Department of Paediatric Medicine, Sir Padampat Institute of Neonatology and Paediatric Health, Sawai Man Singh Medical College and its attached hospitals, Jaipur, Rajasthan, India.

Study Population

Children age 1–17 years admitted with fever of unknown origin (FUO) were screened for eligibility. Fever of unknown origin was defined as fever persisting for more than two weeks

without an identifiable source after detailed history taking, comprehensive physical examination, and initial screening investigations.

Sample Size

The sample size was calculated using the formula:

$n = Z^2pq/d^2$

Assuming an infection prevalence of 37.31%, a 95% confidence level, and an absolute precision of 9%, the minimum required sample size was calculated as 77. To compensate for possible exclusions and incomplete data, 80 children were enrolled.

Inclusion Criteria

- Children age 1–17 years admitted with fever of unknown origin.
- Fever lasting for more than two weeks without an established diagnosis after initial evaluation.
- Written informed consent obtained from parents or legal guardians.

Exclusion Criteria

- Nosocomial fever of unknown origin.
- Primary immunodeficiency disorders.
- Human immunodeficiency virus (HIV) infection.

Data Collection

Eligible participants were enrolled consecutively after obtaining informed consent. A predesigned case record form was used to document demographic characteristics, duration and pattern of fever, associated symptoms, previous medical history, birth history, immunization status, nutritional status, socioeconomic background, drug exposure, and relevant epidemiological information. A detailed systemic examination was performed in every patient, with particular attention to identifying clinical clues that could indicate the underlying etiology.

The study was approved by the Institutional Ethics Committee of SMS Medical College, Jaipur.

Diagnostic Evaluation

All patients underwent a standardized stepwise diagnostic approach. Initial investigations included complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), peripheral smear for malarial parasites, blood culture, urine examination, urine culture, Mantoux test, and chest radiography.

Further investigations were performed according to clinical suspicion and included liver and renal function tests, serum ferritin, antinuclear antibody (ANA), anti-double stranded DNA antibody, Brucella IgM ELISA, viral serology, echocardiography, ultrasonography, contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), cartridge-based nucleic acid amplification test (CBNAAT), cerebrospinal fluid (CSF) analysis, bone marrow aspiration, bone marrow biopsy, and tissue biopsy whenever indicated.

Blood and urine cultures were collected before initiation of antimicrobial therapy using standard aseptic techniques. Repeat cultures and advanced imaging studies were performed whenever the initial investigations remained inconclusive. Lumbar puncture was carried out in children with suspected central nervous system involvement after obtaining informed consent and excluding contraindications.

The final diagnosis was established based on the combined interpretation of clinical findings, laboratory investigations, microbiological studies, radiological imaging, and histopathological examination whenever applicable.

Outcome Measures

The primary outcome was determination of the clinico-epidemiological profile and etiological spectrum of paediatric fever of unknown origin.

Secondary outcomes included:

- Demographic characteristics.
- Duration and severity of fever.
- Clinical presentation.
- Hematological abnormalities.
- Diagnostic yield of various investigations.
- Association between hematological parameters and final etiological diagnosis.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using IBM SPSS Statistics version 26.0. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) according to data distribution. Categorical variables were summarized as frequencies and percentages. Associations between categorical variables were assessed using the Chi-square test or Fisher's exact test, whereas continuous variables were compared using the Student's t-test or Mann-Whitney U test, as appropriate. A p-value <0.05 was considered statistically significant.

RESULTS

Table 1. Baseline demographic and clinical characteristics of the study population (N = 80)

Variable	Value
Age (years), mean ± SD	6.93 ± 5.15
Age group, n (%)	
1–5 years	43 (53.75)
6–10 years	13 (16.25)
11–15 years	19 (23.75)
>15 years	5 (6.25)
Male sex, n (%)	49 (61.25)
Female sex, n (%)	31 (38.75)
Duration of fever (days), mean ± SD	33.05 ± 13.60
15–30 days	42 (52.50)
31–45 days	27 (33.75)
46–60 days	5 (6.25)
>60 days	6 (7.50)
Temperature (°C), mean ± SD	38.08 ± 0.43

Table 2. Clinical presentation and hematological abnormalities

Variable	Number (%)
Clinical features	
Poor activity and appetite	65 (81.25)
Weight loss	41 (51.25)
Neurological symptoms	17 (21.25)
Gastrointestinal symptoms	9 (11.25)
Respiratory symptoms	6 (7.50)
Urogenital symptoms	6 (7.50)
Petechiae/ecchymosis	5 (6.25)
Arthralgia	2 (2.50)
Lymphadenopathy	2 (2.50)
Skin rash	2 (2.50)
Hematological abnormalities	
Anemia	53 (66.25)
Leukocytosis	26 (32.50)
Thrombocytopenia	15 (18.75)
Neutropenia	7 (8.75)
Thrombocytosis	6 (7.50)
Leukopenia	5 (6.25)
Pancytopenia	5 (6.25)

Table 3. Etiological spectrum and final diagnoses

Variable	Number (%)
Etiological category	
Infection	67 (83.75)
Malignancy	7 (8.75)
Connective tissue disease	2 (2.50)
Undiagnosed	4 (5.00)
Final diagnosis	
Tuberculosis	38 (47.50)
Brucellosis	20 (25.00)
Urinary tract infection	6 (7.50)
B-cell acute lymphoblastic leukemia	4 (5.00)
Hemophagocytic lymphohistiocytosis	3 (3.75)

Liver abscess	3 (3.75)
Systemic lupus erythematosus	2 (2.50)
Undiagnosed	4 (5.00)

Table 4. Diagnostic yield of selected investigations according to final diagnosis

Investigation	**Major diagnostic contribution**
Brucella IgM ELISA	Confirmed most cases of brucellosis
Bone marrow aspiration	Diagnosis of hematological malignancy
Bone marrow biopsy	Confirmation of leukemia
ANA testing	Diagnosis of connective tissue disease
CBNAAT	Confirmation of tuberculosis in selected patients
CSF analysis	Diagnosis of neurological infectious disorders
CECT/MRI	Identification of occult infectious foci and complications

Table 5. Association between hematological abnormalities and etiological diagnosis

Hematological parameter	**P value**	**Significant association**
Anemia	0.232	No
Thrombocytopenia	<0.0001	Yes
Thrombocytosis	0.24	No
Leukopenia	<0.0001	Yes
Leukocytosis	0.92	No
Neutropenia	<0.001	Yes
Pancytopenia	<0.001	Yes

DISCUSSION

The present prospective observational study evaluated the clinico-epidemiological profile and etiological spectrum of fever of unknown origin (FUO) in children admitted to a tertiary care centre in Rajasthan. The findings demonstrate that infectious diseases remain the predominant cause of paediatric FUO, with tuberculosis and brucellosis accounting for the majority of cases. In addition, characteristic hematological abnormalities, particularly cytopenias, provided valuable diagnostic clues for identifying malignant disorders.

More than half of the study participants were of age between 1 and 5 years, with a clear male predominance. Similar demographic findings have been reported in previous paediatric FUO studies, where younger children constituted the largest proportion of affected patients. The greater frequency of FUO in early childhood may be attributed to increased susceptibility to infectious diseases, immature immune responses, and greater exposure to environmental pathogens. Male predominance observed in the present study is also consistent with previous reports and may reflect differences in healthcare-seeking behaviour and referral practices rather than true biological susceptibility (9,10).

The mean duration of fever in the present study was approximately one month, indicating that most children presented after prolonged illness despite previous medical evaluation. Most patients had low- to moderate-grade fever, suggesting that fever severity alone is not useful in differentiating the underlying etiology. Similar observations have been reported in previous studies, emphasizing that the duration and pattern of fever should always be interpreted alongside clinical findings rather than being considered independent diagnostic indicators (10,11).

Poor activity, loss of appetite, and weight loss were the most frequent presenting symptoms. These constitutional manifestations are common in prolonged inflammatory and infectious conditions and therefore provide limited etiological specificity. However, their presence should alert clinicians to the possibility of chronic infections such as tuberculosis or systemic inflammatory diseases requiring detailed evaluation. Previous investigators have similarly reported constitutional symptoms as the predominant clinical presentation among children with FUO (10,12).

Anemia was the most common hematological abnormality in our study, followed by leukocytosis and thrombocytopenia. Although anemia was observed across multiple etiological groups, it did not demonstrate a statistically significant association with the final diagnosis. In contrast, thrombocytopenia, leukopenia, neutropenia, and pancytopenia

showed significant associations with malignant disorders. These findings highlight the importance of complete blood count abnormalities as early indicators of underlying hematological malignancy and support the timely use of bone marrow examination when persistent cytopenias are present. Similar observations have been described in recent prediction models evaluating hematological markers in paediatric FUO (13).

The diagnostic approach adopted in this study emphasized sequential investigation guided by clinical suspicion rather than indiscriminate testing. Brucella IgM ELISA demonstrated excellent diagnostic utility in children with suspected brucellosis, whereas bone marrow aspiration and biopsy remained indispensable for confirming hematological malignancies. CBNAAT and advanced imaging contributed substantially to the diagnosis of tuberculosis in selected patients. These findings reinforce current recommendations supporting a structured, evidence-based diagnostic algorithm that balances diagnostic accuracy with appropriate resource utilization (14).

Infections accounted for more than four-fifths of all cases in the present study, confirming that infectious diseases continue to dominate the etiological spectrum of paediatric FUO in developing countries. Tuberculosis emerged as the leading diagnosis, followed by brucellosis and urinary tract infection. The predominance of tuberculosis likely reflects the high endemic burden of disease in India together with socioeconomic factors, overcrowding, nutritional deficiencies, and delayed healthcare access. These findings differ from reports from developed countries, where autoimmune diseases and inflammatory disorders contribute a larger proportion of FUO cases, illustrating the influence of regional epidemiological variation on disease patterns (11,15).

Only 5% of patients remained undiagnosed after comprehensive evaluation, indicating that a systematic diagnostic protocol can substantially improve diagnostic yield. Early recognition of clinical clues, judicious laboratory investigations, and selective use of advanced diagnostic techniques appear to reduce unnecessary investigations while facilitating timely initiation of appropriate treatment.

CONCLUSION

The present prospective observational study demonstrates that infectious diseases remain the predominant cause of fever of unknown origin (FUO) among children age 1–17 years admitted to a tertiary care centre, with tuberculosis and brucellosis accounting for the majority of cases. Younger children were more frequently affected, and constitutional symptoms such as poor activity, loss of appetite, and weight loss were the most common clinical manifestations.

A structured diagnostic approach combining meticulous clinical assessment with targeted laboratory investigations and selective use of advanced diagnostic modalities enabled a high diagnostic yield while minimizing unnecessary investigations. Hematological abnormalities, particularly thrombocytopenia, leukopenia, neutropenia, and pancytopenia, were significantly associated with malignant disorders and may serve as important indicators prompting early evaluation for hematological malignancy.

These findings highlight the continued importance of considering endemic infectious diseases during the evaluation of paediatric FUO in developing countries. Early recognition, rational investigation, and timely institution of appropriate therapy are essential for improving clinical outcomes and reducing morbidity. Further multicentre prospective studies involving larger populations are warranted to validate these findings and develop standardized diagnostic algorithms for children presenting with prolonged unexplained fever.

REFERENCES

1. Long SS, Edwards KE. Prolonged, recurrent and periodic fever syndromes. In: Long SS, Pickering LK, Prober CG, editors. Principles and Practice of Pediatric Infectious Diseases. 4th ed. Philadelphia: Elsevier Churchill Livingstone; 2012.
2. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine (Baltimore). 1961;40:1-30.
3. Cho CY, Lai CC, Lee ML, et al. Clinical analysis of fever of unknown origin in children: a 10-year experience in a northern Taiwan medical center. J Microbiol Immunol Infect. 2015.
4. Tezer H, Ceyhan M, Kara A, Cengiz AB, Devrim I, Seçmeer G. Fever of unknown origin in children: the experience of one

center in Turkey. Turk J Pediatr. 2012;54:583-589.
5. Antoon JW, Potisek NM, Lohr JA. Pediatric fever of unknown origin. Pediatr Rev. 2015;36:380-390.
6. Chow A, Robinson JL. Fever of unknown origin in children: a systematic review. World J Pediatr. 2011;7(1):5-10.
7. Antoon JW, Peritz DC, Parsons MR, Skinner AC, Lohr JA. Etiology and resource use of fever of unknown origin in hospitalized children. Hosp Pediatr. 2018;8:135-140.
8. Dayal R, Agarwal D. Fever in children and fever of unknown origin. Indian J Pediatr. 2016;83:38-43.
9. Attia WEM, Elhussiny MS, AbuElhassan SM. Clinico-epidemiological aspects of fever of unknown origin in children: tertiary hospital study. Alex J Pediatr. 2023;36(1).
10. Shoman W, Galal A, Elshishiny AM, Hamza E. Fever of unknown origin in pediatrics: causes and clinical characteristics in a single-centre experience. Egypt Pediatr Assoc Gaz. 2024;72:65.
11. Govindarajulu S, Kalyanasundaram K, Pyarejan KS, Venkatasamy S. Clinical profile and etiological spectrum of fever of unknown origin in children aged 2 months to 12 years. Int J Contemp Pediatr. 2017;4:62-67.
12. Sri Divya R, Subhash B, Kumar PP, Narendra A. A prospective study of clinical and etiological profile of fever of unknown origin in children. Int J Pharm Clin Res. 2024;16(12):287-292.
13. Rienvichit P, Lerkvaleekul B, Apiwattanakul N, Pakakasama S, Rattanasiri S, Vilaiyuk S. Prediction model for etiology of fever of unknown origin in children. Eur J Pediatr. 2025;184.
14. Paswan R, Kumar A, Jana D. Etiology and clinical profile of fever of unknown origin in children: a prospective observational study in Pediatrics Department of DMCH, Laheriasarai, Bihar. Int J Sci Res. 2020;9(8).
15. Lim HY, Viegelmann G, Lee EY, Raan C, Li J, Nadua KD, et al. Fever of unknown origin in children: a 14-year, single institution retrospective review. SAGE Open Pediatr. 2025;12.