



Editorial



Definition of Fever of Unknown Origin in Indian Patients

Prasan Kumar Panda*, Pathik Dhangar

Department of Internal Medicine (ID Division), All India Institute of Medical Sciences (AIIMS), Rishikesh, Uttarakhand, India.

***Corresponding author:** Prasan Kumar Panda, Department of Internal Medicine (ID Division), All India Institute of Medical Sciences (AIIMS), Rishikesh-249203, Uttarakhand, India.

Email: motherprasanna@rediffmail.com

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INTRODUCTION

The traditional definition of fever of unknown origin (FUO), established over six decades ago, presents several challenges in contemporary medical practice, particularly in resource-constrained settings like India. The requirement of a prolonged illness lasting three weeks before considering a diagnosis of FUO poses significant issues.¹ This waiting period may delay necessary interventions, leading to prolonged patient suffering and potentially worsening their condition. Additionally, the quantification of fever at $\geq 38.3^{\circ}\text{C}$ on two occasions excludes patients with lower-grade fevers, potentially missing crucial diagnostic opportunities, especially considering the variability in fever patterns among individuals and the lack of standardized temperature measurement practices in some healthcare settings.¹ With time, in 1991, Durack and Street divided FUO cases into four distinct subclasses: classic, nosocomial, neutropenic, and HIV-related, but the issue of long waiting period remained the same.²

Moreover, the traditional definition mandates in-hospital evaluation, which may not be feasible or practical in resource-poor settings like India due to limited healthcare infrastructure and financial constraints.³ This requirement could deter patients from seeking timely medical care or burden already overwhelmed healthcare facilities. Furthermore, the rationale behind the prolonged waiting period and the 'wait and watch' policy until a definitive diagnosis is established warrants scrutiny. Delaying diagnosis and

treatment for three weeks or more may exacerbate patients' suffering, increase healthcare costs, and compromise their long-term outcomes.

The term 'Fever of Unknown Origin' itself implies a passive/negative approach to diagnosis, suggesting a state of uncertainty that may perpetuate medical inertia. In resource-limited settings where access to specialized diagnostic tools and expertise is limited, an active and pragmatic approach tailored to local healthcare realities is imperative to expedite diagnosis and mitigate the burden of undiagnosed fever cases. Therefore, revising the criteria for defining FUO in Indian patients is warranted and crucial for optimizing patient care and outcomes. By addressing the issues associated with the traditional definition, such as the prolonged waiting period, rigid temperature cutoffs, and in-hospital evaluations, healthcare providers can adopt a more proactive and patient-centered approach to diagnosing and managing febrile illnesses. This approach aligns with the principles of evidence-based medicine and acknowledges the need for context-specific guidelines to navigate the complex landscape of undiagnosed fevers in diverse patient populations.

INDIAN STUDY TO DEFINE FUO

In this context, a recent study was conducted at the All India Institute of Medical Sciences (AIIMS) in Rishikesh, Uttarakhand, utilizing a retrospective and prospective longitudinal-exploratory design over 12

Citation: Panda PK, Dhangar P. Definition of Fever of Unknown Origin in Indian Patients. *JASPI*. 2024;2(1):1-4. DOI: 10.62541/jaspi028

months.⁴ The study population included patients with fever admitted to AIIMS Rishikesh between January 1, 2018, and December 31, 2022, who met specific inclusion criteria. Inclusion criteria encompassed adult patients with a documented fever of $\geq 99.1^{\circ}\text{F}$ on at least two occasions and a fever lasting more than three days. Patients diagnosed with a cause for their fever within three days of hospitalization were excluded from the study. A total of 228 patients were sampled through universal sampling. Data collection spanned major hospital departments where febrile patients were admitted: General Medicine, Gastroenterology, Neurology, Pulmonary Medicine, Nephrology, and Obstetrics and Gynecology. Retrospective data were extracted from the hospital's medical record department, while prospective data were collected by following eligible patients during their hospital stay. The study proposed novel definitions for FVO based on different durations of non-diagnosis (3-21 days, >21 days), temperature thresholds (99.1°F - 100.9°F and $\geq 101^{\circ}\text{F}$), and durations of hospitalization (3-7 days and >7 days). The frequency of each definition was assessed to gauge its applicability and prevalence in the study population. Outcome variables studied included the prevalence of FVO and the distribution of various FVO definitions.

Most patients (40.8%) met the definition B, followed by definitions A, D, and C (Table 1).

Only 2.2% of patients met the traditional definition of FVO, highlighting concerns about its applicability. A large proportion (Class A&B, 62%) of patients remained undiagnosed before 21 days of hospitalization, with temperatures between 99.1°F to 100.9°F , challenging the classical cutoff of $>101^{\circ}\text{F}$ for defining FVO. Definition B did not significantly affect the distribution of underlying causes of FVO including infection, malignancy, and autoimmune diseases. Notably, there was no significant difference in patient mortality at discharge and the 180-day follow-up among the various definitions, suggesting that revising the criteria would not compromise patient outcomes. This highlights the feasibility and safety of implementing revised FVO criteria in clinical practice, reassuring healthcare providers and policymakers.⁵

This is the first Indian study that sheds light on the challenges and implications of redefining FVO criteria tailored to the Indian context. Firstly, the study's findings underscore the limitations of the traditional definition of FVO in accurately capturing the spectrum of undiagnosed febrile illnesses in Indian patients. In the traditional definition of FVO, the duration of illness was a pivotal criterion. However, this approach overlooked a crucial aspect of delay in seeking medical attention. Regardless of the duration of the illness, if patients do not present themselves to healthcare providers, the diagnosis of FVO becomes impossible.

Table 1: Proposed new definitions (A-G) and traditional definitions (H) of FVO

Definition	Days of un-diagnosis	Temp ($^{\circ}\text{F}$)	Days of inpatient evaluation	Days of illness/fever* Median (IQR)	No. of patients	Percentage	95% CI
A	3-21	99.1-100.9	3-7	15 (10-90)	49	21.5%	16.5% - 27.5%
B	3-21	99.1-100.9	>7	15 (8-45)	93	40.8%	34.4% - 47.5%
C	3-21	≥ 101	3-7	8 (5-33)	28	12.3%	8.5% - 17.4%
D	3-21	≥ 101	>7	20 (10-60)	44	19.3%	14.5% - 25.1%
E	>21	99.1-100.9	3-7	13 (13-13)	1	0.4%	0.0% - 2.8%
F	>21	99.1-100.9	>7	90 (60-135)	7	3.1%	1.4% - 6.5%
G	>21	≥ 101	3-7	5 (5-5)	1	0.4%	0.0% - 2.8%
H	>21	≥ 101	>7	15 (10-20)	5	2.2%	0.8% - 5.3%

**It is given to compare various classes with a median duration of illness/fever in an Indian set-up; however, it doesn't add any value to the proposed classification of FVO.*

This inherent limitation underscores the necessity of re-evaluating the criteria for FVO diagnosis,

emphasizing the duration of undiagnosis rather than the duration of illness. By shifting the focus to the duration of undiagnosis, healthcare providers can

better address the challenges posed by patients who delay seeking medical care, ensuring timely diagnosis and appropriate management of FUO cases. Contrary to the traditional definition requiring a prolonged illness lasting three weeks, the study revealed that a large proportion of patients remained undiagnosed before 21 days of illness, highlighting the inadequacy of this rigid time frame. The delay in diagnosis may have detrimental effects on patient outcomes, emphasizing the need for a more pragmatic approach to defining FUO that prioritizes early intervention and management.

Furthermore, the traditional temperature cutoff of $\geq 101^{\circ}\text{F}$ on two occasions may exclude patients with lower-grade fevers, as observed in the study where temperatures between 99.1°F to 100.9°F were prevalent among undiagnosed cases.³ This suggests that adopting a broader temperature range, as proposed in the study's revised definitions, could enhance the sensitivity of FUO criteria in identifying patients requiring further evaluation.

The study's proposal to adapt FUO definitions based on different ranges of duration of non-diagnosis, temperature thresholds, and durations of hospitalization reflects the need for flexibility and customization in defining FUO in diverse patient populations. By considering local epidemiology and healthcare resources, such as the prevalence of infectious diseases, malignancies, and autoimmune conditions in India, the proposed definitions aim to optimize diagnostic yield and patient outcomes. The implications of redefining FUO criteria extend beyond diagnostic accuracy to resource utilization and healthcare delivery. In resource-constrained settings like India, where access to specialized diagnostic tools and in-hospital evaluations may be limited, the traditional definition's emphasis on inpatient evaluation may need to be more practical.⁶ By shifting the focus toward comprehensive clinical assessment and monitoring of patient's response to empirical treatment, the proposed definitions advocate for a more efficient and cost-effective approach to managing FUO.

Hence, the definition of FUO should be simple, feasible, inclusive, dynamic, and pragmatic for treating clinicians in local settings with available investigations. We propose the Indian FUO definition: temperature of 99.1°F or higher with a minimum duration of 3 days of treating clinician's observation without an established etiological diagnosis. However, for research purposes, any definition of FUO (A to H in Table 1) may be used depending on the local setting, the aim of the study, and

the treatment approach.

Nevertheless, challenges persist in implementing revised FUO criteria, including standardization across healthcare settings and acceptance within the medical community. Further research and collaboration are warranted to validate the proposed definitions and establish consensus guidelines for diagnosing and managing FUO in Indian patients.⁷

CONCLUSIONS

The study provides compelling evidence supporting the revision of classic FUO criteria in the Indian context to at least eight classification criteria, but the majority (>90%) belongs to four types with a duration of fever of 3-21 days. This means we should not wait for three weeks of the rigid period of the old classic definition to diagnose a febrile patient as FUO. Similarly, the temperature cutoff is changed to 99.1°F , not 101°F ; hospital stays can be three days. Adapting the criteria to reflect local healthcare realities better could enhance proper disease documentation and policy-making, early diagnosis, and management, ultimately improving patient outcomes. The findings call for further research and collaboration within the medical community to develop comprehensive and context-specific guidelines for diagnosing and managing FUO in the diverse population of India.

ACKNOWLEDGEMENT

None

CONFLICT OF INTERESTS STATEMENT

The authors declare no conflict of interest

SOURCE OF FUNDING

None

ETHICS STATEMENT INCLUDING PATIENT CONSENT

Not applicable

AUTHORS' CONTRIBUTIONS

PKP: Writing the draft; Resources

PD: Conceptualization; Supervision; Review & editing

AI DECLARATION

No AI tool was used to generate research data, perform data analysis, interpret findings, formulate scientific conclusions, or make editorial decisions. All AI-assisted content was critically reviewed, verified, and revised by the authors. The authors take full responsibility for the

accuracy, originality, integrity, and final content of the manuscript.

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