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A STUDY OF CLINICAL AND ETIOLOGICAL PROFILE OF NON-INFECTIVE CAUSE OF PYREXIA OF UNKNOWN ORIGIN IN HOSPITALISED PATIENTS

General Medicine

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ABSTRACT

Introduction: Pyrexia of Unknown Origin (PUO) presents a diagnostic challenge due to its wide range of potential causes, which can vary significantly based on geographic region. Infections, non-infectious inflammatory diseases (NIID), and malignancies are common causes. Despite advances in diagnostic technology, many cases remain unresolved, particularly in resource-limited settings. This study focuses on the non-infective causes of PUO in hospitalized patients in a teaching hospital in South Karnataka, India. **Objective:** To investigate the clinical and etiological profile of non-infective causes of PUO among hospitalized patients and identify patterns that could aid in better diagnosis and management. **Methods:** This hospital-based descriptive study was conducted from January 2023 to June 2024 at ESIC-MC & PGIMSR Bengaluru. A total of 91 patients aged over 18 years with documented PUO were included. Exclusion criteria were patients with known malignancies, HIV, or other immunocompromised conditions. Detailed diagnostic workup including imaging, serology, and clinical examination was performed. **Results:** Of the 91 patients, 58.2% were male with a median age of 49 years. Rheumatological conditions, including rheumatoid arthritis (25.3%) and vasculitis (8.8%), were the most common non-infective causes. Malignancies accounted for 29.7% of cases, with hepatic malignancies being the most frequent. PET scans were abnormal in 11% of cases, aiding in the diagnosis of malignancies. Bone marrow biopsy confirmed diagnoses in 5.5% of cases. Despite extensive evaluation, 3.3% of cases remained undiagnosed. **Conclusion:** Rheumatological conditions and malignancies are significant non-infective causes of PUO. Comprehensive diagnostic approaches, including imaging and serological testing, are essential for accurate diagnosis. Future strategies should focus on enhancing diagnostic capacities in resource-limited settings.

KEYWORDS

Pyrexia of Unknown Origin; Rheumatological Conditions; Malignancies; Non-infective PUO; Diagnostic Evaluation; Imaging; Serology

INTRODUCTION

Pyrexia of unknown origin (PUO), also referred to as fever of unknown origin (FUO), is a complex medical condition characterized by persistent, unexplained fever despite extensive medical investigation. PUO encompasses a wide range of unrelated medical conditions that share the common symptom of fever, which remains undiagnosed after initial evaluations. Diagnosing PUO is challenging for physicians due to its broad spectrum of potential causes and the geographical variability in its epidemiology [1].

The concept of FUO was first defined by Petersdorf and Beeson in 1961. In their original definition, it was described as a fever higher than 38.3°C (101°F) on several occasions, lasting for more than three weeks, and remaining undiagnosed after one week of inpatient evaluation. This definition provided a framework for clinicians dealing with persistent, difficult-to-diagnose fevers [2]. However, with the advancement of medical knowledge and diagnostic technologies, it became necessary to update the definition. In 1991, Durack and Street revised the criteria for FUO to incorporate modern diagnostic tools such as imaging techniques and laboratory diagnostics [3]. Their revised definition described FUO as a temperature exceeding 38.3°C (101°F) on multiple occasions, lasting more than three weeks, and remaining undiagnosed after appropriate diagnostic efforts, including at least three outpatient visits or three days of inpatient evaluation [4].

The epidemiology of PUO also varies widely based on geographic location, environmental factors, and the prevalence of local diseases, making it a complex condition for healthcare professionals to address. In developed nations, non-infectious inflammatory diseases (NIID) and neoplasms are often the leading causes of PUO, while infections are more prominent in developing countries, where endemic diseases, limited healthcare access, and delayed diagnosis are contributing factors [5].

Understanding the global and regional differences in PUO is critical for effective diagnosis. Infections are the most common cause of PUO, responsible for 21–54% of cases, and their prevalence varies by location. In developing countries like India, infections such as tuberculosis, malaria, and typhoid fever are common causes, while in developed countries, autoimmune diseases and cancers are more frequently implicated [6].

PUO's aetiology is broad, with more than 200 medical conditions potentially leading to the diagnosis. These conditions can be grouped into four main categories: infections, NIIDs, neoplasms, and miscellaneous causes. Infections account for the majority of PUO cases, particularly in developing countries, where diseases like tuberculosis and malaria are endemic [7]. Non-infectious inflammatory diseases (NIIDs), such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and sarcoidosis, are more frequently diagnosed in developed countries due to advances in diagnostic techniques. Neoplasms, or cancers, account for 6–31% of PUO cases, particularly in older populations where cancer incidence is higher [8]. Lymphoma is a notable cause of neoplastic PUO. Miscellaneous causes, which include drug reactions, factitious fever, and genetic conditions like familial Mediterranean fever, make up 4–6.5% of PUO cases [9].

Despite extensive investigation, a significant portion of PUO cases remains unresolved. Studies suggest that up to 51% of patients with PUO do not receive a definitive diagnosis, even after thorough evaluation. In some cases, the fever may resolve on its own, while in others, it persists as a chronic condition with no clear cause [10].

In developing countries like India, the diagnosis of pyrexia of unknown origin (PUO) is particularly challenging due to the high prevalence of infections and limited healthcare resources. Infections, such as tuberculosis, typhoid fever, malaria, and dengue, are the predominant causes of PUO, driven by endemic diseases, overcrowding, and socioeconomic factors [11]. Delayed access to healthcare, often due to resource constraints and geographical barriers, exacerbates the difficulty of early detection and accurate diagnosis. Moreover, inadequate diagnostic infrastructure, including limited access to advanced imaging and specialized laboratory tests, further complicates the identification of underlying causes [12].

In addition to infections, non-infectious inflammatory diseases (NIIDs), neoplasms, and miscellaneous causes also contribute to PUO in developing regions. The diagnostic complexity increases when infectious diseases intersect with other conditions [13]. For instance, patients with HIV/AIDS often present with PUO due to opportunistic infections or coexisting autoimmune diseases, making differential diagnosis more intricate. A systematic and comprehensive approach is essential for diagnosing PUO, but the variability in healthcare capabilities across regions presents significant obstacles [14]. Despite advancements in diagnostic techniques, the underlying causes of PUO can remain elusive, especially in resource-limited settings. This highlights the need for improved healthcare access, enhanced diagnostic tools, and region-specific strategies to better manage PUO in developing countries [15].

The aim of this hospital-based descriptive study is to investigate the causes and clinical spectrum of pyrexia of unknown origin (PUO) among patients in a teaching hospital in South Karnataka, India. This study will explore the prevalence of infections, non-infectious inflammatory diseases (NIIDs), neoplasms, and other causes of PUO. Additionally, it will assess patient demographics, clinical presentations, and diagnostic outcomes to identify patterns that can improve the diagnosis and management of PUO, particularly in resource-limited settings.

MATERIALS AND METHODS

This hospital-based descriptive study was conducted from January 2023 to June 2024 at ESIC-MC & PGIMSR, Bengaluru, including all patients admitted to the Department of General Medicine who met the inclusion and exclusion criteria. The sample size was estimated to be 91, based on a prior study by Praseilla Rupali et al., with tuberculosis constituting 44% of PUO cases in India. Inclusion criteria were patients over 18 years old with a documented temperature >38.3°C for over three weeks and undiagnosed after appropriate outpatient or inpatient evaluation. Exclusion criteria included moribund patients, those with malignancies, HIV-positive, or neutropenic individuals.

RESULTS

In a sample of 91 individuals, 53 are male (58.2%) and 38 are female (41.8%), indicating a higher male representation. The median age of those with non-infective causes of PUO is 49 years, with an age range of 20-78 years. Occupationally, 31.9% were daily wage workers, 20.9% homemakers, and 15.4% factory workers. Accountants represent 7.7%, with store keepers and students at 4.4% each. Other occupations, including auto drivers, clerks, and retirees, range from 1.1% to 2.2%.

Table :1 PET Scan

PET scan	Frequency	Percentage
Normal	81	89.0%
Abnormal	10	11.0%
Total	91	100.0%

This table suggests that the majority of the individuals assessed did not exhibit any detectable issues during their PET scans, highlighting a predominance of normal findings within this group.

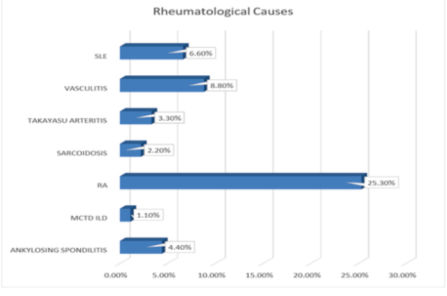

Figure -1 Graphical representation of the important rheumatological cause of PUO – Rheumatoid arthritis 25.3%

The bar chart illustrates the prevalence of various rheumatological causes among a study group. Rheumatoid Arthritis (RA) is the most common, accounting for 25.3% of cases. Vasculitis follows at 8.8%, and Ankylosing Spondylitis at 4.4%. Systemic Lupus Erythematosus (SLE) and Takayasu Arteritis are also noted at 6.6% and 3.3%, respectively, with Sarcoidosis and MCTD ILD being the least common.

Table :2 Bone Marrow Biopsy

Bone marrow Biopsy	Frequency	Percentage
Not done	86	94.5%
Diagnosis Confirmed	5	5.5%
Total	91	100.0%

The table details the results of bone marrow biopsy tests conducted on a group of 91 individuals. It shows that a majority, 86 individuals (94.5%), did not undergo the biopsy, while only 5 individuals (5.5%) had a biopsy that confirmed their diagnosis. This indicates a high percentage of cases where a bone marrow biopsy was not performed or deemed necessary.

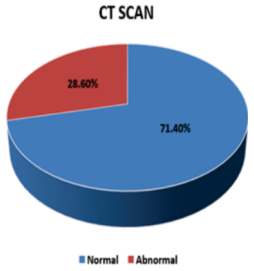

Figure -2 Pie chart showing proportion of patients with findings on CT scan - 28.6%%

The pie chart represents the distribution of CT scan results, where 71.4% of the scans were reported as normal and 28.6% as abnormal. This indicates that a majority of the individuals evaluated through the CT scans showed no detectable issues, while a significant minority had findings that deviated from the normal, possibly indicating health concerns that require further investigation.

Table :3 Echocardiography Results: Distribution of Normal and Abnormal Findings

Echocardiography	Frequency	Percentage
Normal - No vegetation	86	94.5%
RWMA	5	5.5%
Total	91	100.0%

The table displays echocardiography results for 91 individuals, showing that 86 individuals (94.5%) had normal results with no vegetation observed. Conversely, 5 individuals (5.5%) exhibited regional wall motion abnormalities (RWMA). This indicates that the vast majority of the echocardiograms did not reveal any significant cardiac issues, while a small percentage showed cardiac functional abnormalities.

Table 4: Ultrasonography (USG) Results: Distribution of Normal and Abnormal Findings

USG	Frequency	Percentage
Normal	85	93.4%
Ovarian Mass in Ovary	1	1.1%
Spleenomegaly	5	5.5%
Total	91	100.0%

The table outlines the ultrasonography (USG) results for 91 individuals. The data show that 85 individuals (93.4%) had normal USG results. A single case (1.1%) was identified with an ovarian mass in the ovary, and 5 individuals (5.5%) were diagnosed with spleenomegaly. This highlights that the vast majority of the USGs performed were normal, with a few specific abnormalities detected.

Table 5: Procalcitonin Test Results: Distribution Among 91 Individuals

Procalcitonin	Frequency	Percentage
Negative	74	81.3
Positive	17	18.68
Total	91	100.0%

The table displays the results for procalcitonin tests among 91 individuals. It shows that 74 individuals (81.3%) tested negative for procalcitonin, indicating a likely absence of severe bacterial infections. Conversely, 17 individuals (18.68%) tested positive, which could suggest bacterial infections or other inflammatory conditions that elevate procalcitonin levels. This distribution underlines the majority of the group showing no significant procalcitonin-related findings.

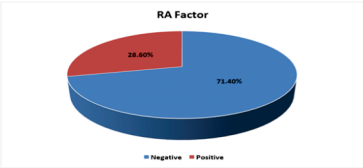

Figure -3 Pie chart showing proportion of patients with RA FACTOR positive - 28.6%

The pie chart illustrates the results for RA (Rheumatoid Arthritis) Factor testing among a group. It shows that 71.4% of the tests were negative, indicating no detectable RA Factor, while 28.6% were positive, suggesting the presence of RA Factor which is associated with Rheumatoid Arthritis. This significant portion of positive results highlights the presence of this autoimmune marker in nearly a third of the tested individuals.

Table 6: Thyroid Function Test Results

TFT	Frequency	Percentage
Normal	80	87.9%
Hypothyroidism	11	12.1%
Total	91	100.0%

The table presents the results of Thyroid Function Tests (TFT) for 91 individuals. It shows that 80 individuals (87.9%) had normal thyroid function, while 11 individuals (12.1%) were diagnosed with hypothyroidism, indicating an underactive thyroid gland. This highlights that the majority of the individuals tested have normal thyroid function, with a smaller percentage experiencing thyroid-related issues.

DISCUSSION

Pyrexia of unknown origin (PUO), or fever of unknown origin (FUO), is defined by persistent, unexplained fever despite extensive medical investigation. First defined in 1961 and later updated in 1991, PUO's causes vary globally, with infections predominating in developing countries and non-infectious diseases and neoplasms more common in developed regions. Despite modern diagnostics, up to 51% of PUO cases remain unresolved, particularly in areas with limited healthcare resources like India [16].

A study of 91 patients at ESI MC & PGIMSR Bengaluru found 58.2% male and 41.8% female participants, with an average age of 50 years (median 49; range 20-78). PUO was common in daily wage workers (31.9%) and homemakers (20.9%). All patients presented with fever, fulfilling PUO criteria by Durack and Street et al. In comparison, Priscilla Rupali et al. (CMC Vellore) found 65% male participants with an average age of 40 years [17,18].

In this study, the main clinical features included fatigue (63.7%), joint pain (42.9%), and weight loss (13.3%). Lifestyle diseases were common, with diabetes (35.2%), hypertension (29.7%), and ischemic heart disease (5.5%). Smoking and alcohol use were reported in 22% of patients. Initial investigations guided diagnosis in 19%, with thrombocytopenia, abnormal leukocyte counts, and elevated alkaline phosphatase indicating further testing. Hepatic malignancy was detected in 77.8% of patients with raised liver enzymes.

In our study, elevated ESR (mean 40, cut-off 15) aided in diagnosing non-infective causes of PUO, while CRP was raised in 38.5% of cases. Chest X-rays had limited diagnostic value, being normal in 72.2%, but identified lung malignancy in 5.5% and rheumatological causes like sarcoidosis in 13.2%. In comparison, Priscilla Rupali et al.'s study reported diagnostic yields of 25.3% with chest X-ray, 83.2% with CT scans, and 66.7% with PET scans [18].

In this study, serological markers were crucial for diagnosing non-infective causes of PUO. RA factor was positive in 28.6% of patients, ANA in 15.4%, and ANCA in 18.7%, indicating connective tissue diseases. Blood, urine, and sputum cultures were negative, offering no diagnostic value, unlike Priscilla Rupali et al.'s study, where cultures had a diagnostic yield of 18.5% for infective causes of PUO [18].

In this study, USG abdomen, pelvis, and trans-thoracic echocardiography were not helpful in diagnosing non-infective causes of PUO, unlike Priscilla Rupali et al.'s study, which reported a 66% diagnostic yield for infective causes. CT scans identified the cause in 28.6% of cases and confirmed diagnoses in 10%, compared to a higher yield of 83.2% reported by Rupali et al. for CT scans in PUO diagnosis [18].

PET scans were helpful in diagnosing non-infective causes of PUO in 11% of patients and detected malignancies in 80% of cases, while Priscilla Rupali et al. reported a 66.7% diagnostic yield for PET scans in identifying PUO causes. Studies by Zhai Pan, Wang Yuqiang, and others showed infectious etiology as the leading cause of PUO outside India, with non-infectious causes ranging from 12.8% to 33%. Takeda R et al. highlighted a rise in non-infectious inflammatory diseases as the primary cause of PUO in developed countries, accounting for 22% to 43% [18, 19, 20, 21].

Variations in the etiological distribution of PUO are influenced by factors like public health access, diagnostic techniques, and economic advancement. Studies in India, including those by Kejariwal et al., Bandyopadhyay et al., Priscilla Rupali et al., Shantaram et al., and Mir et al., found infectious diseases as the most common cause of PUO, accounting for 43.9% to 60%. Neoplasms were the second most common cause (17%-22%). Rheumatological causes were also significant, with 51.7% of non-infective PUO cases, including rheumatoid arthritis (25.3%) and vasculitis (8.8%). Priscilla Rupali et al. noted systemic lupus erythematosus (26%) as the leading non-infectious cause [18, 22, 23, 24, 25].

In the study, malignancies were the second most common non-infective cause of PUO (29.7%), with hepatic malignancies being the most frequent (7.7%). Priscilla Rupali et al. identified 22% of FUO cases as neoplasms, with 78% being hematological malignancies—lymphoma (60%) and leukemias/multiple myeloma (9%). Solid organ malignancies, like colon, lung, and prostate cancers, accounted for 18%. Undiagnosed cases in this study were 3.3%, compared to 1.6% in Rupali et al., and 7% and 51% in Bleeker-Rovers and Naito et al.'s studies. Diagnostic confirmation was achieved using invasive or non-invasive methods as needed [18, 26, 27].

CONCLUSION

This study, conducted on 91 patients at ESIC MC & PGIMSR, Bengaluru, aimed to identify the non-infective causes of PUO among hospitalized patients. Utilizing a standard diagnostic workup algorithm, a diagnosis was made in 96.7% of cases. The most common non-infective cause of PUO was found to be rheumatological conditions, followed by malignancies, highlighting the importance of comprehensive diagnostic evaluation in determining the aetiology of PUO.

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18. Etiology of Classic Fever of Unknown Origin (FUO) among Immunocompetent Indian

Adults Priscilla Rupali1*, Divyani Garg2, Surekha Viggweswarupu3, Thambu David Sudarsanam3, Visalakshi Jeyaseelan4, Ooriapadickal Cherian Abraham3.
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