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Research Paper

The Role of Invasive and Non-Invasive Procedures in Diagnosing Fever of Unknown Origin

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Abstract

Background: The etiology of fever of unknown origin has changed because of the recent advances in and widespread use of invasive and non-invasive diagnostic tools. However, undiagnosed patients still constitute a significant number.

Objective: To determine the etiological distribution and role of non-invasive and invasive diagnostic tools in the diagnosis of fever of unknown origin.

Materials & Methods: One hundred patients who were hospitalized between June 2001 and 2009 with a fever of unknown origin were included in this study. Clinical and laboratory data were collected from the patients' medical records retrospectively.

Results: Fifty three percent of the patients were male, with a mean age of 45 years. The etiology of fever was determined to be infectious diseases in 26, collagen vascular diseases in 38, neoplastic diseases in 14, miscellaneous in 2 and undiagnosed in 20 patients. When the etiologic distribution was analyzed over time, it was noted that the rate of infectious diseases decreased, whereas the rate of rheumatological and undiagnosed diseases relatively increased because of the advances in imaging and microbiological studies. Seventy patients had a definitive diagnosis, whereas 10 patients had a possible diagnosis. The diagnoses were established based on clinical features and non-invasive tests for 61% of the patients and diagnostic benefit was obtained for 49% of the patients undergoing invasive tests. Biopsy procedures contributed a rate of 42% to diagnoses in patients who received biopsies.

Conclusion: Clinical features (such as detailed medical history-taking and physical examination) may contribute to diagnoses, particularly in cases of collagen vascular diseases. Imaging studies exhibit certain pathologies that guide invasive studies. Biopsy procedures contribute greatly to diagnoses, particularly for malignancies and infectious diseases that are not diagnosed by non-invasive procedures.

Key words: fever of unknown origin, invasive investigations, non-invasive techniques

INTRODUCTION

Fever of unknown origin (FUO) is a clinical condition that was first described by Petersdorf et al. in 1961 as a fever lasting more than three weeks, despite the patient being examined for one week in a hospital [1]. In addition to classical FUO, other conditions such as nosocomial FUO, FUO in patients with

febrile neutropenia and FUO during HIV infection have been described [2]. Recent recommendations have included performing specific examinations on patients instead of examining them for 1 week in a hospital [3,4]. Etiological studies demonstrated that infections were among the most common diagnoses, malignancies had a decreasing proportion with time and rheumatologic diseases had an increasing prevalence; however, the exact proportions may differ depending on geographical region [3,5,6]. The etiology of FUO has changed because of the advances in and widespread use of diagnostic tools. However, undiagnosed patients have constituted a significant and increasing number of FUO cases in recent years [7]. Timely use and interpretation of diagnostic tools are crucial for the diagnosis and early treatment of patients with FUO. Although clinical features and routine diagnostic studies propose an etiology for a significant subset of the patients, the remaining patients need invasive procedures. The invasive procedures contribute to the diagnoses in several ways: by directly observing the affected area, by revealing the characteristic tissue histology and by obtaining cultures from the clinical samples.

The objective of our study was to examine cases that fulfilled the criteria of fever of unknown origin and determine the role of non-invasive and invasive diagnostic tools in the diagnosis of FUO.

MATERIALS AND METHODS

Patients who were hospitalized at the Department of Infectious Diseases and Clinical Microbiology between June 2001 and June 2009 to determine the etiology of fever or with a presumed diagnosis of fever of unknown origin were included in this study. Clinical and laboratory data were collected from the patients' medical records retrospectively. Only those patients who fulfilled the criteria of classical FUO using the definition described by Durack and Street (patients who have had fever above 38°C for more than 3 weeks and have not been diagnosed, despite being examined for 3 days) were included in the study [2]. Patients with immunosuppressive diseases (having a previous history of neutropenia or a hematological malignancy, a history of solid organ transplantation or HIV) and patients receiving steroids at high dosages (>10 mg/day, for more than 3 weeks of prednisolone or an equivalent) were excluded. Demographic features, history, physical examination findings and laboratory data were recorded. Baseline examinations of the patients included their medical history, physical examination, complete blood count (CBC) and peripheral smear, biochemical tests, urine analysis, specific tests for certain locally common diseases (including brucellosis, subacute thyroiditis, Behcet's disease), serological and other microbiological examinations, abdominal imaging and chest X-ray performed at baseline. Patients who received a diagnosis at this stage were not considered to have FUO. Patients for whom there were no diagnostic clues after 3 days of examination were subjected to further examination and considered to have FUO.

Further examinations were grouped into 2 categories as non-invasive and invasive procedures. Table 1 summarizes the classification of procedures, abnormal tests and diagnoses addressed in this study.

The data were analyzed using SPSS 16.0. Chi-square test and Kruskal-Wallis test or T test were used to compare categorical and continuous variables, respectively. The Bonferroni correction was used for group comparisons as a conservative method to control type II errors.

Table 1. Classification of procedures, abnormal tests and diagnosis.

Non-invasive procedures
Complete blood count
Biochemical tests (liver and kidney function tests, LDH, CPK, TSH, FT4, ferritin)
Urine analysis
Immunological and viral serological tests
Cultures of blood and other body fluids
Molecular studies
Imaging studies (chest x-ray, USG, CT, MRI, FDG-PET/CT)
Invasive procedures
Biopsies
Aspiration of synovial fluid
Lumbar puncture
Paracentesis, thoracentesis
Laparoscopy
Laparotomy
Abnormal test results
'relevant' : if they led to the diagnosis or were listed among the diagnostic criteria of the disease
'not relevant' or 'false positive': if they were not associated with the final diagnosis or if the disease could not be diagnosed at the end
Diagnosis
Definite diagnosis: based on histopathological and microbiological examinations or clinical criteria
Possible diagnosis: based on exclusion of other diseases and treatment response to test therapeutical approaches
Contribution to diagnosis: Positive findings revealing a specific disorder, providing a possible and/or definite diagnosis
Non-contribution to diagnosis: Failure to find any disorder or findings irrelevant to final diagnosis

RESULTS

One hundred patients who fulfilled the criteria of FUO were included in the study. Fifty-three percent of the enrolled patients were male, with a mean age of

45 years (ranging from 16-82 years). The median duration of diagnosis was 25 days (with a range of 8-180 days) starting from the first date of hospitalization and the mean duration of hospitalization was 30 days. The etiology of the FUO cases was determined to be infectious diseases (ID) in 26, collagen vascular diseases (CVD) in 38, neoplastic diseases (ND) in 14, miscellaneous diseases (MD) in 2 and undiagnosed diseases (UD) in 20 patients. The details of the etiologies are presented in Table 2. Seventy patients had definitive diagnoses, whereas 10 patients had possible diagnoses of FUO. The detailed contributions of non-invasive and invasive procedures are described below.

The contribution of non-invasive procedures to the diagnosis

For the patients who received a diagnosis, the diagnosis was established using clinical features and non-invasive tests in 49 (61%) out of 80 patients.

History and physical examination findings

The detailed medical history revealed no symptoms of diagnostic value in 12 of the patients. Symptoms were relevant to the disease in 51 (58%) out of 88 patients

No abnormal findings were determined in 16 patients following physical examination. Abnormal physical findings were associated with the etiology in 39% of the cases and were not associated with the etiology in 45% of the cases. Table 3 summarizes the initial examination findings for the patients.

Complete blood count and biochemical tests

Biochemical tests contributed to the diagnoses of 38 patients. Peripheral blood smear analyses led to diagnoses of acute myeloid leukemia (2 patients) and chronic myelocytic leukemia (1 patient).

Several blood count abnormalities were observed. Leukocytosis and leukopenia were observed in 28 and 10 patients, respectively. Anemia was present in 81% of the patients. Thrombocytosis and thrombocytopenia were found in 25 and 9 patients, respectively.

Table 2. The etiology in patients with fever of unknown origin.

ID (26)	CVD (38)	ND (14)	MD (2)
Tuberculosis (18)	ASD (15)	Lymphoma (6)	Hypereosinophilic syndrome (1)
Miliary tuberculosis (3)	SLE (6)	AML (2)	Drug related lupus (1)
Lymphadenitis (3)	PMR (5)	CML (1)	
Pleuropericarditis (3)	FMF (5)	MM (1)	
Peritonitis (3)	Vasculitis (4)	MDS (1)	
Lung tuberculosis (3)	Seronegative rheumatoid	Nephroblastoma (1)	
Renal tuberculosis (3)	arthritis (3)	Mesothelioma (1)	
Pleural tuberculosis (1)		Castleman's disease (1)	
Periodontal abscess (3)			
Brucellosis (1)			
Toxoplasmosis (1)			
Liver abscess (1)			
Q fever (1)			
Subacute endocarditis (1)			

ID: infectious diseases, CVD: collagen vascular diseases, ND: neoplastic diseases, MD: miscellaneous diseases, ASD: Adult Still's Disease, SLE: Systemic Lupus Erythematosus, PMR: Polimyalgia rheumatica, FMF: Familial Mediterranean Fever, AML: acute myeloid leukemia, CML: chronic myelocytic leukemia, MM: multiple myeloma, MDS: myelodysplastic syndrome.

Table 3. Contribution of baseline findings to the diagnosis.

Contribution to diagnosis	ID n (%)	CVD + MD n (%)	ND n (%)	UD n (%)	Total
History	14 (53.8)	31 (77.5)*	6 (43)	0	51
Physical examination	11 (42.3)	23 (57.5)	5 (35.7)	0	39
Biochemical tests	7 (27)*	23 (57.5)	8 (57.1)	0	38

ID: infectious diseases, CVD: collagen vascular diseases, ND: neoplastic diseases, MD: miscellaneous diseases, UD: undiagnosed.
* $p<0.001$ when compared to the other groups.

C- reactive protein (CRP) was increased in all of the patients (2 to 88 times), and a significant increase (>100 mm/hour) in erythrocyte sedimentation rate (ESR) level was observed in 56 patients. CRP and ESR levels were comparable among all of the groups. These findings did not contribute to the diagnoses directly.

Urinalysis contributed to the diagnoses of 5% of the patients, including 1 patient with SLE, 2 with vasculitis, 1 with renal tuberculosis (TB) and another patient with subacute endocarditis. False negative results were obtained for 2 patients with renal TB.

Tests for autoimmune antibodies were performed in 77 of the patients, and these tests contributed to the diagnosis of only 9 (11.7%) patients, providing false positive results for 10 patients. Autoantibody tests contributed to the diagnosis of 8 (20.5%) out of 39 patients with non-infectious inflammatory diseases. False positivity for the autoantibody tests was determined in 5 of the patients and false negativity was observed for 4 patients.

Microbiological studies

Microbiological studies led to the diagnoses of 21 (80.7%) out of 26 patients with infectious etiologies.

Culture studies

Blood and urine cultures yielded microorganism growth in 12 (12.2%) out of 98 patients. TB blood cultures were performed in all of the patients who were presumed to have TB. However, bacilli were isolated from only 1 patient with miliary TB. TB culture tests contributed to the diagnoses of 55.6% (10/18) of the patients.

Serology and polymerase chain reaction (PCR)

Serological studies, which identified toxoplasma, CMV, Q fever and brucellosis infections, contributed to the diagnoses of 4 (9.3%) out of 43 patients. CMV and TB PCR's were studied for 4 and 27 patients, respectively and a significant positivity was determined in only 16% (4 TB and 1 CMV) of the patients. False negative results were obtained using PCR for 8 patients diagnosed with TB.

The MEFV gene mutation was studied in 12 of the patients with periodic fever. The mutation was observed in 4 (33.3%) of the patients who were diagnosed as having Familial Mediterranean Fever (FMF).

Imaging studies

The contribution of baseline and further imaging studies is shown in Table 4. The findings contributed to the diagnoses of 47% of the patients, whereas they did not contribute to the diagnoses of 35 of the remaining 53 patients.

Abnormal findings were determined by the chest X -rays of 14 (14.5%) out of 96 patients, and these findings were associated with the definitive diagnoses of 11 (11.4%) of these patients.

Abdominal ultrasonography (USG) demonstrated significant findings in 27 (56%) out of 48 patients. However, these findings were associated with the final diagnoses of only 8 (16.6%) of the patients.

Computerized tomography (CT) results were obtained for 95 patients. No findings were determined for 26 patients, whereas abnormal findings were determined for 69 (72.6%) of the patients. The abnormal CT findings contributed to the diagnoses of 32 (33.6%) of the patients. Abnormal findings were obtained for 52 (65%) of the 80 patients with abdominal CT tests, which were correlated with the diagnoses of 16 (20%) patients. Thorax CT examination revealed abnormal findings for 47 (54.6%) out of 86 patients and these findings led to the diagnoses of 26 (30.2%) of the patients. Negative predictive values (NPV) were 100% for abdominal and thorax CT scans. Positive predictive values (PPV) for thorax and abdominal CT scans were 55% and 31%, respectively (Table 5).

Cranial magnetic resonance imaging (MRI) tests performed for 11 patients were non-contributory to the final diagnoses of any of the cases. Lumbar MRI results contributed to the final diagnoses of 2 patients, who were referred for examination with lumbar pain and were diagnosed with chronic myelocytic leukemia and multiple myeloma after further examinations.

Echocardiography was performed for 59 patients and direct diagnostic benefit was not obtained for any of the patients. However, results that were supportive of the diagnoses were obtained for 6 (10%) of the patients.

Fluorine-18 fluorodeoxyglucose-positron emission tomography combined with CT (FDG-PET/CT) scans assisted in the diagnoses of 6 (50%) out of 12 patients. FDG-PET/CT analyses also identified cancer in 5 patients.

Contribution of invasive procedures to diagnosis

Invasive procedures were performed in 63 of the 80 (79%) patients and 32 of the patients were diagnosed using clinical and other non-invasive tests. Consequently, a diagnostic benefit was obtained for 49% of the patients who underwent invasive tests. The tests were contributory to diagnosis in 59%, 19% and 100% of the patients diagnosed with ID, CVD+MD and ND, respectively.

Endoscopic examinations

Bronchoscopy examinations contributed to the diagnosis of 5 out of 9 patients. The diagnoses of pulmonary and miliary TB were established in 2 and 3 patients, respectively. Upper and lower gastrointestinal system (GIS) endoscopies were performed in 8 and 9 patients, respectively, but these tests did not contribute to the diagnosis of any of the patients.

Examination of body fluid samples

Thoracentesis examinations contributed to the diagnosis of tuberculous pleuritis in 3 out of 4 patients. Paracentesis was performed in 6 patients and 2 of them received the diagnosis of TB.

Biopsy procedures

A total of 81 biopsy procedures were performed in 59 patients, which contributed to the diagnoses of only 25 (42%) of the patients. The NPV and PPV for the overall biopsies were 85% and 100%, respectively (Table 5). The detailed contribution of biopsies to the diagnosis is shown in Table 6.

Skin biopsy was performed in 7 of the patients, and this procedure contributed to the diagnosis of 1 patient with MDS and Sweet's syndrome. Subcutaneous nodule biopsy was performed in this patient, which led to the diagnosis of vasculitis.

Laparoscopy and laparotomy were performed in 3 and 2 patients, respectively. Laparoscopy contributed to a diagnosis in only 1 patient with TB peritonitis, whereas the procedure did not contribute to the final diagnosis in the other 2 patients. One of the latter patients was diagnosed as FMF following the procedures, and the other patient was diagnosed with Castleman's disease during the laparotomy procedure. The other patient undergoing laparotomy was diagnosed with lymphoma and a diagnosis of lymphoma was established in another patient at the postmortem autopsy.

Table 4. Contribution of imaging studies to the diagnosis.

Contribution to diagnosis	ID	CVD+ MD	ND	UD	N/(%)
All imaging studies	21 *	17	9	(-)	47 (47)
Abdominal USG (n:48)	4	3	1	(-)	8 (16.6%)
Chest x-ray (n:96)	8 **	3	0	0	11(11.4%)
Thorax CT (n:86)	13	11	2	(-)	26 (30.2%)
Abdominal CT (n:80)	7	6	3	(-)	16 (20%)

ID: infectious diseases, CVD: collagen vascular diseases, MD: miscellaneous diseases, ND: neoplastic diseases, UD: undiagnosed.
* $p<0.001$ when compared to the other groups.
** $p=0.001$ when compared to the other groups.

Table 5. Diagnostic role of imaging studies and invasive procedures.

	Sensitivity	Specificity	NPV	PPV
Thorax CT	100	65	100	55
Abdominal USG	100	67	100	30
Abdominal CT	100	44	100	31
Biopsies	85	100	85	100

NPV: negative predictive value, PPV: positive predictive value, USG: ultrasonography, CT: computerized tomography

Table 6. Diagnostic contribution of tissue biopsies.

Biopsy procedure (positive contribution to diagnosis/(total number of patients undertaken biopsies) (rate of contribution to the diagnosis)	Diseases diagnosed by biopsy
Lymph node biopsy (9/16)	Tuberculosis (4) Lymphoma (4) Castleman's disease (1)
Peritoneal biopsy	Tuberculosis (1)

(2/3)	Mesothelioma (1)
Renal biopsy (2/2)	SLE (1) Vasculitis (1)
Nephrectomy (2/2)	Tuberculosis (1) Nephroblastoma (1)
Bone marrow biopsy (7/18)	Tuberculosis (non-caseating granuloma in 1 patient) MDS, MM, AML (2), CML, Lymphoma
Transbronchial biopsy (2/4)	Tuberculosis
Temporal artery biopsy (0/7)	
Skin biopsy (2/7)	Sweet syndrome (patient diagnosed with MDS) Vasculitis

SLE: Systemic Lupus Erythematosus, MDS: myelodysplastic syndrome, MM: multiple myeloma, AML: acute myeloid leukemia, CML: chronic myelocytic leukemia

DISCUSSION

Typical physical examination findings are usually absent in patients with FUO and the symptoms of the disorder are often insignificant [6,8]. Diagnostic tests are usually successful in patients with typical physical examination findings. However, these procedures often remain unsuccessful in patients who do not present with typical findings. The sensitivity and specificity of the tests decrease when they are performed in patients who have no probable diagnosis. None of the diagnostic tests have adequate sensitivity and specificity for the diagnosis of FUO when used alone [3].

A FUO case series including more than 100 patients has been published since 1961 [1,7,9-16]. It is remarkable that with the advances in imaging and culture studies, the proportion of cancers in the FUO cases decreased, whereas the proportion of rheumatological diseases showed an increase in these cases [3-6]. The low rate of cancers (14%) determined in our study and the presence of only one case of endocarditis and intra-abdominal abscess are supportive of this notion. However, the ratio of CVD's was higher in this study compared to that of the other series and TB, ASD and lymphoma diagnoses were the most prominent diagnoses in the groups of ID, CVD and ND, respectively. In our previous series published in 2003, the etiology was ID, CVD, ND and MD in 34%, 23%, 19% and 10% of the patients, respectively. In 14% of the cases, the etiology could not be found [13]. In the current study, however, the ratio of CVD's was increased from 23% to 38%, the ID's ratio decreased from 34% to 26% and 20% of the patients remained undiagnosed.

A good evaluation of history and physical examination may lead to diagnoses in patients who would otherwise be classified as FUO [17,18]. A detailed history is particularly important in hereditary and autoimmune diseases such as FMF and RA [17]. In this study, the history of 16 patients included clues correlated with the definitive diagnosis. The history and physical examination findings contribute to the diagnoses of up to 30% of the cases in the literature [4,7]. In our study, however, symptoms and abnormal physical examination findings related to the disease were present in 51% and 39% of the patients, respectively.

CBC and other biochemical studies yielded findings that were related to the final diagnoses of 38 patients. Studies show that these laboratory studies rarely contribute directly to a diagnosis [4]. The findings associated with the etiology were determined by peripheral smear in only 3 patients. The rate of leukocytosis was significantly higher in the CVD+ MD group (42%), whereas Kucukardali et al. reported that leukocyte count was higher in infectious and neoplastic diseases [16]. ESR and CRP levels were higher than normal in all of the patients. There was no significant difference among the groups in terms of a significant increase in sedimentation and CRP levels similar to the other FUO series [7,16]. The results of

our study and other studies indicate that biochemical tests rarely contribute to a definitive diagnosis [18].

Autoimmune serology was studied in 77 patients and these tests contributed to the diagnoses of approximately 50% of the patients with positive results. Kucukardali et al. determined that the rate of contribution to diagnosis was 40% in patients having positive autoimmune serology and the authors reported a high rate of false positivity [16].

The FUO diagnosis is established by performing microbiological studies in the majority of patients with infectious diseases. In the study of Vanderschueren et al., 65% of the subjects were diagnosed with microbiological studies and this rate was 80.7% in our study [7]. Thirteen patients were diagnosed with culture positivity in our series. These patients included 1 case of endocarditis, 1 liver abscess and 11 cases of tuberculosis.

Viral serological tests were performed in 43 of our patients and contributed to the diagnoses of 4 (9.3%) of them. Similarly, viral serology contributed to the diagnoses of 6% and 5% of the patients in the studies of Vanderschueren et al. and Bleeker et al., respectively [4,7].

Imaging studies often localize the abnormalities that can guide invasive procedures rather than providing a direct diagnosis [20]. This contribution was only 25% in the study of Kucukardali et al., whereas this rate was 47% in our study [16]. A diagnosis might be established directly by imaging studies only in certain infectious diseases: The patients with miliary TB, 3 patients with periodontal abscess and 1 patient with liver abscess were diagnosed directly by imaging studies. Chest X-ray provided clues to the diagnoses of 13% of all of the cases and 50% of the TB cases. All of the subjects with abnormal findings were further examined by CT. Hence, chest X-ray is used rather for the exclusion of other diagnoses in FUO and is among the mandatory baseline tests in several studies [4,16,18]. The diagnostic contribution of thorax CT was determined to be as high as 30% in our study and in several other studies [4,21].

No significant differences were determined with regard to contribution to the diagnosis between abdominal USG (16.6%) and CT (19%) examinations. The contribution of abdominal USG and CT tests has been reported as 10% and 17%-20% in other studies, respectively [4,21]. Considering the low specificity of abdominal imaging studies, abdominal USG might be the first choice due to its ease of performance and cost effectiveness.

FDG-PET/CT has a sensitivity and specificity of approximately 80% [18,20]. The contribution of FDG-PET/CT examination was reported as 33% in the study of Bleeker et al. Similar to the study of Balink et al., significant involvement was demonstrated with FDG-PET/CT in 50% of the patients in our study [4,22]. This difference might be explained by the fact that FDG-PET/CT was performed only in unresolved cases in our study, whereas Bleeker et al. performed this method in all of the patients. In their meta-analysis, Dong et al. also emphasized that FDG-PET/CT would be beneficial in patients of FUO in whom conventional diagnostics tests have not been successful [23].

The PPV of abdominal and thorax CT examinations range between 41%-50% and 53%-75%, respectively, in the literature [4,24,25]. These figures were 31% and 55%, respectively, in our series. The NPV of abdominal and thorax CT scans ranged between 97%-100% and 93%-96%, respectively [4,24,25]. In our series, these values were 100% in both modalities.

More than one invasive procedure may be needed to establish a diagnosis in patients with FUO. However, most studies have reported the rate of absolute diagnostic contribution of biopsy and pathological examination as moderate. Biopsies performed under imaging studies have increased the efficacy of diagnoses in recent years [20]. In our study, invasive procedures were performed in 63 patients (more than two in a quarter of the patients) and a diagnosis could be established in 49% of these patients. The rate of contribution to the diagnosis has been reported as 20%-40% in several series [21,26,27]. In our study, invasive procedures provided significantly greater contribution to the diagnosis of the ID group compared to the group of CVD + MD (59% and 19%, respectively; $p<0.05$). The diagnosis was established by invasive procedures and histopathological examination in all of the cancer patients.

In our series, endoscopic procedures contributed to the diagnoses of 19.2% of the patients, which is a figure that entirely represented patients undergoing bronchoscopy. The contribution of GIS endoscopy to the diagnosis of FUO has been limited [4].

The most commonly used and the most diagnostically beneficial invasive studies are biopsy procedures. In our study, a total of 81 biopsy procedures were performed in 59 patients and a diagnosis was established in 42% of the cases. Vanderschueren et al. have reported that biopsy contributed to the diagnosis of 34% of their patients, whereas the rate of contribution has been reported as 29% by Onal et al. [7,21].

Lymph node biopsy contributed to the diagnoses of 56% of our cases. This figure has been reported to range from 46% to 80% in other series [4,26].

Bone marrow biopsy contributed to the diagnoses of approximately 39% of the patients examined,

the majority of whom had hematological cancers. Several studies have reported varying rates (10%-35%) of contribution of bone marrow biopsy to the diagnosis [4,21,26].

The role of invasive procedures is not clear from previous studies [4,24]. In a recent review, the NPV and PPV of liver biopsy were 97% and 100%, respectively [25]. Our study revealed very high NPV (85%) and PPV (100%) for overall procedures.

Laparoscopy is currently preferred rather than laparotomy, particularly in the diagnosis of solid cancers, lymphoma and tuberculosis [4,24]. Although advanced diagnostic methods have decreased the need for laparotomy in FUO, these methods might still contribute to diagnoses in cases when non-invasive and invasive diagnostic measures fail to yield a diagnosis. Patient selection and timing of the procedure are important in the success of laparotomy procedures [28].

In conclusion, it has been observed that the rate of infectious diseases has decreased, whereas the rate of rheumatological and undiagnosed diseases has increased relatively with time because of the advances in imaging studies and culture systems. Detailed history taking and physical examination may particularly contribute to the diagnoses in CVD. Blood count and other biochemical tests may contribute to these diagnoses, although these tests have a low rate of contribution to diagnosis. Serological tests often prove to be non-beneficial in cases with no signs of infectious diseases. Imaging studies provide a diagnosis in only a limited number of infectious diseases, but these tests may localize certain pathologies to guide invasive studies. FDG-PET/CT may contribute greatly to diagnoses when used only in unresolved cases. Biopsy procedures, which are the most commonly used and diagnostically beneficial invasive procedures, contribute greatly to the diagnosis, particularly in cancers and ID that are not diagnosed by non-invasive methods.

Competing Interests

The authors have declared that no competing interest exists.

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