Original Article

Infectious causes of fever of unknown origin in developing countries: An international ID-IRI study

Hakan Erdem [1,*], Jaffar A. Al-Tawfiq [2,3], Maha Abid [4], Wissal Ben Yahia [5], George Akafity [6], Manar Ezzelarab Ramadan [7], Fatma Amer [8], Amani El-Kholy [9], Atousa Hakamifard [10], Bilal Ahmad Rahimi [11], Farouq Dayyab [12], Hulya Caskurlu [13], Reham Khedr [14], Muhammad Tahir [15], Lysien Zambrano [16], Mumtaz Ali Khan [17], Aun Raza [18], Nagwa Mostafa El-Sayed [19], Magdalena Baymakova [20], Aysun Yalci [1], Yasemin Cag [13], Umran Elbahr [21], Aamer Ikram [17]

[1] Department of Infectious Diseases & Clinical Microbiology, Gulhane School of Medicine, Turkish Health Sciences University, Ankara, Turkey
[2] Specialty Internal Medicine and Quality and Patient Safety Department, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia
[3] Division of Infectious Diseases, Indiana University School of Medicine, Indianapolis, IN, USA
[4] Department of Infectious Diseases, Farhat Hached University Hospital, Ibn El Jazzar Medical School, University of Sousse, Sousse, Tunisia
[5] Internal Medicine Department, Farhat Hached University Hospital, Ibn El Jazzar Medical School, University of Sousse, Sousse, Tunisia
[6] Cape Coast Teaching Hospital, Cape Coast, Ghana
[7] Medical Parasitology, Faculty of Medicine, Suez University, Suez, Egypt
[8] Department of Medical Microbiology and Immunology, Faculty of Medicine, Zagazig University, Zagazig, Egypt
[9] Department of Clinical Pathology, Faculty of Medicine, Cairo University, Giza, Egypt
[10] Department of Infectious Diseases, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[11] Department of Infectious Diseases, Kandahar University Medical Faculty, Teaching Hospital, Kandahar, Afghanistan
[12] Department of Infectious Diseases, Mohammed Bn Khalifa Bn Salman Alkhalifa Specialist Cardiac Center, Awali, Bahrain
[13] Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Istanbul Medeniyet University, Istanbul, Turkey
[14] Department of Pediatric Oncology, National Cancer Institute – Cairo University, Children Cancer Hospital Egypt, Cairo, Egypt
[15] Department of Medicine, Federal General Hospital, Islamabad, Pakistan
[16] Institute for Research in Medical Sciences and Right to Health (ICIMEDES), Scientific Research Unit (UIC), Faculty of Medical Sciences (FCM), National Autonomous University of Honduras (UNAH), Tegucigalpa, Honduras
[17] National Institute of Health, Islamabad, Pakistan
[18] Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, Pakistan
[19] Medical Parasitology Department, Research Institute of Ophthalmology, Giza, Egypt
[20] Department of Infectious Diseases, Military Medical Academy, Sofia, Bulgaria
[21] Department of Infectious Diseases, Bahrain Oncology Center, King Hamad University Hospital, Al Muharraq, Bahrain

ARTICLE INFO

ABSTRACT

Background: Fever of unknown origin (FUO) in developing countries is an important dilemma and further research is needed to elucidate the infectious causes of FUO.

Methods: A multi-center study for infectious causes of FUO in lower middle-income countries (LMIC) and low-income countries (LIC) was conducted between January 1, 2018 and January 1, 2023. In total, 15 participating centers from seven different countries provided the data, which were collected through the Infectious Diseases-International Research Initiative platform. Only adult patients with confirmed infection as the cause of FUO were included in the study. The severity parameters were quick Sequential Organ Failure Assessment (qSOFA) ≥ 2, intensive care unit (ICU) admission, vasopressor use, and invasive mechanical ventilation (IMV).

Results: A total of 160 patients with infectious FUO were included in the study. Overall, 148 (92.5%) patients had community-acquired infections and 12 (7.5%) had hospital-acquired infections. The most common infec-

* Corresponding author: Hakan Erdem, Full Professor of Infectious Diseases, Department of Infectious Diseases & Clinical Microbiology, Gulhane School of Medicine, Turkish Health Sciences University and ID-IRI Lead Coordinator, Ankara 06010, Turkey.
E-mail address: erdemhakan@gmail.com (H. Erdem).

tious syndromes were tuberculosis (TB) (*n*=27, 16.9%), infective endocarditis (*n*=25, 15.6%), malaria (*n*=21, 13.1%), brucellosis (*n*=15, 9.4%), and typhoid fever (*n*=9, 5.6%). *Plasmodium falciparum, Mycobacterium tuberculosis*, Brucellae, *Staphylococcus aureus, Salmonella typhi*, and Rickettsiae were the leading infectious agents in this study. A total of 56 (35.0%) cases had invasive procedures for diagnosis. The mean qSOFA score was 0.76±0.94 {median (interquartile range [IQR]): 0 (0–1)}. ICU admission (*n*=26, 16.2%), vasopressor use (*n*=14, 8.8%), and IMV (*n*=10, 6.3%) were not rare. Overall, 38 (23.8%) patients had at least one of the severity parameters. The mortality rate was 15 (9.4%), and the mortality was attributable to the infection causing FUO in 12 (7.5%) patients.

Conclusions: In LMIC and LIC, tuberculosis and cardiac infections were the most severe and the leading infections causing FUO.

Introduction

Fever of unknown origin (FUO) is a major clinical problem and refers to patients who continue to have fever with no identified source despite intensive clinical and diagnostic evaluations. The common causes of FUO can be infectious or non-infectious, such as neoplasms, collagen vascular disorders, undiagnosed, and miscellaneous disease groups.[1] Compared with other causes of FUO, infections can be treated and resolved if diagnosed accurately and promptly. In a systematic review covering January 1, 1997 to March 31, 2021, FUO patients in Southeast Asia were more likely to have an infection, stressing the importance of changing epidemiology in different geographical areas.[2] Conversely, in a recent international FUO study, although there were significantly more reports of collagen vascular disorders from richer countries, there was no significant difference in the context of infection based on economic statuses.[3] There have been multiple studies of FUO globally, but only limited data are available from developing countries.[4,5] In addition, the severity of FUO patients with infections in these countries is a matter of debate and, to our knowledge, no robust data exist in the literature.

Therefore, it is important to evaluate the etiology, severity, and diagnostic difficulties of FUO originating from infections in lower middle-income countries (LMIC) and low-income countries (LIC). Thus, we analyzed the infectious causes of FUO in developing countries in this international study.

Methods

Definitions

FUO was defined as follows: (1) febrile illness of more than 3 weeks; (2) fever higher than 38.3 °C on several occasions; and (3) absence of diagnosis after 3 inpatient days or three outpatient visits to a physician. A critical infection was defined as when a patient had one of the following parameters: qSOFA ≥ 2, intensive care unit (ICU) admission, use of inotropes, or invasive mechanical ventilation (IMV). Sequel was defined as persisting damage related to infection when the antimicrobial treatment was finalized.

Inclusion and exclusion criteria

The inclusion criteria were the following: (1) adult patients; (2) patients ultimately proven to have an infection as the reason of FUO; and (3) patients followed in centers in LMIC or LIC.

The exclusion criteria were the following: (1) patients ≤ 15 years of age; (2) non-infectious causes of FUO; and (3) FUO patients without a diagnosis.

Data collection and participants

This study was performed through the Infectious Diseases-International Research Initiative (ID-IRI) platform (https://infectdisiri.com/). Demographic parameters, clinical presentation, laboratory results, and clinical outcomes of the patients were retrospectively obtained from hospitals' electronic medical records. Patients followed between January 1, 2018 and January 1, 2023 were included in the study. Checking of the databases of this study and the previous ID-IRI FUO study[3] revealed that there were only five patients submitted to both studies by the participant centers.

Stratification of the economic status

According to the World Bank Atlas method, developing countries in the world are divided into two groups[6]: "LIC" – gross national income (GNI) per capita of ≤US$ 1085, and "LMIC" – GNI per capita between US$ 1086 and US$ 4255. Centers from the following countries were included in this research: Afghanistan (current GNI per capita: US$ 368), Egypt (US$ 3698), Ghana (US$ 2363), Honduras (US$ 2771), Iran (US$ 4091), Pakistan (US$ 1505), and Tunisia (US$ 3807).

Statistical analysis

Descriptive statistical analysis was performed to describe the characteristics and outcome of the included patients. Measured data with a normal distribution were expressed as mean±standard deviation, and data not conforming to a normal distribution were expressed as median (interquartile range [IQR]). Numerical data were expressed as numbers (percentage).

Results

Fifteen participating centers from seven different countries provided the following patient numbers: Afghanistan, (*n*=10), Egypt (*n*=53), Ghana (*n*=5), Honduras (*n*=4), Iran (*n*=8); Pakistan (*n*=25), and Tunisia (*n*=55). Of the 160 total patients, 65 (40.6%) were female. The median age was 42 (IQR: 30–55) years. The median length of hospital stay was 14 (IQR: 8–22) days. The median duration of diagnosis after hospitalization was 7 (IQR: 2–32) days. The descriptive clinical data of the patients are presented in Table 1.

Table 1

Overall characteristics of the included 160 patients with FUO.

Characteristics	Values
Demographics	
Female	65 (40.6)
Age (years), median (IQR)	42 (30–55)
Length of hospital stay (days), median (IQR)	14 (8–22)
Source of infection	
Community-acquired	148 (92.5)
Hospital-acquired	12 (7.5)
Major infections causing FUO	
Zoonotic infections	32 (20)
Vector-borne diseases	33 (20)
Cardiac infections	31 (19.4)
TB	27 (16.9)
Respiratory tract infections	12 (7.5)
Abscess	7 (4.4)
Invasive diagnostic testing	
Lumbar puncture	24 (15)
Biopsy	21 (13.1)
Bronchoscopy	6 (3.7)
Gastroscopy	4 (2.5)
Peritoneal fluid aspiration	2 (1.2)
Colonoscopy	1 (0.6)
Bone marrow biopsy	1 (0.6)
Outcome	
Discharged with cure	109 (68.1)
Discharged with sequential therapy	10 (6.2)
Discharged with sequelae	20 (12.5)
Transferred to other hospitals	6 (3.7)
Mortality	15 (9.4)
Characteristics	
Severity of the illness on admission: qSOFA	0.76±0.94
Laboratory data	
WBC (cells/mm^3)	9854.07±12,430.49
CRP (mg/dL)	74.54±75.55
Procalcitonin (µg/L)	0.57±0.45
ESR (mm/h)	71.29±67.93

Data are expressed as *n* (%), median (IQR) or mean±standard deviation.
CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; FUO: Fever of unknown origin; IQR: Interquartile range; qSOFA: Quick Sequential Organ Failure Assessment; TB: Tuberculosis; WBC: White blood cell.

Source of infection

The FUO was attributed to community-acquired infections in 148 (92.5%) of the patients and hospital-acquired infections in 12 (7.5%) patients. The hospital-acquired infections comprised infective endocarditis (*n*=4), pacemaker (PM) endocarditis (*n*=2), typhlitis (*n*=2), human herpesvirus 6 (HHV6) encephalitis (*n*=1), liver abscess (*n*=1), renal abscess (*n*=1), and pulmonary aspergillosis (*n*=1).

Infections causing FUO

The most common infectious syndromes were tuberculosis (TB) (*n*=27, 16.9%), infective endocarditis (*n*=25, 15.6%), malaria (*n*=21, 13.1%), brucellosis (*n*=15, 9.4%), and typhoid fever (*n*=9, 5.6%) (Figure 1). In patients comprised in the immunological compromise subgroup (*n*=23, 14.4%) (neutropenia, malignancy, human immunodeficiency virus [HIV], steroid use), TB (*n*=5, 21.7%), pulmonary aspergillosis (*n*=3, 13.0%), malaria (*n*=3, 13.0%), typhlitis (*n*=2, 8.7%), and infective endocarditis (*n*=2, 8.7%) were the common causes. The distribution of infections causing FUO is presented in Table 2.

Geographical distributions of the patients

A large percentage of patients were from Egypt and Tunisia (*n*=108, 67.5%). The leading FUO diagnoses in these two coun-
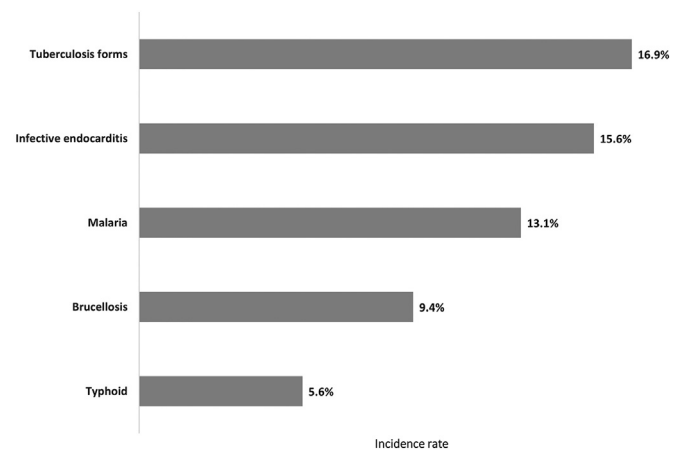
Figure 1. The most common infectious causes of FUO among the 160 total cases included in the study. FUO: fever of unknown origin.

tries were TB of all types (*n*=13, 12.0%), brucellosis (*n*=12, 11.1%), native valve endocarditis (*n*=23, 21.3%), and malaria of all types (*n*=19, 17.6%). Accordingly, in the rest of the countries (*n*=52, 32.5%), TB of all types (*n*=13, 25.0%), brucellosis (*n*=6, 11.5%), native valve endocarditis (*n*=3, 5.8%), and malaria of all types (*n*=3, 5.8%) were the leading infections causing FUO.

Comorbid conditions

Overall, 86 (53.8%) patients had at least one comorbid condition. These included diabetes mellitus (*n*=37), cardiovascular diseases (*n*=32), neutropenia (*n*=13), organ malignancy (*n*=13), chronic renal failure (*n*=9), immune suppression (*n*=8), HIV/acquired immunodeficiency syndrome (AIDS) (*n*=7), chronic respiratory diseases (*n*=6), systemic lupus erythematosus (*n*=2), cerebrovascular disease (*n*=1), major depression (*n*=1), schizophrenia (*n*=1), allergic rhinitis (*n*=1), spondylodiscitis (*n*=1), non-Hodgkin's lymphoma (*n*=1), deep vein thrombosis (*n*=1), polycystic kidney disease (*n*=1), and hypothyroidism (*n*=1).

Inflammatory markers on admission

The means of white blood cell (WBC) count (*n*=155), C-reactive protein (CRP; *n*=150), procalcitonin (*n*=34), and erythrocyte sedimentation rate (ESR; *n*=120) were 9854.07±12,430.49 cells/mm^3, 74.54±75.55 mg/dL, 0.57±0.45 µg/L, and 71.29±67.93 mm/h, respectively.

Microbiological diagnosis

Microbiological tests disclosed infecting pathogens in 129 (80.6%) patients. Various microbiological tests were used in the cases in this study, including blood culture (*n*=137, 85.6%), urine culture (*n*=104, 65.0%), cerebrospinal fluid culture (*n*=24, 15.0%), sterile body fluids culture (*n*=21, 13.1%), viral polymerase chain reaction (PCR) panel (*n*=100, 62.5%), stool culture (*n*=27, 16.9%), and other tests (*n*=45, 28.1%). The positivity rates of the microbiological tests were as follows: blood cultures (*n*=39, 28.5%), urine culture (*n*=7, 6.7%), cerebrospinal fluid culture (*n*=3, 12.5%), sterile body fluids culture (*n*=5, 23.8%), viral PCR panel (*n*=15, 15.0%), stool culture (*n*=4,

Table 2
The distribution of infections causing FUO.

Infection	Number of patients	Percentage (%)
Zoonotic infections	32	20.0
Brucellosis	15	9.4
Typhoid fever	9	5.6
Q-fever	3	1.9
Toxoplasmosis	2	1.2
Visceral toxocariasis	2	1.2
Vector-borne diseases	32	20.0
Malaria	21	13.1
Rickettsiosis	7	4.4
Visceral leishmaniasis	3	1.9
West Nile fever	1	0.6
Cardiac infections	31	19.4
Infective endocarditis	25	15.6
Prosthetic valve endocarditis	2	1.2
PM endocarditis	2	1.2
Acute pericarditis	1	0.6
Myocarditis	1	0.6
TB	27	16.9
Pulmonary TB	9	5.6
Tuberculous lymphadenitis	7	4.4
Tuberculous meningitis	5	3.1
Disseminated TB	3	1.9
Hepatic TB	2	1.2
Psoas abscess	1	0.6
Respiratory tract infections	12	7.5
Pneumonia	6	3.8
Aspergillosis	3	1.9
Sinusitis	2	1.2
P. jirovecii pneumonia	1	0.6
Abscess	7	4.4
Liver abscess	4	2.5
Pelvic abscess	1	0.6
Renal abscess	1	0.6
Amebic liver abscess	1	0.6
Major viral syndromes	4	2.5
Cytomegalovirus infection	3	1.9
SARS-CoV-2 (variant strain)	1	0.6
Urinary tract infections	4	2.5
Pyelonephritis	2	1.2
Urinary tract infection	2	1.2
Intra-abdominal infection	3	1.9
Typhlitis	2	1.2
Abdominal infection (gastric leak)	1	0.6
Central nervous system infection	2	1.2
HHV6 encephalitis	1	0.6
Meningitis	1	0.6
Others	6	3.8
Sepsis of unidentified origin	2	1.2
Spondylodiscitis	2	1.2
Chronic lymphadenitis	1	0.6
Periodontitis	1	0.6

FUO: Fever of unknown origin; HHV6: Human herpesvirus 6; *P. jirovecii*: *Pneumocystis jirovecii*; PM: Pacemaker; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; TB: Tuberculosis.

Table 3
Microbiologically identified pathogens.

Pathogens	Culture	Serology	Molecular tests	Direct smear/ staining
Fungi				
Aspergillus spp. (*n*=2)	2	2		
Candida albicans (*n*=1)	1			
Pneumocystis jirovecii (*n*=1)		1		
Viruses				
Cytomegalovirus (*n*=3)		3	1	
West Nile Virus (*n*=1)		1		
SARS-CoV-2 (*n*=1)			1	
Herpes Virus Type-6 (*n*=1)			1	
Bacteria				
Brucellae (*n*=17)		17		
Mycobacterium tuberculosis (*n*=17)	5	4	7	6
Rickettsia spp. (*n*=7)		6		
Coxiella burnetii (*n*=3)		3		
Escherichia coli (*n*=6)	6			
Enterobacter cloacae (*n*=1)	1			
Enterococcus faecalis (*n*=5)	5			
Klebsiella pneumoniae (*n*=5)	5			
Klebsiella oxytoca (*n*=1)	1			
Staphylococcus aureus (*n*=9)	9			
Staphylococcus epidermidis (*n*=1)	1			
Streptococcus pneumoniae (*n*=2)	1		1	
Staphylococcus saprophyticus (*n*=1)	1			
Streptococcus viridans (*n*=4)	4			
Salmonella typhi (*n*=9)	6	3		
Serratia marcescens (*n*=1)	1			
Parasites				
Plasmodium falciparum (*n*=18)		15		11
Plasmodium vivax (*n*=3)		1		2
Plasmodium, untyped (*n*=1)				1
Entamoeba histolytica (*n*=1)		1		
Leishmania spp. (*n*=3)		3		
Toxoplasma gondii (*n*=3)		3		
Toxacara spp. (*n*=2)		2		

SARS-CoV-2: Severe acute respiratory syndrome Coronavirus 2.

Invasive diagnostic testing

Overall, 56 (35.0%) patients had an invasive diagnostic procedure. These procedures included lumbar puncture (*n*=24, 15.0%), biopsy (*n*=21, 13.1%), bronchoscopy (*n*=6, 3.8%), gastroscopy (*n*=4, 2.5%), peritoneal fluid aspiration (*n*=2, 1.3%), colonoscopy (*n*=1, 0.6%), and other invasive procedures (*n*=6, 3.7%, which comprised abscess drainage [*n*=4, 2.5%], abdominal exploration [*n*=1, 0.6%], and bone marrow biopsy [*n*=1, 0.6%]).

Severity of the illness on admission

A total of 38 (23.7%) patients had at least one of the severity parameters (qSOFA ≥2, ICU admission, vasopressor use, or IMV) (Table 4). The mean qSOFA score was 0.76±0.94 (median [IQR]: 0 [0–1]), and the numbers of patients requiring ICU admission, vasopressor use, and/or IMV were 26 (16.3%), 14 (8.8%), and 10 (6.3%), respectively.

Outcomes

Of the 160 patients included in the study, 109 were discharged with a cure (68.1%).

Ten patients (6.2%) were discharged with sequential therapy, and the dominant infection in this group was TB (5 [3.1%]

14.8%), serology (*n*=56, 35%), and other tests (*n*=31, 19.4%) (Table 3).

Radiological diagnosis

Computerized tomography (CT; *n*=53, 33.1%), ultrasonography (USG; *n*=34, 21.2%), transthoracic echocardiogram (TTE; *n*=34, 21.3%), transesophageal echocardiogram (TEE; *n*=25, 15.6%), magnetic resonance imaging (MRI; *n*=14, 8.8%), positron emission tomography (PET-CT; *n*=2, 1.3%), and scintigraphy (*n*=1, 0.6%) were employed for radiological diagnoses. In 66 (41.3%) patients, none of these radiological tests were applied.

Table 4

Critical status of the patients.

Item	qSOFA >2	ICU admission	Inotrope use	IMV	Overall*
Infective endocarditis (*n*=25)	14 (56.0)	10 (40.0)	11 (44.0)	7 (28.0)	15 (60.0)
P. falciparum malaria (*n*=21)	5 (24.8)	6 (28.6)	0	0	6 (28.6)
Brucellosis (*n*=15)	2 (13.3)	1 (6.7)	0	0	2 (13.3)
Pulmonary TB (*n*=9)	2 (22.2)	1 (11.1)	0	0	2 (22.2)
Abdominal infection (*n*=3)	1 (33.3)	2 (66.7)	1 (33.3)	1 (33.3)	2 (66.7)
Pneumonia (*n*=6)	2 (33.3)	1 (33.3)	0	1 (33.3)	2 (66.7)
TB meningitis (*n*=5)	5 (100)	4 (80.0)	0	0	5 (100)
Liver abscess (*n*=4)	0	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)
Disseminated TB (*n*=3)	1 (33.3)	0	0	0	1 (33.3)
Sepsis, unidentified (*n*=2)	1 (50.0)	0	0	0	1 (50.0)
PM endocarditis (*n*=2)	0	0	1 (50.0)	0	1 (50.0)
TB, all forms (*n*=27)	9 (33.3)	5 (18.5)	0	0	8 (29.6)
Total (*n*=160)	33 (20.6)	26 (16.2)	14 (8.7)	10 (6.2)	38 (23.7)

Data are expressed as *n*(%).

*Positive for one of the critical status parameters (qSOFA >2, ICU admission, inotrope use, or IMV).

ICU: Intensive care unit; IMV: Invasive mechanical ventilation; *P. falciparum*: *Plasmodium falciparum*; PM: Pacemaker; qSOFA: Quick Sequential Organ Failure Assessment; TB: Tuberculosis.

patients), comprising pulmonary TB (*n*=2, one with HIV), lymph node TB (*n*=2), and tuberculous psoas abscess (*n*=1). The other infections included liver abscess (*n*=1), brucellosis (*n*=1), chronic lymphadenitis (*n*=1), infective endocarditis (*n*=1), and prosthetic valve endocarditis (*n*=1).

There were 20 patients (12.5%) discharged with sequelae. The dominant infection in this group was TB (*n*=7, 4.4%). The total infections in this group comprised infective endocarditis (*n*=6), tuberculous meningitis (*n*=5), toxoplasmosis (*n*=2), disseminated TB (*n*=1), pulmonary TB (*n*=1), amebic liver abscess (*n*=1), brucellosis (*n*=1), encephalitis (*n*=1), falciparum malaria (*n*=1), and pneumonia (*n*=1).

Six patients (3.8%) were transferred to other hospitals. The most common infectious syndromes resulting in transfer to other hospitals were cardiac infections (*n*=3, 1.9%). Overall, the infectious syndromes present in the transferred patients were infective endocarditis (*n*=1), myocarditis (*n*=1), prosthetic valve endocarditis (*n*=1), sepsis of unidentified origin (*n*=1), brucellosis (*n*=1), and pelvic abscess (*n*=1).

Fifteen patients in the study died, equating to a mortality rate of 9.4%. Death was attributable to the infection causing FUO in 12 (7.5%) patients, and the leading infectious syndromes were cardiac infections (*n*=7). Overall, the infectious syndromes leading to death comprised infective endocarditis (*n*=6), pulmonary TB (*n*=2), PM endocarditis (*n*=1), liver abscess (*n*=1), pneumonia (*n*=1), and sepsis of unidentified origin (*n*=1).

Discussion

In this study, we evaluated infectious causes of FUO in LMIC and LIC. The most common infectious syndrome was TB in one-sixth of the patients, followed by infective endocarditis, malaria, brucellosis, and typhoid fever in descending order. *Plasmodium falciparum, Mycobacterium tuberculosis*, Brucellae, *Staphylococcus aureus, Salmonella typhi,* and Rickettsiae were the dominant infectious agents causing FUO. In addition, the most severe infection was TB, particularly TB meningitis, followed by infective endocarditis and falciparum malaria. Two-third of the infectious FUO patients were relatively stable and were categorized as non-critical. One-tenth of the patients died, with an at-

tributable mortality of 7.5%, which was predominantly related to cardiac infections.

It is unsurprising that TB was the leading infectious etiology among patients with FUO. Previous studies showed that TB was the most common cause of FUO, particularly in developing countries.[1–3,7–9] Furthermore, TB can have a long presentation before an actual diagnosis is reached. Protean manifestations are especially common with extrapulmonary disease or when the disease occurs in individuals with underlying pulmonary or immunosuppressive conditions. Indeed, two-thirds of the patients with TB in this study had an extrapulmonary disease like lymphadenitis, meningitis, disseminated disease, liver involvement, and psoas abscess in descending order. Relatively low diagnostic sensitivity is another contributing factor for delayed TB diagnosis. Thus, a combination of diagnostic tests, such as TB culture (Lowenstein Jensen media), automated TB cultures, Ehrlich–Ziehl–Neelsen staining, interferon-gamma release assay, adenosine deaminase (ADA), and PCR, is needed to establish diagnosis as early as possible.[10,11] Although the number of patients with HIV in our study is low, it is important to note that TB was the reported cause of FUO in approximately half of the cases in this subset in one study.[7]

The second most common infectious cause of FUO in this study was infective endocarditis. Endocarditis is a multisystem disorder with numerous complications and a high mortality rate.[12] It is one of the most common causes of FUO across multiple geographic locations,[13] and constituted 7.5% of cases, with variability in different regions, such as 4.5% in the Western Pacific region and 14% in the Eastern Mediterranean region.[2] Endocarditis has particular importance in FUO given that a proportion of cases are culture-negative and additional tests such as an echocardiogram may be needed for diagnosis. However, the more sensitive modality is TEE, which might not be available in LMIC or LIC.

According to our data, zoonotic and vector-borne infections constituted 20% each as the etiologies of FUO. The leading infectious syndromes were malaria, brucellosis, typhoid fever, and rickettsiosis. In a study from Tanzania, dengue, malaria, rickettsiosis, brucellosis, and salmonellosis were the most common etiologies,[14] whereas malaria accounted for 7% of cases of FUO.[14,15] These diagnoses are of particular importance

in LMIC and LIC are based on the local epidemiology, and also should be considered in travelers returning from these regions.[16]

In this study, 7.5% of the patients had hospital-acquired infections – mostly cardiac infections – as the causes of FUO. This is an important consideration when evaluating hospitalized patients with FUO. In an FUO study analyzing hospitalized patients, there was an increased risk for sinusitis, which was the sole cause of FUO in 16.2% of the cases, and the contributing factor in 13.8% of the cases.[17]

Different radiographic and laboratory tests are needed for definitive diagnosis of patients with FUO. Although advanced radiological imaging is central to FUO diagnosis, advanced imaging techniques like CT, USG, TTE, TEE, MRI, PET-CT, and scintigraphy were not applied to 41% of the patients in this study, indicating the limited resources of the countries involved. However, various invasive diagnostic procedures were employed, with 35% of the patients undergoing lumbar puncture, tissue biopsy followed by bronchoscopy, gastroscopy, peritoneal fluid aspiration, colonoscopy, abscess drainage, abdominal exploration, or bone marrow biopsy. Some updated guidelines indicated that appropriate lymph node and liver biopsies would provide added value in the appropriate patients.[18] One study reported the benefit of ESR, CRP, MRI, bone scan, and echocardiography for the diagnosis of FUO.[19] In our study, the mean levels of CRP, procalcitonin, and ESR were 74.54±75.55 mg/dL, 0.57±0.45 μg/L, and 71.29±67.93 mm/h, respectively. As a general understanding, the levels of CRP were thought to be specific for patients with infectious etiology. However, one prospective study showed no associations between CRP level and the category of FUO, and the utility of procalcitonin levels in determining the FUO category could not be established.[20] An international study showed that inflammatory markers were homogeneous among FUO categories, but for the group without a confirmed diagnosis only.[3]

The attributed mortality of infectious causes of FUO in this study was 7.5%. Previous studies have reported varied mortality rates that ranged from 2% to 35%.[21–24] The difference in the mortality rates among various FUO studies is likely to be related to differences in underlying comorbid conditions and the ultimate diagnosis of FUO. The availability of effective antimicrobial agents is of paramount importance for the therapeutic success of FUO-related infections in LMIC and LIC.

This study is an important addition to understanding infectious causes of FUO in LMIC and LIC. A strength of the study is the inclusion of infectious FUO patients followed over 5 years in different countries. However, there are a few limitations to this study. One limitation is the retrospective nature of the study, which means the analyses and conclusions are dependent on data extracted from the available medical records rather than employing a systematic prospective approach to data collection. The descriptive nature of the study also makes it difficult to establish a firm hypothesis for testing or comparing it to another group. Second, although the study involved multiple institutes from different countries, the diagnostic capabilities of these institutions are variable. Third, the reported mortality rate might have been affected by the unavailability of required antimicrobial medications in different participating institutions in different developing countries. A

fourth limitation of the study is that a large percentage of patients were from Egypt and Tunisia, which may have resulted in an imbalance; however, the predominant infectious syndromes in the other countries were similar to those of Egypt and Tunisia.

In conclusion, although the epidemiology of FUO appears to differ in different geographical areas, TB and cardiac infections are the most severe infections and the leading infectious diagnoses causing FUO.

Author Contributions

Acknowledgments

Funding

Ethics Statement

The Ethical Counsel of Istanbul Medeniyet University, Faculty of Medicine, Istanbul (08.02.2023/0093) approved the study.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

References

[1] Kucukardali Y, Oncul O, Cavuslu S, Danaci M, Calangu S, Erdem H, et al. The spectrum of diseases causing fever of unknown origin in Turkey: a multicenter study. Int J Infect Dis 2008;12(1):71–9. doi:10.1016/j.ijid.2007.04.013.

[2] Wright WF, Yenokyan G, Simner PJ, Carroll KC, Auwaerter PG. Geographic variation of infectious disease diagnoses among patients with fever of unknown origin: a systematic review and meta-analysis. Open Forum Infect Dis 2022;9(5):ofac151. doi:10.1093/ofid/ofac151.

[3] Erdem H, Baymakova M, Alkan S, Letaief A, Yahia WB, Dayyab F, et al. Classical fever of unknown origin in 21 countries with different economic development: an international ID-IRI study. Eur J Clin Microbiol Infect Dis 2023;42(4):387–98. doi:10.1007/s10096-023-04561-5.

[4] Al-Layla D, Ghanim H, Al-Kazzaz H, Al-Hayali RMA. Fever of unknown origin: a prospective study in Northern Iraq. Ann Coll Med Mosul 2010;36(1 & 2):26–35. doi:10.33899/mmed.2010.8927.

[5] Ali-Eldin FA, Abdelhakam SM, Ali-Eldin ZA. Clinical spectrum of fever of unknown origin among adult Egyptian patients admitted to Ain Shams University Hospitals: a hospital based study. J Egypt Soc Parasitol 2011;41(2):379–86.

[6] World Bank Country and Lending Groups. Available from: https://datahelpdesk. worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. [Last accessed on 2023 May 2].

[7] Nguyen TK, Nguyen YH, Nguyen HT, Khong QM, Tran NK. Etiologies of fever of unknown origin in HIV/AIDS patients, Hanoi, Vietnam. BMC Infect Dis 2022;22(1):61. doi:10.1186/s12879-022-07049-3.

[8] Yadav BK, Pannu AK, Kumar R, Rohilla M, Kumari S. Fever of unknown origin in older adults: a prospective observational study from North India. J Assoc Physicians India 2021;69(10):11–12.

[9] Alavi SM, Nadimi M, Zamani GA. Changing pattern of infectious etiology of fever of unknown origin (FUO) in adult patients in Ahvaz, Iran. Caspian J Intern Med 2013;4(3):722–6.

[10] Erdem H, Ozturk-Engin D, Elaldi N, Gulsun S, Sengoz G, Crisan A, et al. The microbiological diagnosis of tuberculous meningitis: results of Haydarpasa-1 study. Clin Microbiol Infect 2014;20(10):O600–8. doi:10.1111/1469-0691.12478.

[11] Saktiawati AMI, Subronto YW, Stienstra Y, Sumardi, Supit F, van der Werf TS. Sensitivity and specificity of routine diagnostic work-up for tuberculosis in lung clinics in Yogyakarta, Indonesia: a cohort study. BMC Public Health 2019;19(1):363. doi:10.1186/s12889-019-6658-8.

[12] Erdem H, Puca E, Ruch Y, Santos L, Ghanem-Zoubi N, Argemi X, et al. Portraying infective endocarditis: results of multinational ID-IRI study. Eur J Clin Microbiol Infect Dis 2019;38(9):1753–63. doi:10.1007/s10096-019-03607-x.

[13] Fusco FM, Pisapia R, Nardiello S, Cicala SD, Gaeta GB, Brancaccio G. Fever of unknown origin (FUO): which are the factors influencing the final diagnosis? A 2005-2015 systematic review. BMC Infect Dis 2019;19(1):653. doi:10.1186/s12879-019-4285-8.

[14] Ali MA, James OC, Mohamed AA, Joachim A, Mubi M, Omodior O. Etiologic agents of fever of unknown origin among patients attending Mnazi Mmoja Hospital, Zanzibar. J Community Health 2020;45(5):1073–80. doi:10.1007/s10900-020-00832-w.

[15] Aboul-Hassan S, el-Shazly AM, Farag MK, Habib KS, Morsy TA. Epidemiological, clinical and laboratory studies on parasitic infections as a cause of fever of undetermined origin in Dakahlia Governorate. Egypt. J Egypt Soc Parasitol 1997;27(1):47–57.

[16] Korzeniewski K, Gaweł B, Krankowska D, Wasilczuk K. Fever of unknown origin in returning travellers. Int Marit Health 2015;66(2):77–83. doi:10.5603/IMH.2015.0019.

[17] van Zanten AR, Dixon JM, Nipshagen MD, de Bree R, Girbes AR, Polderman KH. Hospital-acquired sinusitis is a common cause of fever of unknown origin in orotracheally intubated critically ill patients. Crit Care 2005;9(5):R583–90. doi:10.1186/cc3805.

[18] Hayakawa K, Ramasamy B, Chandrasekar PH. Fever of unknown origin: an evidence-based review. Am J Med Sci 2012;344(4):307–16. doi:10.1097/MAJ.0b013e31824ae504.

[19] Mourad O, Palda V, Detsky AS. A comprehensive evidence-based approach to fever of unknown origin. Arch Intern Med 2003;163(5):545–51. doi:10.1001/archinte.163.5.545.

[20] Naito T, Torikai K, Mizooka M, Mitsumoto F, Kanazawa K, Ohno S, et al. Relationships between causes of fever of unknown origin and inflammatory markers: a multicenter collaborative retrospective study. Intern Med 2015;54(16):1989–94. doi:10.2169/internalmedicine.54.3313.

[21] Pedersen TI, Roed C, Knudsen LS, Loft A, Skinhoj P, Nielsen SD. Fever of unknown origin: a retrospective study of 52 cases with evaluation of the diagnostic utility of FDG-PET/CT. Scand J Infect Dis 2012;44(1):18–23. doi:10.3109/00365548.2011.603741.

[22] Mulders-Manders CM, Engwerda C, Simon A, van der Meer JWM, Bleeker-Rovers CP. Long-term prognosis, treatment, and outcome of patients with fever of unknown origin in whom no diagnosis was made despite extensive investigation: a questionnaire based study. Medicine 2018;97(25):e11241. doi:10.1097/MD.0000000000011241.

[23] Zenone T. Fever of unknown origin in adults: evaluation of 144 cases in a non-university hospital. Scand J Infect Dis 2006;38(8):632–8. doi:10.1080/00365540600606564.

[24] Robine A, Hot A, Maucort-Boulch D, Iwaz J, Broussolle C, Sève P. Fever of unknown origin in the 2000s: evaluation of 103 cases over eleven years. Presse Med 2014;43(9):e233–40. doi:10.1016/j.lpm.2014.02.026.