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Original article

FEVER OF UNKNOWN ORIGIN: DIAGNOSTIC CHALLENGES FROM INFECTIOUS DISEASES PERSPECTIVE

Poposki Kostadin, Grozdanovski Krsto, Dimzova Marija, Georgievska Dajana, Bosilkovski Mile
University Clinic for Infectious Diseases and Febrile Conditions, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, North Macedonia
e-mail: kostadin.poposki@hotmail.com

Abstract

Aim: To evaluate the diagnostic value of potentially diagnostic clues in distinguishing infectious from non-infectious causes of fever of unknown origin (FUO).

Material and methods: We conducted a retrospective–prospective, single-center study involving patients older than 14 years who met the criteria for classical FUO. Medical history, physical examination findings, and a standardized laboratory panel were collected for all participants. After the final diagnosis, patients were divided into infectious and non-infectious groups. Demographic characteristics, clinical features, and laboratory results were compared between groups.

Results: A total of 79 patients were included, with a mean age of 50.6±17.1 years (range 15–77). Males represented 61.1% of cases and were more common in the infectious FUO group (p=0.016), with this group showing higher febrile peak (p<0.001). Infectious diseases accounted for 51.9% of cases. In this group, notable clinical findings included fatigue (sensitivity 63.4%), fever (sensitivity 75.6%), heart murmur (positive likelihood ratio [+LR] 4.8), and splenomegaly (+LR 2.23). Key features of the non-infectious group were arthralgia (+LR 3.96), neck pain (+LR 3.49), joint swelling (+LR 6.44), and rash (+LR 3.49). Elevated procalcitonin (p=0.006), ALT (p=0.04), AST (p=0.02), and globulin levels (p=0.016) was noted in infectious FUO, while ferritin (p=0.047) and LDH (p=0.03) were higher in the non-infectious group.

Conclusions: The identified differences in diagnostic variables between infectious and noninfectious causes of classical FUO may assist initial etiologic differentiation and improve utilization of the diagnostic process.

Keywords: fever of unknown origin, potential diagnostic clues, infectious etiology

Introduction

Fever of unknown origin (FUO) is a clinical syndrome recognized for more than six decades. In 1961, Petersdorf and Beeson defined FUO as an illness lasting longer than three weeks, with body temperature exceeding 38.3°C on several occasions, and no diagnosis established after one week of inpatient evaluation[1]. Thirty years later, Durack and Street proposed two major modifications: (a) distinguishing classical FUO from three additional variants: nosocomial, neutropenic, and HIV-associated FUO; and (b) shortening the required evaluation period while allowing outpatient assessment[2]. In 1997, de Kleijn *et al.* suggested supplementing the definition

with standardized baseline investigations[3], and the same group later proposed a structured diagnostic protocol to improve clinical practice and research consistency[4].

Despite these recommendations, the approach has not been universally adopted. In most settings, the diagnostic work-up for FUO remains guided by clinical manifestations, medical history, resource availability, cost, and potential harms of diagnostic investigations[5]. Early studies already recognized the importance of medical history, physical examination, and basic laboratory abnormalities in the diagnostic process[6]. De Kleijn introduced the concept of potentially diagnostic clues (PDCs)[3], whose value has since been emphasized by other investigators[7,8]. Although cohort studies and case series have shown the potential of PDC-based algorithms[9-11], the overall level of evidence remains modest. The spectrum of PDCs largely reflects the underlying causes of FUO, which are influenced by endemic infectious diseases, socioeconomic conditions, available diagnostic resources, population aging, and the prevalence of chronic diseases[12]. As a result, the absence of a standardized and efficient diagnostic strategy often leads to excessive, costly, and sometimes harmful investigations[5].

The aim of this study was to compare PDCs between infectious and non-infectious causes of classical FUO and to assess their diagnostic utility in establishing the final diagnosis.

Material and methods

Study design and participants

This retrospective-prospective, single-center study was carried out between 2019 and 2024 at the University Clinic for Infectious Diseases and Febrile Conditions in Skopje. We enrolled consecutive immunocompetent patients aged 14 and above, all of whom met the FUO criteria defined by Durack and Street. Patients without a final diagnosis, those with HIV infection, nosocomial or neutropenic FUO, FUO in other immunocompromised conditions, individuals under the age of 14, and those who refused to participate in the study or diagnostic examination at our center were additionally excluded.

Diagnostic evaluation and data collection

Upon admission, each patient underwent a detailed medical history and a thorough physical examination to document demographic data and preliminary clinical findings. Patients were examined and interviewed frequently throughout their stay at the clinic in order to monitor disease progression and detect new signs and symptoms. All patients received an identical baseline diagnostic panel. This included erythrocyte sedimentation rate, complete blood count with differential, serum urea and creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), creatine kinase (CK), total serum protein, albumin and globulin, ferritin, C-reactive protein (CRP), and procalcitonin. Each patient underwent standard imaging and microbiological procedures, including chest radiography, abdominal ultrasonography, electrocardiography, two sets of blood cultures, urine culture, and HIV testing. When clinically appropriate, additional targeted investigations were performed based on the presence of potentially diagnostic clues (PDCs), such as microbiological, biochemical, radiologic, invasive, and histopathologic exams to confirm the diagnosis. Patients were followed prospectively until a definite diagnosis was made. Figure 1 shows a summary of the participant selection and diagnostic approach.

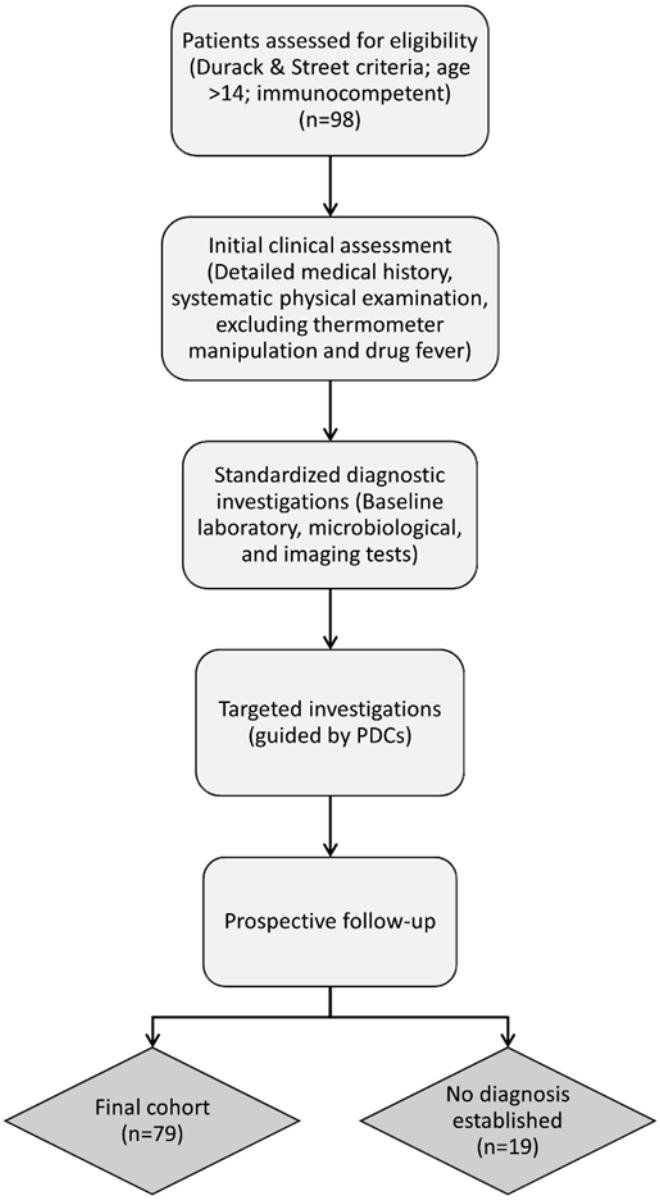

Fig. 1. Flowchart of enrollment and diagnostic assessment of participants

Etiological classification and statistical analysis

Following a final diagnosis, cases were classified into four categories: infectious, noninfectious inflammatory disorders (NIID), malignant diseases, and miscellaneous causes. For comparison purposes, patients were then divided into two groups: (a) those with infectious FUO and (b) those with noninfectious FUO. Data from the standardized evaluation were compared between these groups.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratio for a positive test (LR) were calculated for individual clinical signs and symptoms to assess their diagnostic contribution. A test was considered relevant if it met at least one of the following criteria: sensitivity ≥50%, positive LR ≥2, or PPV >60%[10].

The Shapiro-Wilk test was used to assess the normality of distribution. Continuous variables are expressed as mean ± standard deviation (SD) or median with interquartile range (IQR, 25th-75th percentile). Student's t-test was used for normally distributed data, and Mann–Whitney U test for non-normally distributed data. Categorical variables are presented as counts and percentages, with comparisons made using Pearson's chi-square or Fisher's exact test. Statistical significance was set at $p<0.05$. Analyses were carried out using SPSS software, version 25.0 (SPSS Inc., Chicago, IL, USA).

Ethical Approval

The study was approved by the Ethics Committee for Research Involving Humans at the Faculty of Medicine in Skopje (approval no. 03-2031/18), and written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki[10].

Results

A total of 98 patients was initially studied, of whom 19 remained undiagnosed, leaving 79 cases available for analysis. Table 1 shows the etiologic prevalence in the cohort. The most common cause was infectious diseases, accounting for 51.9% of cases, with visceral leishmaniasis and infective endocarditis as the leading diagnoses. Noninfectious inflammatory diseases accounted for 20.2% of cases, mostly Still's disease, rheumatoid arthritis, and polymyalgia rheumatica. Malignancy was diagnosed in eight patients and included both solid organ and hematologic cancers. The miscellaneous group accounted for 17.7% of cases and included subacute thyroiditis, habitual hyperthermia, idiopathic pericarditis, sarcoidosis, and thrombophlebitis.

Table 1. Etiological spectrum of FUO

Category	Diagnosis	n (%)
Infectious diseases (41, 51.9%)	Visceral leishmaniasis	13 (16.5)
	Infective endocarditis	14 (17.7)
	Cytomegalovirus infection	3 (3.8)
	Tuberculosis	3 (3.8)
	Localized abscesses (hepatic, perianal)	2 (2.5)
	Primary bacteremia (no identified focus), Urinary tract infection, Lyme borreliosis, rickettsiosis, parvovirus B19, syphilis	1 (1.3) each
Noninfectious inflammatory disorders (16, 20.2%)	Adult-onset Still's disease	7 (8.9)
	Rheumatoid arthritis, Polymyalgia rheumatica	2 (2.5) each
	Sarcoidosis, Familial Mediterranean fever, vasculitis, reactive arthritis, gout	1 (1.3) each
Malignancies (8, 10.1%)	Lymphoma, Lung cancer	2 (2.5) each
	Acute leukemia, Bladder cancer, Renal cell carcinoma, Prostate cancer	1 (1.3) each
Miscellaneous conditions (14, 17.7%)	Subacute thyroiditis	5 (6.3)
	Habitual hyperthermia	6 (7.6)
	Idiopathic pericarditis	2 (2.5)
	Thrombophlebitis	1 (1.3)

The mean age of patients was 50.6 ± 17.1 years (range 15-77), with a male predominance (61.1%). Infectious diseases were more frequent in males (80.5%) compared to females (19.5%), p=0.016; odds ratio (OR)=3.34; 95% confidence interval (95% CI)=1.23-9.10. The median duration of fever before admission was 30 days (IQR 21-60), with no significant difference between the groups.

The median recorded temperature was 39°C (IQR 38.5-40). Patients with infectious diseases had higher fever than those with noninfectious etiologies (39.4 ± 0.6 °C *vs*. 38.7 ± 0.9 °C, p<0.001).

Clinical symptoms and signs in the infectious and noninfectious FUO groups are presented in Tables 2 and 3. The most frequently reported symptoms were rigors, malaise, sweating, arthralgia, and myalgia. When comparing the groups, malaise, rigors, and headache were more frequent in the infectious group (63.4% *vs*. 42.1%, p=0.048; 75.6% *vs*. 24.4%, p=0.005; 34.1% *vs*. 13.2%, p=0.029, respectively). Arthralgia (57.9% *vs*. 14.6%, p<0.001) was the predominant symptom in patients with noninfectious FUO. The most common physical findings were hepatomegaly, splenomegaly, and rash, followed by joint swelling, pulmonary auscultatory findings, and heart murmur. In the infectious FUO group, heart murmur and splenomegaly were significantly more frequent (24.4% *vs*. 2.6%, p=0.001; 53.7% *vs*. 23.7%, p=0.006, respectively). Joint swelling and rash were the predominant findings among patients in the noninfectious FUO group (31.6% *vs.* 4.9%, p=0.002; 34.2% *vs*. 9.8%, p=0.008, respectively).

Table 2. Symptoms in patients with FUO

Symptom	Infectious group n=41	Noninfectious group n=38	p-value (<0.05)
Malaise	26 (63.4%)	16 (42.1%)	**0.048**
Chills	8 (19.5%)	10 (26.3%)	0.471
Rigors	31 (75.6%)	17 (44.7%)	**0.005**
Loss of appetite	11 (26.8%)	6 (15.8%)	0.233
Weight loss	12 (29.3%)	9 (23.7%)	0.575
Sweating	18 (43.9%)	11 (28.9%)	0.168
Headache	14 (34.1%)	5 (13.2%)	**0.029**
Neck pain	4 (9.8%)	13 (34.2%)	**0.008**
Cough	8 (19.5%)	13 (34.2%)	0.140
Nausea	3 (7.3%)	6 (15.8%)	0.236
Myalgia	10 (24.4%)	13 (34.2%)	0.337
Arthralgia	6 (14.6%)	22 (57.9%)	**<0.001**

Table 3. Clinical signs in patients with FUO

Clinical sign	Infectious group n=41	Noninfectious group n=38	p-value (<0.05)
Heart murmur	10 (24.4%)	1 (2.6%)	**0.001**
Hepatomegaly	16 (39%)	8 (21.1%)	0.083
Splenomegaly	22 (53.7%)	9 (23.7%)	**0.006**
Lymphadenopathy	6 (14.6%)	9 (23.7%)	0.305
Joint swelling	2 (4.9%)	12 (31.6%)	**0.002**
Rash	4 (9.8%)	13 (34.2%)	**0.008**

The diagnostic utility of individual clinical sign and symptom in making the final diagnosis is presented in Tables 4 and 5. In the infectious disease group, the sensitivity of malaise and rigors (63.4% and 75.6%, respectively) was notable for their diagnostic utility. A high positive predictive value was observed for headache, loss of appetite, and sweating in the infectious etiology of FUO (73.7%, 64.7%, and 62.1%, respectively). Heart murmur and splenomegaly (PPV 98% and 71%, +LR 4.8 and 2.23, respectively) emerged as the most reliable diagnostic indicators for the infectious group. Arthralgia (PPV 78.6%, +LR 3.96), nausea (PPV 66.7%, +LR 2.16), and neck pain (PPV 76.5%, +LR 3.49) were the most relevant symptoms, whereas joint swelling (PPV 85.7%, +LR

6.44) and rash (PPV 76.5%, +LR 3.49) were the most significant signs in the noninfectious FUO group presented in this series.

Table 4. Clinically significant diagnostic manifestations in the infectious FUO group

Clinical manifestation	Sensitivity	Specificity	PPV	NPV	+LR
Malaise	63.4%	57.9%	61.9%	59.5%	1.50
Rigors	75.6%	55.3%	64.6%	67.7%	1.66
Loss of appetite	26.8%	84.2%	64.7%	51.6%	1.62
Sweating	43.9%	71.1%	62.1%	54.0%	1.48
Headache	34.1%	86.8%	73.7%	55.0%	2.42
Heart murmur	24.4%	95.8%	98.0%	55.1%	4.80
Splenomegaly	53.7%	76.3%	71.0%	60.4%	2.23

Table 5. Clinically significant diagnostic manifestations in the noninfectious FUO group

Clinical manifestation	Sensitivity	Specificity	PPV	NPV	+LR
Neck pain	34.2%	90.2%	76.5%	59.7%	3.49
Nausea	15.8%	92.7%	66.7%	54.3%	2.16
Arthralgia	57.9%	85.4%	78.6%	68.6%	3.96
Joint swelling	31.6%	95.1%	85.7%	60.0%	6.44
Rash	34.2%	90.2%	76.5%	59.7%	3.49

The laboratory and biochemical profile is presented in Table 6. Patients showed elevated inflammatory markers: erythrocyte sedimentation rate (82 ± 33.71 mm/hr), C-reactive protein (123.04 ± 100.11 mg/L), and ferritin (1299.17 ± 2799.06 µg/L). Higher values were also seen for lactate dehydrogenase (462.05 ± 373.74 IU/ml). Compared with the noninfectious group, the infectious group had lower albumin (30.37 ± 5.9 g/L *vs.* 37.28 ± 7.91 g/L, p=0.001), higher globulin levels (40 ± 14.54 g/L *vs.* 32.83 ± 6.73 g/L, p=0.016), and higher procalcitonin (1.72 ± 2.24 ng/ml *vs*. 0.37 ± 1.04 ng/ml, p=0.006). Other significant differences were observed for aminotransferases (ALT: 88.05 ± 108.56 U/L *vs.* 48.71 ± 51.75 U/L, p=0.04; AST: 78 ± 94.57 U/L *vs*. 39.37 ± 37.71 U/L, p=0.02). In contrast, the noninfectious group showed higher LDH (557.19 ± 462.63 IU/ml *vs*. 371.79 ± 236.12 IU/ml, p=0.03) and ferritin levels (1916 ± 3654.5 µg/L *vs*. 526.90 ± 307.67 µg/L, p=0.047).

Discussion

This study aimed to explore the diagnostic challenges of classical FUO, with particular focus on distinguishing infectious from noninfectious causes. The predominance of infectious diseases in our cohort is consistent with earlier FUO studies in the country[13] and aligns with reports from neighboring and Balkan nations in the region[14–17].

Visceral leishmaniasis, responsible for almost one-third of infectious diseases in this series, is a protozoan parasitic infection caused by the genus Leishmania and is endemic in this part of the world[18]. Its high prevalence as a cause of FUO is consistent with earlier national reports[13], though in the wider literature it is described as a rare etiology of FUO, primarily reported in studies from Mediterranean countries and Southeast Asia[13,19,20]. The relatively high burden in our setting, despite its endemicity, may be explained by delayed recognition, nonspecific clinical presentation, and limited access to diagnostic facilities outside the capital.

Table 6. Laboratory and biochemical profile of patients with FUO

Parameter (reference range)	Total n=79 (mean ± SD)	Infectious group n=41	Noninfectious group n=38	p-value (<0.05)
Erythrocyte sedimentation rate	69.82 ± 33.71	73.44 ± 33.45	66.49 ± 34.05	0.389
Hemoglobin	113.95 ± 20.86	111.73 ± 21.78	116.00 ± 19.83	0.329
Erythrocytes	4.08 ± 0.62	4.01 ± 0.66	4.16 ± 0.58	0.320
Leukocytes	9.70 ± 5.16	9.20 ± 5.81	10.24 ± 4.36	0.375
Platelets	277.96 ± 162.28	209.95 ± 141.65	351.34 ± 152.22	<0.001
Neutrophils	70.24 ± 15.94	67.46 ± 18.85	73.24 ± 11.57	0.100
Lymphocytes	20.95 ± 14.83	23.66 ± 17.56	18.03 ± 10.30	0.090
Monocytes	8.05 ± 3.40	8.27 ± 3.49	7.81 ± 3.33	0.556
Eosinophils	1.74 ± 1.01	1.43 ± 0.70	2.00 ± 1.17	0.080
Urea	6.04 ± 7.79	6.78 ± 9.53	5.25 ± 5.41	0.388
Creatinine	80.88 ± 56.64	82.18 ± 32.00	79.44 ± 75.69	0.835
Aspartate aminotransferase	59.42 ± 75.09	78.00 ± 94.57	39.37 ± 37.71	0.020
Alanine aminotransferase	69.13 ± 87.78	88.05 ± 108.56	48.71 ± 51.75	0.040
Alkaline phosphatase	145.28 ± 102.99	160.56 ± 121.97	130.45 ± 79.63	0.245
Gamma-glutamyl transferase	101.84 ± 93.52	107.03 ± 96.69	96.16 ± 91.12	0.638
Lactate dehydrogenase	462.05 ± 373.74	371.79 ± 236.12	557.19 ± 462.63	0.030
Creatine kinase	64.52 ± 79.44	55.95 ± 62.13	77.04 ± 95.57	0.343
Total proteins	70.51 ± 12.77	70.91 ± 15.88	70.07 ± 8.35	0.801
Albumin	33.84 ± 7.62	30.37 ± 5.90	37.28 ± 7.91	0.001
Globulins	36.59 ± 11.97	40.00 ± 14.54	32.83 ± 6.73	0.016
Ferritin	1299.17 ± 2799.06	526.90 ± 307.67	1916.00 ± 3654.50	0.047
C-reactive protein	123.04 ± 100.11	129.00 ± 107.58	116.32 ± 92.18	0.577
Procalcitonin	1.05 ± 1.87	1.72 ± 2.24	0.37 ± 1.04	0.006

Infective endocarditis represents another key diagnostic challenge. It is a multisystemic infection with numerous complications and high mortality[21], and is one of the more frequent causes of FUO worldwide. Meta-analyses across different geographic regions report a prevalence of 7.5-9.9% of FUO cases[20,22]. In our study, infective endocarditis accounted for 17.7% of infectious FUO cases, which is higher compared with the prevalence reported in the literature. Its diagnostic difficulty, owing to prior broad-spectrum antibiotic use resulting in negative blood cultures, and the limited availability of echocardiography (particularly transesophageal echocardiography) in resource-limited settings, makes infective endocarditis a complex but important etiology of FUO in such contexts.

Noninfectious inflammatory diseases are the leading cause of FUO in Western Europe, with reported prevalence ranging from 25.1%[23] to 30.1%[24] and 29.9%[25]. Adult-onset Still's disease is the most frequent diagnosis in this group[26], consistent with our findings. Among malignant causes of FUO, lymphoma and solid organ malignancies are the most frequently reported[22,26], whereas thyroiditis and habitual hyperthermia are leading conditions in the miscellaneous FUO group[22,26]. These findings are in line with the present study.

In our analysis, clinical symptoms and signs were evaluated to assess their diagnostic contribution. Malaise, rigors, and headache, as well as physical findings such as heart murmur and splenomegaly, were strongly associated with infectious etiology. This corresponds to the high frequency of visceral leishmaniasis (splenomegaly)[27] and infective endocarditis (heart murmur)[21]. Conversely, arthralgia, neck pain, joint swelling, and rash emerged as diagnostic clues for noninfectious FUO, in agreement with prior studies[9,10,28].

Elevated inflammatory markers, regardless of etiology, are a universal laboratory finding in FUO[11]. They also form part of the definition of inflammation of unknown origin (IUO), which is investigated in the same way as FUO, and for which some authors consider FUO and IUO to represent the same clinical entity[29,30].

Procalcitonin (PCT) is a prohormone of calcitonin secreted by thyroid C-cells in the setting of hypercalcemia[31]. Its secretion is triggered by cytokines as part of the systemic inflammatory response, particularly in bacterial infections[31]. Simon *et al.*[32] identified serum PCT as a useful marker to discriminate between bacterial, viral, and noninfectious causes of systemic inflammation. In a meta-analysis by Lan Hu *et al*.[33], the diagnostic performance of CRP and PCT in FUO patients was evaluated, confirming their value in distinguishing severe bacterial FUO from nonbacterial and noninfectious causes. Similarly, Cui-Ping *et al*.[34] highlighted PCT as a significant marker for differentiating infectious from noninfectious FUO etiologies. These reports are consistent with our findings.

A variety of diseases can cause elevated serum aminotransferases, and their diagnostic value depends on the distribution of underlying diseases in FUO cohorts. Malignancies (lymphoma, hepatocellular carcinoma, metastatic carcinoma), viral hepatitis, and CMV infection are commonly associated with hepatic involvement in FUO[3]. In this study, elevated aminotransferases were mainly observed in the infectious group, reflecting the high burden of visceral leishmaniasis and other infections with hepatic involvement (CMV infection, rickettsiosis, hepatic abscess).

Ferritin is a serum protein used primarily as an index of body iron stores, but it also functions as an acute-phase reactant[35]. Cunha *et al*.[36] reported that ferritin >500 ng/ml in the initial FUO workup, together with history, examination, and serology, can help exclude infectious causes. In another study, ferritin <500 ng/ml, in combination with eosinopenia (<40/mm^3) and elevated CRP (>60 mg/L), was associated with infectious FUO[28]. Kim *et al*. reported median ferritin levels of 282.4 ng/ml in infectious FUO *versus* 1818.2 ng/ml in noninfectious FUO[35]. The strong association of high ferritin with noninfectious FUO in our study is consistent with these findings.

Lactate dehydrogenase (LDH) is a ubiquitous cytosolic enzyme found in nearly all human tissues[37]. LDH levels reflect the degree of tissue injury and are typically elevated in conditions such as hemolytic anemia, myocardial infarction, inflammation of the liver, lungs, or brain, malignancy, and other diseases with high cellular turnover[38]. In FUO, a diagnostic model suggested that LDH >320 U/L, when combined with leukopenia and lymphadenopathy, provided >89% specificity for excluding infectious etiology[39]. In adult-onset Still's disease, LDH values >247 IU were observed in 92.5% of cases[40]. The elevated LDH values in our study are consistent with these observations.

Conclusion

Our study showed that the differences in potential diagnostic variables between infectious and noninfectious causes of classical FUO may be beneficial for initial etiologic differentiation. This strategy may aid in improved utilization of diagnostic resources and earlier establishment of the underlying diagnosis. A definitive association of the detected findings and FUO etiology was established, whereas the diagnostic utility and function of the parameters should be again confirmed in a prospective study as part of a standardized algorithm.

Conflict of interest statement. None declared.

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