Title:

Fever of unknown origin (FUO) on a land on cross-roads between Asia and Europa; a multicenter study from Turkey

Running title:

Fever of unknown origin etiology in Turkey

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Abstract

Aims: The differential diagnosis of Fever of Unknown Origin (FUO) is still a major clinical challenge despite the advances in diagnostic procedures. In this multicenter study, we aimed to reveal FUO etiology and factors influencing the final diagnosis of FUO in Turkey.

Methods: A total of 214 patients with FUO between the years 2015-2019 from 13 tertiary training and research hospitals were retrospectively evaluated.

Results: The etiologic distribution of FUO was infections (44.9%), malignancies (15.42%), autoimmune/inflammatory (11.68%) diseases, miscellaneous diseases (8.41%) and undiagnosed cases (19.62%). Brucellosis (10.25%), extrapulmonary tuberculosis (6.54%) and infective endocarditis (6.54%) were the most frequent three infective causes. Solid malignancies (7.1%) and lymphoma (5.6%), adult-onset still's disease (6.07%) and thyroiditis (5.14%) were other frequent diseases. The etiologic spectrum did not differ in elderly ($p<0.05$). Infections were less frequent in Western (34.62%) compared to Eastern regions of Turkey (60.71%) ($p< 0.001$, OR: 0.31, 95% Cl: 0.19 to 0.60). The ratio of undiagnosed etiology was significantly higher in elderly (p: 0.046, OR: 2.34, 95% Cl: 1.00 to 5.48) and significantly lower in Western Turkey (p: 0.004, OR: 3.07, 95% Cl: 1.39 to 6.71).

Conclusions: Brucellosis, extrapulmonary tuberculosis and infective endocarditis remain to be the most frequent infective causes of FUO in Turkey. Solid tumors and lymphomas, AOSD and thyroiditis are the other common diseases. The etiologic spectrum did not differ in elderly, on the other hand, infections were more common in Eastern Turkey. A considerable amount of etiology remained undiagnosed despite the state-of-the-art technology in healthcare services.

Keywords: Adult, Fever of unknown origin, FUO, causes of fever, Turkey,

What is known about FUO?

* The differential diagnosis of FUO is one of the most challenging issues, and about one fourth of cases are remains undiagnosed

* In a pool analysis report from Turkey in 2007; Infections, collagen vascular diseases, and neoplasms were found to be the reason of fever in 403 (47.0%), 137 (15.9%), and 126 (14.7%) of the in all 857 patients. The most common infectious disease was tuberculosis (147/403, 36.4%) followed by brucellosis (51/403, 12.6%) and infective endocarditis (39/403, 9.6%). The most common collagen vascular disease was adult-onset Still's Disease (49/137, 35.7%). The most common neoplasms were Hodgkin's disease (32/126, 25.3%) and non-Hodgkin's lymphoma (32/126, 25.3%). The reason of fever could not be defined in 138/857 (16.1%) patients.

* However after the year 2007, demography has changed in Turkey, especially eastern regions, due to refugees from Syria and other Middle East regions. And there is no study having large number of cases after these years to reveal FUO etiology in Turkey's overall.

What is new about FUO according to our study results?

* As a part of Health Transformation Program in Turkey, both accessibility and the quality of the health system, especially the number of the state-of-the-art technology medical devices like computerized tomography (CT), magnetic resonance imaging or PET-CT has incrementally increased especially after 2010's.

* There is no study after the year 2013 from Turkey, and this study is the first report of FUO in years with state-of-the-art technologies in medicine.

* Present study has the highest number of FUO cases in literature in recent years

* Present study is the only study to reveal FUO etiology in Turkey's overall. Because, all of the studies in literature were performed in hospitals in Western geographical regions of Turkey.

* In present study, we revealed that infections are still the most frequent cause of FUO in Turkey.

* We, first time in literature, revealed that infections were less frequent in Western Turkey compared to Eastern Turkey.

* We, first time in literature, revealed that the etiologic spectrum of FUO did not differ in elderly (age >65), while non-infectious diseases were more frequent over 40 years-old.

* Brucellosis, a highly endemic diseases in Eastern Turkey and easy to diagnose disease with basic laboratory tests, is still the most important cause of FUO in Eastern Turkey.

* Tuberculosis and infective endocarditis remain to be the most frequent cause of FUO in Turkey.

* Unlike literature, solid tumors were more frequent than lymphomas in cases with FUO

* Similarly to literature, AOSD is an important cause of FUO.

* First time in literature, we revealed that thyroiditis should be considered as an important cause of FUO.

* First time in literature, we revealed that duration of fever, type of fever, concomitant complaints besides fever, ESR and hemogram findings were not significant parameters to distinguish infectious and non-infectious etiology in FUO. On the other hand, CRP might be an important laboratory parameter to differentiate infection and non-infections etiology in patients with FUO (But higher CRP is associated with non-infectious diseases).

* Despite the state-of-the-art technology in healthcare services in Turkey, we revealed that a considerable amount of etiology in patients with FUO remained undiagnosed.

* We believe that the results of this multicenter study reflecting Turkey's overall may help clinicians to set strategies for optimizing the diagnostic approach for FUO.

Introduction

Fever of unknown origin (FUO), defined by Petersdorf and Beeson in 1961, is still remains as a challenge in medicine despite the state-of-the-art diagnostic procedures [1]. Although the ultimate diagnosis among the patients with prolonged fever is commonly non-infectious diseases like autoimmune disorders or malignancies, the vast majority of the patients with prolonged fever are referred to an infectious diseases specialist in Turkey. The number of FUO cases, the etiology and the clinical manifestations of FUO has been changing over the years due to the improvement in the diagnostic procedures, vaccination policies, frequent use of antibiotics, infrastructure improvements in cities. As a part of Health Transformation Program in Turkey, both accessibility and the quality of the health system, especially the number of the state-of-the-art technology medical devices like computerized tomography (CT), magnetic resonance imaging or PET-CT has incrementally increased since 2003 [2,3]. On the other hand, some factors like increased number of elderly people, newly emerging or re-emerging diseases, malignancies and AIDS epidemic in the World influence on FUO epidemiology. More particularly for Turkey, uncontrolled migration due to civil wars and conflicts in the Middle East Region exposes additional risk for emerging or re-emerging infectious diseases [4,5]. Turkey hosts world's largest refugee population, with more than 3.6 million Syrian refugees and close to 400,000 refugees and asylum seekers of other nationalities [6]. Some of them reach to European countries as refugee status or some cross the European borders illegally. Turkey occupies at the geographic, cultural cross-roads between Europe and Asia. Thus, Turkey's current data may pose a future perspective for the distribution of FUO etiology for the other European countries.

In this multicenter study, we aimed to reveal both infectious and non-infectious FUO etiology in the last five years-period in Turkey. We also aimed to reveal relationship between FUO etiology and demographic, clinical and laboratory variables.

Materials and Methods

The study was conducted in thirteen tertiary teaching and research hospitals from different regions in Turkey. Patients over 18 years-old between January 2014 and December 2019 who fulfilled the modified FUO criteria were included in the study [7]. Only the patients fulfilling the classical FUO criteria included while others identified as nosocomial FUO, neutropenic FUO or HIV-associated FUO were excluded from the study.

Medical records of these patients were retrospectively obtained by the hospital database systems and the data were recorded into excel form. The forms are consisted of demographics and medical data that included history of the patients and the clinical characteristics of the febrile illness, admission and discharge dates, diagnostic tests including laboratory, radiological and invasive procedures, empirical and targeted treatments, final diagnosis and outcome. The etiology of FUO was categorized into five main groups as (1) infectious, (2) malign, (3) autoimmune-inflammatory, (4) miscellaneous diseases and (5) undiagnosed. Diagnoses of infections were determined by serologic, molecular tests, bacterial cultures, radiology and / or histopathology. Diagnoses of malignancies were determined by histopathology. Diagnoses of autoimmune-inflammatory and miscellaneous diseases were determined by biochemical tests and / or histopathology. Patients without any specific final diagnosis were determined as undiagnosed / true FUO. Excluding undiagnosed cases, patients were divided into two groups as patients diagnosed with infectious diseases and non-infectious diseases, and the risk estimation / probability analysis between demographic, clinical and laboratory variables and the etiology were performed. Etiologic distribution according to age category and geographical regions were revealed. Western Turkey included Marmara, Aegean, Mediterranean and Central Anatolia Regions, while Eastern Turkey included Black Sea, Eastern and Southeastern Anatolia Regions.

Statistical analyses were conducted by the Statistical Package for Social Sciences version 15.0. Descriptive statistics were expressed as frequency, mean, median, standard deviation, minimum and

maximum. Student's t test was used for comparison of parametric variables. Difference analyses and risk estimation for categorical variables were performed by chi-square test. Confidence level for statistical significance was preferred as 95 percent (α=0.05).

The study was approved by the Institutional Ethics Committee of the Health Sciences University, Istanbul (28 03.2020, 20/77)

Results

During the five-year-study period, a total of 214 patients from twelve hospitals who fulfilled the FUO criteria enrolled in the study. Of the patients, 130 were from the Western part of Turkey (Marmara region n: 65), while 84 were from the Eastern part of Turkey (Southeastern Anatolia region n: 75) **(Figure 1)**. Eighty-seven (40.7 %) of the patients were female. Mean age of the patients were 47 ± 16.4 (range 18 - 90) years, mean duration of fever in history was 42.9 ± 108.9 (range 21- 1600) days, mean time to diagnosis was 31 ± 126.7 (range 3 - 1650) days, mean duration of follow-up was 60.3 ± 132.7 (range 3 - 1670) days and mean time to control fever in follow-up was 10.3 ± 9.9 (range 1- 80) days **(Table 1)**.

Among all patients in the study, infections were the most frequent cause of FUO (n: 96, 44.9%) **(Table 2)**. Malignancies (n: 33, 15.42%), autoimmune/inflammatory (n: 25, 11.68%) and miscellaneous diseases (n: 18, 8.41%) were the remaining causes of FUO. In 42 (19.62%) of the patients, no specific etiology was established. Brucellosis (n: 23, 10.25% in all causes and 23.9% of infections), extrapulmonary tuberculosis (n: 14, 6.54% in all causes and 14.6% of infections) and infective endocarditis (n: 14, 6.54% in all causes and 14.6% of infections) were the most frequent three infective causes. In Western Turkey, infective endocarditis (n: 11/14 of patients with infective endocarditis, 8.46% in all patients) and extrapulmonary tuberculosis (n: 6/14 of patients with extrapulmonary tuberculosis, 4.61% in all patients) were the most common infections, while brucellosis (n: 20/23 of patients with brucellosis, 23.8% in all patients) and extrapulmonary tuberculosis (n: 8/14 of patients with extrapulmonary tuberculosis, 9.52% in all patients) were the

most common infective causes in Eastern Turkey. Solid malignancies (n: 15, 7.1% in all causes and 45.4% in malign etiology) and lymphoma (n: 12, 5.6% in all causes and 36.3% in neoplasms) were the most common malign causes. Nine of 11 patients (6.92% in all patients) who were diagnosed as lymphoma were in Western Turkey, while 7 of 15 patients (8.33% in all patients) with solid malignancies were in Eastern Turkey. Adult onset still's disease (AOSD) (n: 13, 6.07% in all causes and 52% in autoimmune/Inflammatory diseases) was the most common autoimmune/Inflammatory disease, twelve of whom were from Western Turkey. And thyroiditis (n: 11, 5.14% in all causes and 61.1% in miscellaneous diseases) was the most common disease in miscellaneous diseases category. The etiologic and regional distribution of the patients with FUO is revealed in **Table 2**. The etiologic spectrum did not differ between patients younger and older than 65 years-old. However, the ratio of undiagnosed etiology was significantly higher in patients older than 65 years-old compared to younger patients with the rate of 34.48% and 18.38%, respectively (p: 0.046, OR: 2.34, 95% Cl: 1.00 to 5.48) **(Table 3A)**.

In association analysis between the etiology and geography, infections were less frequent in Western Turkey (34.62%) compared to Eastern Turkey (60.71%) (p< 0.001, OR: 0.31, 95% Cl: 0.19 to 0.60). Autoimmune/Inflammatory diseases were more frequent in Western (15.38%) compared to Eastern Turkey (5.95%) (p: 0.036, OR: 2.87, 95% Cl: 1.03 to 7.98). And also, undiagnosed/true FUO cases were more common in Western Turkey (26.92%) compared to Eastern (10.71%) (p: 0.004, OR: 3.07, 95% Cl: 1.39 to 6.71) **(Table 3B)**.

In patients presented with FUO who had definite diagnosis (n: 172), the risk estimation / probability analysis in patients with definite diagnosis between demographic, clinical and laboratory variables and etiology are revealed in **Table 4**. The probability of having infectious etiology compared to non-infectious diseases were lower with statistically significance in patients older than 40 years-old (p: 0.038, OR: 0.49, 95% Cl: 0.25 to 0.97). The probability of having infectious etiology were higher with statistically significance in patients living in Eastern part of Turkey compared to Western (p: 0.005,

OR: 2.46, 95% Cl: 1.31 to 4.60). The probability of having infectious etiology were significantly lower in patients with 1, 5 and 10 times higher ULNs of CRP compared to normal values (p: 0.048, OR: 0.36, 95% Cl: 0.12 to 1.02; p: 0.004, OR: 0.38, 95% Cl: 0.14 to 0.74; and p: 0.06, OR: 0.42, 95% Cl: 0.22 to 0.78, respectively). In patients having lower CRP values than 5-times-ULN with lower sedimentation values than 2-times-ULN, the probability of infectious diseases was significantly higher (p: 0.021, OR: 2.47, 95% Cl: 1.13 to 5.38), while the probability of infectious diseases was significantly lower than non-infectious diseases in patients having higher CRP values than 5-times-ULN with higher sedimentation values than 2-times-ULN (p: 0.018, OR: 0.47, 95% Cl: 0.25 to 0.88). The probability of infectious diseases was significantly higher than non-infectious diseases in patients with procalcitonin value above 2 ng/dl (p: 0.014, OR: 4.40, 95% Cl: 1.26 to 15.34). If a pathological procedure performed in patients presented with FUO, the probability of getting a diagnosis of infectious diseases were significantly lower than non-infectious diseases (p: 0.001, OR: 0.33, 95% Cl: 0.17 to 0.63). The probability of infectious diseases was significantly higher than non-infectious diseases if a diagnosis was established within 7 days after admission or if an empirical antibiotic therapy were administered in the follow-up (p: 0.017, OR: 2.42, 95% Cl: 1.16 to 5.07 and p: 0.002, OR: 3.40, 95% Cl: 1.53 to 7.56, respectively) **(Table 4)**.

Discussion

The differential diagnosis of FUO is one of the most challenging issues despite the state-of-the-art technologies in medicine; there have been more than 200 reported conditions identified as a cause of FUO and moreover, about one fourth of cases are remains undiagnosed [8].

The studies in Turkey in last 20 years-period revealing the etiological distribution of FUO in literature are presented in **Table 5** [9-25]. There is a decreasing trend in the number of the studies on FUO published in Turkey after 2010, furthermore no studies have been published after the year 2013. The decrease in the general interest towards FUO over time in Turkey may be the reason for that. Or, as a result of advances in medical technology, more patients have final diagnose sooner, so fewer

patients can be classified as FUO [7]. This is conflicting by two systematic reviews including world data by the same study groups. There were more FUO cases in their latest study in the period between 2005 - 2015 which included 3164 patients in 18 studies compared to their previous analysis including 1488 patients in 11 studies between 1995 – 2004 [26,27]. Having the maximum number of FUO cases and being one of the few studies reflecting Turkey's overall in literature, our multicenter study is the most important study in recent years revealing FUO etiology in Turkey.

The spectrum of diseases in FUO etiology varies from region to region according to several reasons including demographic factors, socioeconomic status, and capacity of healthcare system and access to healthcare. Despite improvements in these factors, infectious diseases remain to be in the first place in almost all adult FUO series from all over the world. In 1970s and 1980s, the rate of infective etiology in FUO series varied between 30% and 40%, with the highest rate in all series [28]. In two systemic reviews of the literature for the periods of 1995 – 2004 and 2005 -2015, the most frequent FUO category was infection with the rate of 36.6% and 37.8, respectively [26,27]. The ratio of infection in FUO series from Turkey is generally higher than World's average, and the infection rate in FUO series is higher than 45% in two thirds of the studies (**Table 5**). In our study, we revealed that infectious diseases in FUO etiology was still in the first place in Turkey with the rate of 44.9% which was higher than World's average. The reason for the high rate was due to significantly higher infection rate in Eastern (60.71%) compared to Western Turkey (30.62%) because of the socioeconomic and demographic factors in Eastern Turkey. Western is developed and industrialized part of Turkey while livestock industry and farming is still the main means of living in Eastern Turkey. The main disease to increase the infection rate in Eastern Turkey was brucellosis. This is concordant with the literature revealing that Turkey, particularly Eastern part, is highly endemic for brucellosis with an incidence of 18.000 cases or 256.7 cases per million [29]. Brucellosis is a very easy infectious disease to diagnose with a comprehensive history taking and first-line laboratory testing including standard tube agglutination test (STA) and Rose Bengal agglutination. In consequence, the high numbers of FUO with brucellosis in an endemic region shows that there is still a lack of awareness of

brucellosis among clinicians. We revealed mycobacterial diseases, infective endocarditis and intraabdominal abscess besides brucellosis were still common infective diseases as the cause of FUO in Turkey. The spectrum of infectious etiology of FUO in our study, excluding the high rate of brucellosis, was similar with literature [27,28].

Autoimmune/inflammatory diseases are the second common category in FUO series followed by malignancies, and the ratio of autoimmune/inflammatory diseases is significantly higher in latest FUO series including the period 2005-2015 compared to 1995-2004 [26,27]. In only four of 17 FUO series from Turkey, malign diseases are more frequent than autoimmune/inflammatory diseases while autoimmune/inflammatory diseases are in the second in vast majority of studies **(Table 5)**. The ratio in these FUO series varies between 7.6% and 22% for malignancy and between 7% and 39.4% for autoimmune/inflammatory diseases. We revealed malignancy was the second common cause of FUO in our study followed by autoimmune/inflammatory diseases. There was no significant difference in ratio of malign etiology between patients younger and older than 65 years-old, or between patient in Western and Eastern Turkey. In our study, autoimmune/inflammatory diseases were more common in Western than Eastern Turkey. Although the ratio of autoimmune/inflammatory diseases were almost two times higher in patients younger than 65 years-old, the difference was not statistically significant. We thought the reason for statistical non-significance was that there were only two patients with autoimmune/inflammatory etiology in the <65 years-old group. Concordantly with the literature, AOSD in autoimmune/inflammatory diseases, solid tumors and lymphomas in malign diseases were the most common causes of FUO. According to our results, 52% of FUO causes in autoimmune/inflammatory category were AOSD while this rate was 35.7% in a pooled analysis revealing data in Turkey and 27.6% in a systematic review revealing World data [27,30]. In the pooled analysis from Turkey, 50.8% of malign etiology was lymphomas and 31% was solid tumors [30]. While in the systematic review of Fusco *et al*., 58.5% and at least 20.4% of malign etiology was lymphomas and solid tumors, respectively [27]. According to our results, solid malignancies were more frequent than lymphomas with the ratio of 45.4% of malign causes. Our study was carried out in Infectious

diseases outpatient and inpatient clinics. In Turkey, patients with fever and swollen lymph nodes are mostly referred to haematology clinics. Therefore, this may be the reason for the relatively lower ratio of lymphoma within malign etiology of FUO in our study. Thyroiditis mainly presents with neck pain and tenderness, while sometimes fever may be prominent symptom, and it is recognized as one of the uncommon causes of FUO in literature [31]. According to our study results, thyroiditis was one of the non-negligible causes of FUO, so careful examination of thyroid glands should be realized in patients with prolonged fever.

Despite increasing rate of accessibility to health system and the quality of the health system as a part of Health Transformation Program in Turkey, a noticeable amount of the FUO cases in our study remained undiagnosed. The ratio of undiagnosed FUO was significantly higher in Western Turkey and in patients older than 65 years-old in inverse proportion with the share of infections in the categories. This means that we still have difficulties in reaching a diagnosis in FUO with non-infectious disease etiology. There is a great heterogeneity in the ratio of undiagnosed cases in the literature from Turkey varying from 2.3% to 35.1% **(Table 5)**, and the ratio of undiagnosed cases is 23.2% in the systematic review by Fusco *et al*. revealing World's data between 2005 and 2015 [27].

The probability of having infectious diseases etiology as final diagnosis was higher if a patient was living in Eastern Turkey, if a patient had lower CRP value than 5-folds-ULN with ESR lower than two-folds-ULN, if a patient had procalcitonin over 2 ng/dl, if a patient had empirical antibiotic therapy in follow-up, and if a patient had final diagnosis within 7 days. Conversely, the probability of having non-infectious diseases etiology as final diagnosis was higher if a patient with FUO was older than 40 years-old, if a patient is living in Western Turkey, if a patient had higher CRP value than 1, 5 or 10-folds-ULN, if a patient had higher CRP value than 5-folds-ULN with ESR higher than two-folds-ULN, and if a patient had pathologic procedure. Duration of fever, type of fever, concomitant complaints besides fever, ESR and hemogram findings were not significant parameters to distinguish infectious and non-infectious etiology in FUO. According to a study results from Japan, there was a significant

correlation between the final diagnosis of FUO and the age of patients (<65 and ≥65), and there was also no difference in CRP level between patients with and without a final diagnosis [32].

Mortality rates in patients with FUO have continuously decreased over the past decades. FUO with malign etiology remains a cardinal cause of long term death, besides that even the cases with no diagnosis have very good outcome [33]. Mortality rates in patients with undiagnosed FUO in literature vary between 2.0% and 19%, and the variances among studies are concluded to be due to differences in patient selection, study design or healthcare systems. In a study from Japan with high rate of non-infectious etiology, 4 of 30 (13.3%) patients with FUO of unknown cause died during within 6 months in follow-up [32]. In a study from Egypt with high rate of infectious etiology, the mortality rate was 2.2% [34]. Patients showed good outcome in our study, with only one mortal case with undiagnosed FUO etiology.

Conclusions

Infections, Brucellosis in Eastern and infective endocarditis in Western, remain to be the most frequent cause of FUO in Turkey. And extrapulmonary tuberculosis, second common infective disease in both Eastern and Western, is still an important cause of prolonged fever. Solid tumors and lymphomas within malign diseases, AOSD within autoimmune/inflammatory diseases, and also thyroiditis are the other common diseases that should be considered as a cause of FUO when a patient with FUO is referred to relevant clinicians. The etiologic spectrum did not differ in elderly, on the other hand, infections were more common in Eastern Turkey, while autoimmune/inflammatory diseases were more common in Western Turkey. A considerable amount of etiology remained undiagnosed despite the state-of-the-art technology in healthcare services. The results of this multicenter study reflecting Turkey’s overall may help clinicians to set strategies for optimizing the diagnostic approach for FUO.

Limitations of the study

Present study was carried out in Infectious diseases outpatient and inpatient clinics in Turkey. Due to this reason, the amount of infectious etiology may be slightly higher in our study, although vast majority of patients with prolonged fever is referred to infectious diseases clinicians in Turkey.

Some authors suggest a minimal diagnostic work-up, to be performed before qualifying a fever as a FUO [35]. Considering the differences in diagnostic resources in different countries or even different geographic areas, this seems to be a more reasonable suggestion to set more standard criteria for FUO. In present study, a minimal diagnostic work-up was not applied due to the study's retrospective design.

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References

1. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine (Baltimore). 1961;40:1-30. doi:10.1097/00005792-196102000-00001
2. Cinaroglu S, Baser O. Spatial Distribution of Total Number of Medical Devices in Turkey: A Classification Analysis. Int J Med. Public Health. 2017;7(2):102-106.
3. Bozer A, Agirbas I. Quantitative Evaluation of the Status and Use of Medical Imaging Devices. Journal of Ankara University Faculty of Medicine 2016;69(3):193-201
4. Ozaras R, Leblebicioglu H, Sunbul M, Tabak F, Balkan II, Yemisen M, et al. The Syrian conflict and infectious diseases. Expert Rev Anti Infect Ther. 2016;14(6):547-555. doi:10.1080/14787210.2016.1177457
5. Ergonul O, Tulek N, Kayi I, Irmak H, Erdem O, Dara M. Profiling infectious diseases in Turkey after the influx of 3.5 million Syrian refugees. Clin Microbiol Infect. 2020;26(3):307-312. doi:10.1016/j.cmi.2019.06.022
6. UNHCR Turkey Fact Sheet, October 2019 [Internet]. Avaiable from: https://reliefweb.int/sites/reliefweb.int/files/resources/UNHCR-Turkey-One-Pager-Fact-Sheet-Oct2019.pdf
7. Durack DT, Street AC. Fever of unknown origin--reexamined and redefined. Curr Clin Top Infect Dis. 1991;11:35-51.
8. Mourad O, Palda V, Detsky AS. A comprehensive evidence-based approach to fever of unknown origin. Arch Intern Med. 2003;163:545–51
9. Pehlivan M, Biberoglu K, Tarhan O, Kundak I, Ozcan MA. Fever of unknown origin: report of 62 cases. Flora 1998;3(2):113-119
10. Araz M, Okan V, Sirmatel F, Demirci F, Kepekci Y, Ucarer O. Fever of unknown origin. Evaluation of 30 cases. Klimik Dergisi 2000;13(1):8-11
11. Kücükardali Y, Kocak N, Yazici H, Cankir Z, Nalbant S, Top C, et al. Fever of Unknown Origin: Report of 82 Cases. Flora 2001;6(3):171-177

12. Goktas P, Ceran N, Coskun D, Yenisolak A, Karagul E, Ozyurek S. Fever of unknown origin: Analysis of 35 cases. Flora 2002;7:191-5
13. Tabak F, Mert A, Celik AD, et al. Fever of unknown origin in Turkey. Infection. 2003;31(6):417-420. doi:10.1007/s15010-003-3040-6
14. Oncu S, Ertugrul MB, Cagatay AA, Ozsut H, Eraksoy H, Calangu S. Fever of unknown origin. Analysis of 66 cases. Klimik Dergisi 2003;16(3):108-112
15. Saltoglu N, Tasova Y, Midikli D, Aksu HS, Sanli A, Dündar IH. Fever of unknown origin in Turkey: evaluation of 87 cases during a nine-year-period of study. J Infect. 2004;48(1):81-85. doi:10.1016/j.jinf.2003.08.006
16. Ozer S, Ak O, Gencer S, Ustaoglu R, Karagoz G. Fever of unknown origin. Evaluation of 86 cases. Klimik 2004;1(17):34-37
17. Ergönül O, Willke A, Azap A, Tekeli E. Revised definition of 'fever of unknown origin': limitations and opportunities. J Infect. 2005;50(1):1-5. doi:10.1016/j.jinf.2004.06.007
18. Erten N, Saka B, Ozturk G, Karan MA, Tascioglu C, Dilmener M, et al. Fever of unknown origin: a report of 57 cases. Int J Clin Pract. 2005;59(8):958-960. doi:10.1111/j.1368-5031.2005.00471.x
19. Onal IK, Cankurtaran M, Cakar M, Halil M, Ulger Z, Dogu BB, et al. Fever of unknown origin: what is remarkable in the elderly in a developing country? J Infect. 2006;52(6):399-404. doi:10.1016/j.jinf.2005.08.021
20. Colpan A, Onguru P, Erbay A, Akinci E, Cevik MA, Eren SS, Bodur H. Fever of unknown origin: analysis of 71 consecutive cases. Am J Med Sci. 2007;334(2):92-96. doi:10.1097/MAJ.0b013e31812f5642
21. Satılmıs O, Aktug Demir N, Sumer S, Ural O.Fever of unknown origin: Report of 27 cases.Turkish Journal of Infection 2008;22(2):69-73

22. 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):71-79. doi:10.1016/j.ijid.2007.04.013
23. Alpat SN, Unlu F, Erben N, Kartal ED, Ozgunes İ, Usluer G. Etiology of fever of unknown origin in Eskisehir. FLORA 2009;14(2):67-71
24. Mete B, Vanli E, Yemisen M, Balkan II, Dagtekin H, Ozaras R, et al. The role of invasive and non-invasive procedures in diagnosing fever of unknown origin. Int J Med Sci. 2012;9(8):682-689. doi:10.7150/ijms.4591
25. Solay AH, Uslu M, Tutuncu EE, Yuce D, Sencan I. Evaluation of Fever of Unknown Origin: Our Clinical Experience. FLORA 2013;18(4):161-168
26. Gaeta GB, Fusco FM, Nardiello S. Fever of unknown origin: a systematic review of the literature for 1995-2004. Nucl Med Commun. 2006;27(3):205–11
27. 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
28. Kaya A, Ergul N, Kaya SY, et al. The management and the diagnosis of fever of unknown origin. Expert Rev Anti Infect Ther. 2013;11(8):805-815. doi:10.1586/14787210.2013.814436
29. Yumuk Z, O'Callaghan D. Brucellosis in Turkey -- an overview. Int J Infect Dis. 2012;16(4):e228-e235. doi:10.1016/j.ijid.2011.12.011
30. Sipahi OR, Senol S, Arsu G, Pullukcu H, Tasbakan M, Yamazhan T et al. Pooled analysis of 857 published adult fever of unknown origin cases in Turkey between 1990-2006. Med Sci Monit. 2007;13(7):CR318-CR322.
31. Raj R, Yada S, Jacob A, Unnikrishnan D, Ghali W. Fever of Unknown Origin as a Sole Presentation of Subacute Thyroiditis in an Elderly Patient: A Case Report with Literature Review. Case Rep Endocrinol. 2018;2018:5041724. doi:10.1155/2018/5041724

32. Naito T, Tanei M, Ikeda N, et al. Key diagnostic characteristics of fever of unknown origin in Japanese patients: a prospective multicentre study. BMJ Open. 2019;9(11):e032059. doi:10.1136/bmjopen-2019-032059
33. Vanderschueren S, Eyckmans T, De Munter P, Knockaert D. Mortality in patients presenting with fever of unknown origin. Acta Clin Belg. 2014;69(1):12-16. doi:10.1179/0001551213Z.0000000005
34. Kabapy AF, Kotkat AM, Shatat HZ, Abd El Wahab EW. Clinico-epidemiological profile of fever of unknown origin in an Egyptian setting: A hospital-based study (2009-2010). J Infect Dev Ctries. 2016;10(1):30-42. doi:10.3855/jidc.7198
35. Bosilkovski M, Baymakova M, Dimzova M. Fever of Unknown Origin (FUO): Towards a Uniform Definition and Classification System. Erciyes Med J 2020;42(2):121–6.

Table 1. General demographic, clinical variables of the patients

	Total				Infection				Non-infection			
	Mean	**STD**	**Min**	**Max**	**Mean**	**STD**	**Min**	**Max**	**Mean**	**STD**	**Min**	**Max**
Age (Years)	47.0	16.4	18	90	46.2	16.2	18	87	48.3	15.7	19	90
Duration of fever in history (Days)	42.9	108.9	21	1600	51.3	161.1	21	1600	35.6	16.1	21	90
Time to diagnosis	31.0	126.7	3	1650	39.2	172.5	3	1650	22.0	17.7	4	82
Duration of follow-up (Days)	60.3	132.7	3	1670	95.6	190.1	3	1670	35.3	34.6	4	158
Time to control fever in follow-up (Days)	10.3	9.9	1	80	8.9	6.5	1	30	12.9	13.9	1	80

Table 2. Etiology in patient with FUO, and the regional distribution of the etiology

Etiology	Total n: 214			Western Turkey n: 130			Eastern Turkey n: 84		
	n	% [a]	% [b]	n	% [a]	% [b]	n	% [a]	% [b]
Infections	**96**	**44.9**	**100**	**45**	**34.6**	**100**	**51**	**60.7**	**100**
Brucellosis	23	10.75	23.9	3	2.3	6.66	20	23.8	39.2
Extrapulmonary tuberculosis	14	6.54	14.6	6	4.61	13.3	8	9.52	15.7
Tuberculosis (Pulmonary)	2	0.93	2.09	2	1.54	4.44	0	0	0
Infective endocarditis	14	6.54	14.6	11	8.46	24.4	3	3.57	5.88
Intra-abdominal abscess	9	4.2	9.37	3	2.3	6.66	6	7.14	11.8
Pneumonia	7	3.27	7.3	4	3.07	8.88	3	3.57	5.88
Q-fever	4	1.87	4.16	4	3.07	8.88	0	0	0
CMV	3	1.4	3.12	3	2.3	6.66	0	0	0
Cat-scratch disease	2	0.93	2.09	2	1.54	4.44	0	0	0
Tularemia	2	0.93	2.09	0	0	0	2	2.38	3.92
HIV-AIDS	2	0.93	2.09	1	0.77	2.22	1	1.19	1.96
Mastitis	2	0.93	2.09	1	0.77	2.22	1	1.19	1.96
Fasciola hepatica	2	0.93	2.09	0	0	0	2	2.38	3.92
Other infections*	10	4.68	10.4	5	3.85	11.1	5	5.95	9.8
Malignancy	**33**	**15.42**	**100**	**21**	**16.1**	**100**	**12**	**14.3**	**100**
Lymphoma	12	5.6	36.3	9	6.92	42.8	3	3.57	25
Leukemia	4	1.87	12.2	3	2.31	14.3	1	1.19	8.33
Multiple myeloma	2	0.94	6.06	1	0.77	4.75	1	1.19	8.33
Solid malignancies	15	7.1	45.4	8	6.15	38.1	7	8.33	58.3
Autoimmune/Inflammatory	**25**	**11.68**	**100**	**20**	**15.3**	**100**	**5**	**5.95**	**100**
AOSD	13	6.07	52	12	9.23	60	1	1.19	20
Rheumatoid arthritis	3	1.4	12	1	0.77	5	2	2.38	40
Giant cell arteritis	2	0.94	8	2	1.54	10	0	0	0
SLE	2	0.94	8	1	0.77	5	1	1.19	20
FMF	1	0.47	4	1	0.77	5	0	0	0
Behcet's disease	1	0.47	4	1	0.77	5	0	0	0
Takayasu arteritis	1	0.47	4	0	0	0	1	1.19	20
Wegener granulomatosis	1	0.47	4	1	0.77	5	0	0	0
Ankylosing spondylitis	1	0.47	4	1	0.77	5	0	0	0
Miscellaneous	**18**	**8.41**	**100**	**11**	**8.46**	**100**	**7**	**8.33**	**100**
Thyroiditis	11	5.14	61.1	8	6.15	72.7	3	3.57	42.8
Drug-induced fever	2	0.93	11.15.	1	0.77	9.1	1	1.19	14.2
Ulcerative colitis	1	0.47	55	0	0	0	1	1.19	14.2
Pulmonary embolism	1	0.47	5.55	1	0.77	9.1	0	0	0
Sarcoidosis	1	0.47	5.55	0	0	0	1	1.19	14.2
HLH	1	0.47	5.55	1	0.77	9.1	0	0	0
ARF	1	0.47	5.55	0	0	0	1	1.19	14.2
Undiagnosed	**42**	**19.62**		**33**	**25.3**		**9**		**10.7**

[a]: % in all cases, [b]: % in subgroup, AOSD; Adult onset Still's disease, SLE; Systemic lupus erythematosus, FMF; Familial Mediterranean Fever, HLH; Hemophagocytic lymphohistiocytosis (idiopatic), ARF; Acute rheumatic fever

*Meningitis (n:1), EBV (n:1), catheter infection (n:1), cyst hydatid disease (n:1), leptospirosis (n:1), myocarditis (n:1), pericarditis (n:1), toxoplasmosis (n:1), visceral leishmaniosis (n:1), mastoiditis: (n:1)

Table 3. Association of age category (A) and geographic region (B) with FUO etiology (n: 214)

A. Age Category	Age ≥65		Age <65		Total	P	OR	95%CI	
	n	%	n	%	n			Lower	Upper
Infections	10	34.48	86	46.49	96	0.227	0.61	0.27	1.37
Malignancies	5	17.24	27	14.59	32	0.710	1.22	0.43	3.47
Autoimmune/Inflammatory	2	6.90	23	12.43	25	0.388	0.52	0.12	2.34
Miscellaneous	2	6.90	15	8.11	17	0.823	0.84	0.18	3.88
Undiagnosed	10	34.48	34	18.38	44	**0.046**	2.34	1.00	5.48
B. Geographic region	**Western Turkey**		**Eastern Turkey**		**Total**	**P**	**OR**	**95%CI**	
	n	%	n	%	n			Lower	Upper
Infections	45	34.62	51	60.71	96	**<0.001**	0.34	0.19	0.60
Malignancies	21	16.15	12	14.29	33	0.826	1.09	0.50	2.37
Autoimmune/Inflammatory	20	15.38	5	5.95	25	**0.036**	2.87	1.03	7.98
Miscellaneous	11	7.69	7	8.33	18	0.866	0.92	0.33	2.51
Undiagnosed	33	26.92	9	10.71	42	**0.004**	3.07	1.39	6.78

Table 4. The association of demographic, clinical and laboratory variables between patients with infectious and non-infectious causes of FUO in patients with definite diagnosis (n: 172)

	Infectious diseases		Non-infectious diseases		Total	p	Odds Ratio	(95% CI)	
	n	%	n	%	n			Lower	Upper
Age (years)									
>40	59	61.5	58	76.3	117	**0.038**	0.49	0.25	0.97
>65	10	10.4	11	14.5	21	0.420	0.69	0.28	1.72
Female Sex	42	43.75	30	39.47	72	0.572	1.19	0.65	2.20
Eastern Turkey	51	53.13	24	31.58	75	**0.005**	2.46	1.31	4.60
Live in rural areas	33	34.38	22	28.95	55	0.448	1.29	0.67	2.46
History of fever episodes	45	47.37	27	35.53	72	0.119	1.63	0.88	3.03
History of follow-up in another hospital	80	83.33	60	78.95	140	0.463	1.33	0.62	2.88
History of empirical antibiotic use	77	81.05	59	77.63	136	0.582	1.23	0.59	2.60
Most common complaints									
Weakness and fatigue	39	40.63	28	36.84	67	0.613	1.17	0.63	2.18
Myalgia	26	27.08	24	31.58	50	0.519	0.80	0.42	1.56
Weight loss	15	15.63	15	19.74	30	0.480	0.75	0.34	1.66
Irregular fever	40	42.55	35	48.61	75	0.437	0.78	0.42	1.45
Duration of fever									
>1 month	32	33.33	31	40.79	63	0.313	0.73	0.39	1.35
>2 months	14	14.58	11	14.47	25	0.984	1.01	0.43	2.37
>3 months	6	6.25	2	2.63	8	0.263	2.47	0.48	12.58
USG finding									
Lymphadenopathy	27	28.13	25	32.89	52	0.499	0.80	0.42	1.53
Splenomegaly	18	18.75	18	23.68	36	0.430	0.74	0.36	1.55
Hepatomegaly	29	30.21	19	25.00	124	0.449	1.30	0.66	2.56
Hemogram									
Leukopenia	5	5.21	6	7.89	11	0.475	0.64	0.19	2.19
Leukocytosis	39	40.63	36	47.37	75	0.376	0.76	0.41	1.40
Anemia	55	57.89	47	65.28	102	0.332	0.73	0.39	1.38
Thrombocytopenia	15	15.63	10	13.16	25	0.648	1.22	0.52	2.90
CRP									
>ULN	80	83.33	70	93.33	150	**0.048**	0.36	0.12	1.02
>5xULN	54	56.25	58	77.33	112	**0.004**	0.38	0.19	0.74
>10xULN	45	46.88	51	68.00	96	**0.006**	0.42	0.22	0.78
ESR									
>ULN	77	81.91	63	84.00	140	0.721	0.86	0.38	1.94
>2xULN	45	48.39	45	60.00	90	0.134	0.63	0.34	1.16
>100 mm/h	10	10.75	16	21.33	26	0.059	0.44	0.19	1.05
Binary groups including CRP (cut-off of 5xULN) and ESR (cut-off of 2xULN)									
1. CRP < plus ESR <	28	30.11	11	14.86	39	**0.021**	2.47	1.13	5.38
2. CRP < plus ESR >	13	13.98	6	8.11	19	0.235	1.84	0.66	5.11
3. CRP > plus ESR <	20	21.51	18	24.32	38	0.666	0.85	0.41	1.76
4. CRP > plus ESR >	32	34.41	39	52.70	71	**0.018**	0.47	0.25	0.88
Procalcitonin (ng/dl)									
>0.5	17	47.22	14	31.82	31	0.159	1.92	0.77	4.77
>2	11	30.56	4	9.09	15	**0.014**	4.40	1.26	15.34
Pathological procedure	25	27.47	38	53.52	63	**0.001**	0.33	0.17	0.63

Duration of diagnose <7 days <30 days	31 74	33.70 80.43	13 57	17.33 76.00	44 131	**0.017** 0.488	2.42 1.30	1.16 0.62	5.07 2.72
Empirical antibiotic therapy in follow-up	83	88.30	51	68.92	134	**0.002**	3.40	1.53	7.56
Hospitalization	84	87.50	66	86.84	150	0.898	1.06	0.43	2.61
Intensive care	2		1		1	N/A	N/A	N/A	N/A
In-hospital mortality	1		1		0	N/A	N/A	N/A	N/A

ESR; erythrocyte sedimentation rate, ULN; upper limit of normal

Table 5. Etiologic spectrum of the FUO cases in literature reported from Turkey.

Reference	Year of Publishing Region	Methodology	Number of Cases	Diagnosis				
				Infection %	Autoimmune / Inflammatory %	Malignancy %	Miscellaneous %	Undiagnosed (True FUO) %
Pehlivan (9)	1998 Izmir	Retrospective Single center	62	50	21	11	6	11
Araz (10)	2000 Gaziantep	Retrospective Single center	30	47	20	17	3	13
Kucukardali (11)	2001 Istanbul	Retrospective Single center	82	59	7	10.9	2.4	19.5
Goktas (12)	2002 Istanbul	Prospective Single center	35	40	23	14	8.5	14.5
Tabak (13)	2003 Istanbul	Retrospective Single center	117	34	23	19	10	14
Oncu (14)	2003 Istanbul	Retrospective Single center	66	43.9	39.4	7.6	1.5	7.6
Saltoglu (15)	2004 Istanbul	Retrospective Single center	87	58.6	18.3	13.7	2.2	6.8
Ozer (16)	2004 Istanbul	Retrospective Single center	86	52.3	5.8	14	8.1	19.8
Ergonul (17)	2005 Ankara	Prospective Single center	80	52	13	18	6	11
Erten (18)	2005 Istanbul	Retrospective Single center	57	42	30	18	0	10
Onal (19)	2006 Ankara	Retrospective Single center	97	36.1	8.2	15.5	5.2	35.1
Colpan (20)	2007 Ankara	Prospective Single center	71	45.1	26.8	14.1	5.6	8.5
Satilmis (21)	2008 Konya	Retrospective Single center	27	40.8	25.9	22.2	7.4	3.7
Kucukardali (22)	2008 Multicenter	Prospective Multicenter	154	34.4	30.5	14.3	5.2	15.6
Alpat (23)	2009 Eskisehir	Retrospective Single center	53	31.1	18.9	9.4	15.1	24.5
Mete (24)	2012 Istanbul	Retrospective Single center	100	26	38	14	2	20
Solay (25)	2013 Ankara	Prospective Single center	43	45.2	23.8	16.7	14.3	2.3
Present study	2020 Multicenter	Retrospective Multicenter	214	44.9	11.68	15.42	8.41	19.62

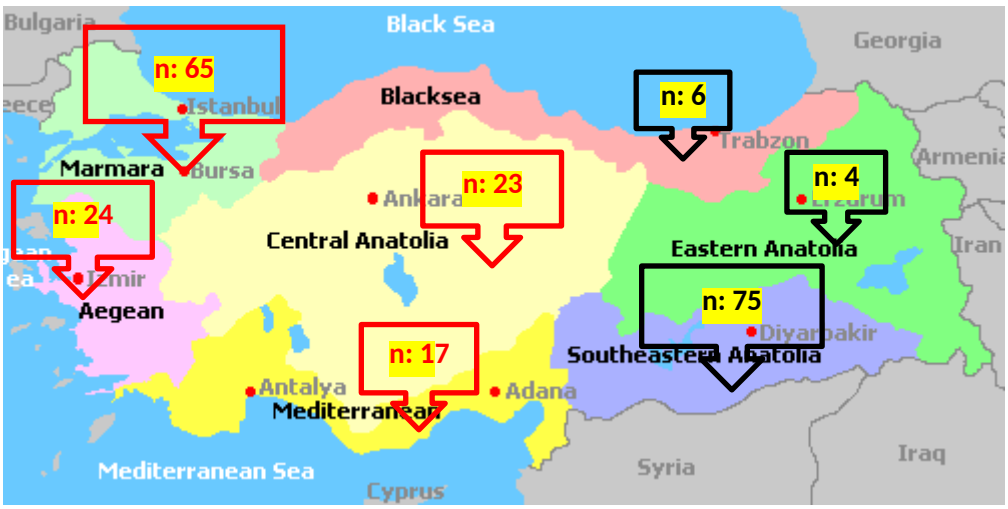

Figure 1. Regional distribution of patients in the study (n: 214). Western Turkey (red color) includes Marmara, Aegean, Mediterranean and Central Anatolia Regions. Eastern Turkey (Black color) includes Black Sea, Eastern and Southeastern Anatolia Regions.