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Original Article

Utility of positron emission tomography–computed tomography in the evaluation of fever of unknown origin in a resource-limited tropical nation

ABSTRACT

Positron emission tomography–computed tomography (PET-CT) has been used as an imaging modality in workup of fever of unknown origin (FUO). The aim of our study is to evaluate the diagnostic utility of PET-CT in FUO workup in a resource-limited setting. We also looked at laboratory parameters as predictors of contributory PET-CT scans and propose an algorithm for evaluation of FUO in resource-limited tropical regions. This retrospective observational study included patients admitted for FUO workup under general medicine in a teaching hospital in South India from June 2013 to May 2016. PET-CT was done when the patient remained undiagnosed after a detailed clinical assessment and first- and second-tier investigations. Among 43 patients included in our study, a definite diagnosis was established in 74% (32). Noninfectious inflammatory diseases, infections, malignancies, and miscellaneous diseases were diagnosed in 37.2% (16/43), 23.3% (10/43), 9.3% (4/43), and 4.7% (2/43), respectively. Tuberculosis was the single most common disease seen in 20.9% (9/43). PET-CT scans were contributory toward establishment of final diagnosis in 90.7% (39/43). High C-reactive protein (CRP) and aspartate aminotransferase (AST) levels were associated with contributory PET-CT scans (P = 0.006 and 0.011, respectively). PET-CT delineating organ/tissue for diagnostic biopsy was associated with final diagnosis of infectious disease (P = 0.001). Sensitivity, specificity, and positive and negative predictive value of PET-CT scans were 76.9% (20/26), 33.3% (2/6), 83% (20/24), and 25% (2/8), respectively. High CRP and AST were predictors of contributory PET-CT scans. PET-CT scans have high sensitivity and positive predictive value when used in evaluation of FUO. Although it is a useful tool in FUO workup, especially in the diagnosis of tropical infections, PET-CT should be done after a comprehensive clinical assessment and basic investigations.

Keywords: Fever of unknown origin, positron emission tomography–computed tomography, positron emission tomography–computed tomography in fever of unknown origin

INTRODUCTION

Fever of unknown origin (FUO) is a clinical syndrome with numerous etiologies.[1] Cause of FUO varies according to geographical region, age-group, and immune status of the patient. Despite availability of modern microbiological and serological tests and increased ease of performing biopsies, 23%–50% of those with FUO remain without a diagnosis.[2-4]

2-deoxy-2-fluoro (F-18)-D-glucose (^{18}FDG) positron emission tomography–computed tomography (PET-CT) scan has been used as one of the imaging modalities for evaluation of FUO.[5] Increase in glucose transporter proteins in infective, inflammatory, and neoplastic foci results in increased ^{18}FDG uptake by cells.[6-8] Characterization of abnormal ^{18}FDG uptake in combination with CT precisely localizes the pathology.

Sohini Das, Sowmya Sathyendra, Julie Hephzibah, Reka Karuppusami[1], Karthik Gunasekaran, Nylla Shanthly, Angel Miraclin, Ramya Iyadurai

Departments of Medicine and [1]Biostatistics, Christian Medical College, Vellore, Tamil Nadu, India

Address for correspondence: Dr. Sowmya Sathyendra, Department of Medicine, Unit 3, Christian Medical College, Vellore - 632 004, Tamil Nadu, India.
E-mail: sowmyaacademic@gmail.com

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PET-CT scans can identify increased metabolic activity before appearance of structural abnormalities and may help diagnose patients in early stages of disease. PET-CT scans also provide imaging of the whole body.

PET-CT has been used as one of the imaging modalities in workup of FUO.[9-12] Drawbacks of PET-CT scans include radiation exposure, limited availability, high costs, and detection of incidental anomalies. Causes of FUO in the Indian subcontinent and other tropical regions are distinctive from that in Europe and North America. It may be difficult to perform PET-CT for FUO patients in some resource-limited settings. Hence, algorithm for FUO evaluation may need to be modified depending on the prevalence of diseases and feasibility of tests.

The aim of our study is to assess the use of PET-CT in FUO workup in a tropical country with limited resources. We evaluated the diagnostic utility of PET-CT in patients with classical FUO at a teaching hospital in South India. We also assessed laboratory and clinical parameters as predictors of contributory PET-CT scans and propose an algorithm for FUO workup.

SUBJECTS AND METHODS

This retrospective observational study was conducted in a teaching hospital in South India. Patients admitted to General Medicine wards for evaluation of FUO from June 2013 to May 2016 who underwent ^{18}FDG PET-CT scan were included in this study. PET-CT scan was done as part of a structured stepwise approach for FUO workup. Patients were categorized as FUO if they fulfilled Petersdorf and Beeson criteria – febrile illness for more than three weeks, temperature >38.3°C on several occasions, and uncertain diagnosis after 1 week of investigations in hospital.[1]

Detailed history was obtained and physical examination was performed for all patients. The presence of enlarged cervical, axillary, inguinal lymph nodes, skin rash, palpable liver, spleen, and arthritis was noted. All patients underwent a first tier of investigations which consisted of complete blood counts, liver and renal function tests, three or more blood cultures, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), human immunodeficiency virus serology, peripheral blood smears for malarial parasites, urine analysis and culture, chest X-ray, sputum smears for acid-fast bacilli (AFB), and thyroid function tests. For those who remained undiagnosed, one or more second-tier tests were conducted depending upon presence of potential diagnostic clues for each patient. The second tier of investigations included echocardiogram, ultrasound abdomen, aspiration of pleural/ascitic fluid, antinuclear antibody (ANA), and antineutrophilic cytoplasmic antibody (ANCA).

PET-CT scan was done if diagnosis had not been established after a detailed workup including first- and second-tier investigations. Demographic details, presenting symptoms, physical examination findings, laboratory parameters, imaging results, biopsy reports, and treatment given were collected from computerized medical records. Final diagnoses were established on the basis of clinical features, laboratory, biopsy and culture reports, and response to therapy (where applicable). Patients were grouped into five categories based on final diagnosis.

1. Infectious disease
2. Non-infectious inflammatory disease (NIID)
3. Malignancy
4. Miscellaneous – Established diagnosis does not fall into categories 1, 2, or 3
5. Final diagnosis could not be established despite extensive evaluation.

PET-CT scans with focal increased ^{18}FDG uptake (excluding physiological uptake) and/or structural abnormalities were considered positive. PET-CT scans were categorized as contributory or non-contributory according to their role in the diagnostic workup. Contributory PET-CT scans had either delineated the organ for a biopsy which was diagnostic or excluded a probable alternate diagnosis.

Institutional Review Board and Ethics Committee approval was obtained prior to commencement of this study (IRB Minute No 10242 dated 24.08.2016). Due to the retrospective nature of this study, requirement for individual patient consent was waived.

For each patient in the study, blood glucose was confirmed to be less than 150mg/dl prior to ^{18}FDG PET-CT scan. ^{18}FDG was administered intravenously. At 60 minutes after injection, imaging was initiated with Siemens Biograph-6 (LSO-crystal/6-slice) PET-CT scanner. CT and PET images were obtained from vertex to heel. Using CT scans for attenuation correction and localization, images were reconstructed. Multiplanar PET images were reviewed concurrently with fused PET/contrast CT images and standardized uptake values were calculated. Each ^{18}FDG PET-CT scan was reviewed by a nuclear medicine specialist, and CT images were reviewed independently by a radiologist.

All laboratory parameters were reported as mean ± standard deviation (SD) with reference range. Imaging (chest X-ray,

ultrasound abdomen, and CT thorax and abdomen) and other parameters were reported as number and percentage. Chi-square test was used to find association between categorical variables. Sensitivity, specificity, and positive and negative predictive values of PET-CT scans were calculated. The data were analyzed using Statistical Package for Social Services Software Version 21.0 (Armonk, NY, USA: IBM Corp).

RESULTS

From June 2013 to May 2016, 118 patients admitted under General Medicine underwent whole body PET-CT scans. Of 118 patients, 49 were admitted for evaluation of prolonged fever. Six patients did not fulfil criteria for FUO and were excluded. Forty-three patients with classical FUO were included in our study. Among 43 patients, 67% (29) were male. The mean age (mean ± SD) was 46.8 ± 15 years (range = 20–75 years). No localizing symptoms were present in 30.2% (13/43). Symptoms of musculoskeletal involvement (arthritis, arthralgia) were present in 18.6% (8/43). More than two-thirds i.e., 69% (30/43) reported loss of appetite. Significant weight loss (i.e., loss of ≥10% body weight in ≤6 months) was seen in 81% (35/43). Average duration of symptoms prior to presentation was 4.9 ± 4.7 months (range = 0.75–24). Diabetes mellitus, chronic kidney disease, and chronic liver disease were present in 30% (13/43), 9.3% (4/43), and 7% (3/43), respectively. None of our patients had HIV infection, pre-existing malignancy, neutropenia or history of organ transplant.

Relevant laboratory and imaging tests are mentioned in Table 1. ESR and CRP were elevated in 68.4% (26/38) and 84.6% (33/39), respectively. High aspartate aminotransferase (AST) and ALT values (i.e., more than 2 times the upper limit of normal) were seen in 11.6% (5/43) and 4.7% (2/43), respectively. ANA and ANCA were positive in 10% (4/40) and 5.4% (2/37) of patients, respectively.

A definite final diagnosis was established in 74% (32/43). NIIDs, infections, malignancies, and miscellaneous diseases were diagnosed in 37.2% (16/43), 23.3% (10/43), 9.3% (4/43), and 4.7% (2/43), respectively. NIIDs included connective tissue disease and vasculitis, adult-onset Still's disease, and sarcoidosis, which accounted for 16.3% (7/43), 11.6% (5/43), and 4.7% (2/43), respectively [Table 2].

We found tuberculosis to be the most frequent diagnosis (20.9%, 9/43, disseminated tuberculosis – 4, tuberculous lymphadenitis – 2, tuberculous pericardial effusion – 1, adrenal tuberculosis – 1, and tuberculous enteritis – 1). All patients with tuberculosis had negative sputum AFB smears and GeneXpert polymerase chain reaction test for *Mycobacterium tuberculosis* prior to PET-CT and invasive diagnostic procedures. PET-CT delineated organ/tissue for diagnostic biopsy in 77% (7/9) patients with tuberculosis ($P = 0.001$).

Mean duration of hospital stay was 20.1 ± 10.5 days. 4 out of 43 subjects (9.3%) required admission to Intensive Care Unit during their hospital stay. 39.5% (17/43) were on antibiotic therapy during hospital stay. Mean duration of antibiotic therapy was 10.1 ± 3.2 days (range 6–17). A 62-year-old patient admitted for FUO evaluation developed pyelonephritis during hospital stay and succumbed to this infection. Etiology of FUO could not be established in this patient. All other patients were discharged from hospital in a stable state.

PET-CT scans were positive in 72% (31/43) and contributory toward establishment of final diagnosis in 90.7% (39/43). Among these 39 subjects with contributory scans, abnormal PET-CT findings led to the diagnostic biopsy in 30.8% (12). PET-CT scans helped us exclude a probable alternate diagnosis in 69.2% (27/39). Among these 27 patients, PET-CT was done to rule out underlying infection as well as malignancy in 8 patients with cachectic symptoms and 4 patients with FUO without localizing features. PET-CT contributed to ruling out suspected underlying malignancy in 12 patients (abdominal pain/jaundice/melena – 5, suspected paraneoplastic arthritis, myositis – 1, pericardial effusion – 1). Three patients had respiratory symptoms (cough and/or breathlessness) in whom PET/CT was helpful in looking for infectious etiology especially tuberculosis.

Final diagnosis in this group was established in 16 patients (NIID – 11, infectious disease – 2, malignancy – 1, autoimmune hemolytic anemia-1, mesangioproliferative glomerulonephritis-1) whereas 11 remained without a diagnosis despite extensive investigations.

Hepatomegaly, splenomegaly, and lymphadenopathy were found in 18.6% (8/43), 23.3% (10/43), and 39.5% (17/43), respectively. Lymph node, renal, and splenic biopsy were found to have high diagnostic yield [Table 3]. CRP value of more than 6 mg/dl and AST levels of more than 80 IU/L were associated with contributory PET-CT scans in our study ($P = 0.006$ and 0.011, respectively). PET-CT scan leading to diagnostic biopsy was associated with final diagnosis of infectious disease ($P = 0.001$). We did not find association between age, gender, symptom duration,

Table 1: Baseline demographic characteristics and relevant laboratory and imaging tests

Demographic characteristics	**%(n)**	
Age (mean±SD)	46.8±15 years (range=20-75 years)	
Sex (males)	67% (29/43)	
Diabetes mellitus	30% (13/43)	
Chronic kidney disease	9.3% (4/43)	
Chronic liver disease	7% (3/43)	
Laboratory parameter	**Mean±SD**	**Reference range**
Hemoglobin	10.1±2.3 g/dL	12-15 g/dl
Total leucocyte count	9893±4560 per μL	4400-11,000 per μL
AST	41.2±32.5 IU/L	10-40 IU/L
ALT	29±23.1 IU/L	10-35 IU/L
Corrected calcium	8.8±0.4 mg/dL	8.5-10.5 mg/dL
Albumin	3.4±0.6 g/dL	3.5-5 g/dL
ESR*	50.8±34.6 mm/h	0-30 mm/h
CRP*	63.2±58.6 mg/dL	<6 mg/dl
Imaging	***n* (%) of patients who underwent imaging (*n*=43)**	**Abnormal results - number (%)**
Chest X ray	43 (100)	8 (18.6)
Ultrasound abdomen	22 (51)	16 (72.7)
CT thorax and abdomen	17 (39.5)	15 (88)

*ESR and CRP values were available for 38 and 39 patients, respectively. SD: Standard deviation, ESR: Erythrocyte sedimentation rate, CRP: C-Reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

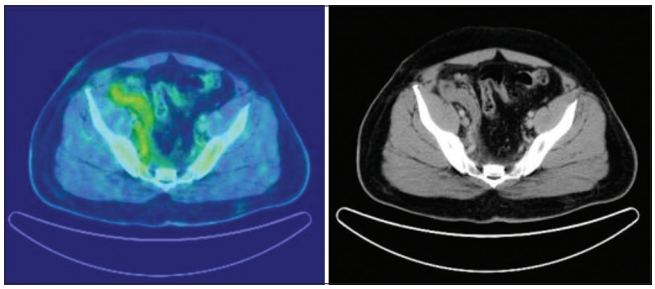

Figure 1: Fascial thickening and haziness with soft tissue density noted in the right pelvic retroperitoneum extending along the right lateral pelvic wall (SUVmax 12.80); maximum thickness 19 mm. Haziness and fat stranding is noted in the adjacent mesentery and mesorectal fat. Biopsy from retroperitoneum did not show abnormalities. Final diagnosis was cutaneous small vessel vasculitis. (False positive positron emission tomography–computed tomography scan)

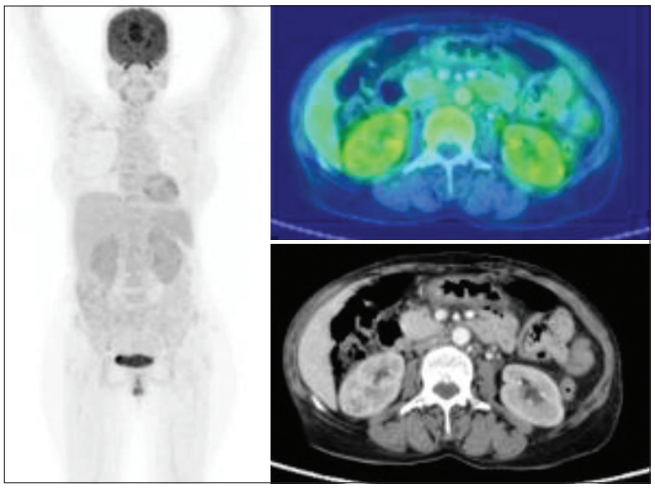

Figure 2: Negative positron emission tomography–computed tomography scan in a patient with granulomatosis with polyangiitis. Final diagnosis was confirmed by antineutrophilic cytoplasmic antibody, and renal biopsy (False negative positron emission tomography–computed tomography scan)

presence of hepatomegaly, splenomegaly, leucocyte count, high ESR with positive or contributory PET-CT scans. 39.5% (17/43) had an at least one underlying medical condition which may cause immunosuppression (diabetes mellitus/chronic kidney disease/chronic liver disease). We did not find an association between presence of immunocompromising conditions and infectious etiology of FUO in our study ($P = 0.065$).

Among patients with a definite final diagnosis, 78% (25/32) had positive PET-CT scans. Sensitivity and specificity of PET-CT scans in this study were 76.9% (20/26) and 33.3% (2/6), respectively. We found positive and negative predictive value of PET-CT scans to be 83% (20/24) and 25% (2/8), respectively [Table 4].

DISCUSSION

Scintigraphic techniques like 18-FDG PET-CT are useful to detect foci of infection, inflammation and malignancy in FUO. Further tests including biopsies can be done based on abnormalities detected on PET-CT scans to ascertain a definite diagnosis.[9]

Elevated CRP levels have been found to be predictive of positive PET-CT scans in several studies.[13-16] This is consistent with our study. Bacterial infections are associated with

Table 2: Positron emission tomography–computed tomography abnormalities and diagnostic tests in patients with a definite final diagnosis

Final Diagnosis (Number of patients)	PET-CT findings	Diagnostic test
NIID - CTD and Vasculitis (7)		
Systemic Lupus Erythematosus (2)	Metabolically active cervical, mediastinal and hilar LNE Metabolically active cervical, axillary, mediastinal and abdominal LNE	Fulfilled SLICC criteria Fulfilled SLICC criteria; renal biopsy - Class 4 lupus nephritis
Renal-limited vasculitis (2)	No abnormalities detected Minimal ascites	Renal biopsy – focal segmental glomerulosclerosis with granuloma Renal biopsy - diffuse proliferative glomerulonephritis
Primary cutaneous small -vessel vasculitis (1)	Metabolically active fascial thickening in the retroperitoneal region [Figure 1]	Skin biopsy – vasculitis; ANCA negative; retroperitoneal fascial biopsy - normal
Undifferentiated CTD (1)	Mild hepatosplenomegaly	ANA positive, nerve biopsy – neurogenic atrophy
Granulomatosis with polyangiitis (1)	Metabolically active para-aortic, aorto-caval and iliac lymph nodes [Figure 2]	C-ANCA positive; renal biopsy – vasculitis with granuloma
Other NIID (9)		
Adult-onset Still's disease (5)	Cervical and axillary LNE, hepatosplenomegaly Metabolically active axillary LNE Axillary, mediastinal, abdominal LNE, hepatosplenomegaly Metabolically active cervical and thoracic LNE, hepatosplenomegaly No abnormalities	All fulfilled Yamaguchi criteria (two patients underwent lymph node biopsy which were reported as normal)
Sarcoidosis (2)	Metabolically active thoracic and abdominal LNE, hepatosplenomegaly Axillary, mediastinal and abdominal LNE, hepatosplenomegaly	Liver biopsy – non-caseating granuloma Response to treatment (lymph node and liver biopsy – inconclusive)
Kikuchi's disease (1)	Metabolically active axillary and mediastinal LNE	Mediastinal lymph node biopsy (axillary lymph node biopsy – inconclusive)
Inflammatory myositis (1)	Metabolically active muscle inflammation	Muscle biopsy
Infectious Diseases (10)		
Tuberculous lymphadenitis (2)	Metabolically active mediastinal LNE Metabolically active mediastinal and hilar LNE	Mediastinal lymph node biopsy Mediastinal lymph node biopsy
Disseminated tuberculosis (4)	Metabolically active mediastinal, hilar LNE, omental, and mesenteric thickening; dilated jejunal loops, mesenteric adhesions Metabolically active mediastinal, hilar, periportal, retroperitoneal LNE, right psoas abscess[&] Metabolically active mediastinal, hilar LNE, pulmonary nodules, pleural thickening Metabolically active mediastinal, hilar, peri-esophageal LNE, pulmonary infiltrates	Omental biopsy Mediastinal node biopsy Transbronchial lung biopsy Transbronchial lung biopsy
Pericardial tuberculosis (1)	Pericardial effusion; no metabolically active focus	Pericardial biopsy
Adrenal tuberculosis (1)	Metabolically active bilateral adrenal glands	CT-guided adrenal biopsy
Tuberculous enteritis (1)	Colonic wall thickening	Colonoscopy and terminal ileum biopsy
Melioidosis (1)	Metabolically active splenic collection and bilateral axillary LNE	Splenic abscess aspiration
Malignancy (4)		
Hodgkin's lymphoma (1)	Metabolically active mediastinal, internal iliac, para-aortic LNE and hepatosplenomegaly	Laparoscopic liver and spleen biopsy (this patient had mildly enlared lymph nodes which were not amenable for biopsy)
Non-Hodgkin's lymphoma (1)	Metabolically active pelvic mass lesion	Pelvic mass lesion biopsy
Colonic myofibroblastic tumor (1)	Metabolically active descending colon mass lesion [Figure 3]	Colonic mass lesion biopsy
Metastatic Carcinoma prostate (1)	Disseminated sclerotic bone metastases; diffuse increased uptake in prostate gland	Bone marrow biopsy – metastatic adenocarcinoma, elevated Prostate Specific Antigen
Miscellaneous (2)		

Contd...

Table 2: Contd...

Final Diagnosis (Number of patients)	PET-CT findings	Diagnostic test
AIHA** (1)	Metabolically active diffuse marrow hyperplasia	Bone marrow biopsy and Direct Coomb's Test
Mesangioproliferative glomerulonephritis (1)	Minimal bilateral pleural effusion	Renal biopsy

CTD: Connective tissue disease; LNE: Lymph Node Enlargement, SLICC: Systemic Lupus International Collaborating Clinics, AIHA: Autoimmune hemolytic anemia, PET-CT: Positron emission tomography–computed tomography, NIID: Noninfectious inflammatory disease

Table 3: Organs/tissues biopsied and percentage of diagnostic biopsies

Organs/tissues biopsied	*n* (%) who underwent biopsy (*n*=43)	*n* (%) of diagnostic biopsies
Bone marrow biopsy	43 (100)	2 (4.7)
Lymph node biopsy	13 (30.2)	7 (53.8)
Nerve and muscle biopsy	5 (11.6)	1 (20)
Renal biopsy	5 (11.6)	4 (80)
Liver biopsy	5 (11.6)	2 (40)
Splenic biopsy	3 (6.9)	2 (66.7)
Prostatic biopsy	1 (2.3)	1 (100)
Omental biopsy	1 (2.3)	1 (100)
Colonic mass lesion biopsy	1 (2.3)	1 (100)
Pericardial biopsy	1 (2.3)	1 (100)
Adrenal gland biopsy	1 (2.3)	1 (100)

Table 4: True positive, false positive, true negative, and false negative positron emission tomography–computed tomography scans among patients with a definite final diagnosis (*n*=32)

	Organ pathology +	Organ Pathology−
PET-CT positive	20 (true positive)	4 (false positive)
PET-CT negative	6 (false negative)	2 (true negative)

extremely high CRP levels. Vasculitis and connective tissue diseases (rheumatoid arthritis, polymyalgia rheumatica) lead to modestly elevated CRP levels.[17-19] PET-CT should be the preferred imaging modality in FUO patients with elevated CRP levels who remain undiagnosed after clinical assessment and basic investigations.

Lymphopenia and neutrophilia were found to be useful indicators of contributory PET-CT scan in a study conducted in Turkey ($P < 0.001$ for both).[15] A German study noted that age >50 years was a predictor of diagnostic PET-CT scans among subjects with fever and inflammation of unknown origin.[20] However, these results remain to be replicated in other studies.

There has been a shift in the predominant etiology of FUO in certain regions, with increase in NIIDs and reduction in infections.[21-23] The number of undiagnosed FUO patients have increased with time.[23] Robine *et al*. found NIIDs in 61% of FUO patients with an established diagnosis, with PET-CT scan being contributory in merely 20.8% (10/48).[2] Similarly,

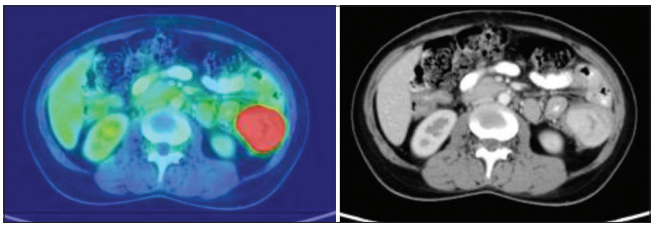

Figure 3: A large well-defined intensely enhancing lesion in the left lumbar region indenting the proximal descending colon with no luminal compromise - probably retroperitoneal in location (Metabolically active, SUVmax 21.62). Biopsy of the lesion was consistent with myofibroblastic tumor. (True positive positron emission tomography–computed tomography scan)

in a study from Denmark, Pederson *et al*. found NIID in 55% of diagnosed FUO patients.[24] In our study, NIIDs accounted for most diagnosed cases. This contrasts with a prospective FUO study from our institution conducted from 2010 to 2012 in which infections and NIIDs accounted for 48% and 20.6% of cases, respectively.[25] This may reflect the changing pattern of FUO in India. It is also important to bear in mind that our study consisted of a subset of FUO cases who were difficult to diagnose and remained without a diagnosis after several investigations.

We found tuberculosis to be the most common diagnosis among our patients with FUO. This is consistent with prospective FUO studies from Eastern and Southern India.[25,26] However, Mir *et al*. found that brucellosis (25%) and salmonellosis (25%) accounted for the most common infections in their study conducted in Srinagar, India.[27] Geographical and climate variations may play a role in influencing the rates of tuberculosis in various regions.

Bleeker-Rovers *et al*. prospectively evaluated 73 patients from community and university hospitals in the Netherlands from 2003 to 2005. NIIDs, infections, and malignancies were diagnosed in 22% (16) 16% (12), and 7% (5), respectively, whereas no diagnosis could be established in 51% (37). FDG-PET was contributory in 33% (23). False-positive and false-negative results were obtained in 14% (10) and 3% (2), respectively. FDG-PET was performed prior to CT abdomen and after first tier of investigations in the structured diagnostic protocol followed in this study.[28] However, the

diagnostic yield of PET-CT is greater than PET scans. Minimal additional information is obtained when abdominal CT is performed after whole body PET-CT in FUO.

Mourad *et al*. proposed a diagnostic algorithm for FUO workup. They recommended performing abdominal CT or technetium-based nuclear imaging test after initial blood tests and chest X-ray. However, their systematic review included studies from North America and Europe, and their recommendations were intended to be used for the same population.[23]

In a systematic review of Asian and European FUO studies published from 2005 to 2015, the risk of having an infectious disease was higher in Asia as compared to Europe (Southern Asia – odds ratio 4.6, Far East Asia – odds ratio 3.0). FUO patients in Europe were 4 times likely to be diagnosed with NIID as compared to patients in South Asia [Table 5]. Low-income countries were likely to have higher percentage of infectious diseases.[4]

Mortality in FUO has been estimated to be 5 to 7%.[39,42] Neoplastic disorders are associated with higher mortality, whereas non-malignant diseases have lower mortality rates.[23,42] Neoplastic disorders should be diagnosed with minimal delay in order to initiate treatment and prevent progression.

PET-CT scans in FUO workup have been estimated to have high sensitivity and low specificity in various studies.[30,43] This is consistent with our study. Sensitivity and specificity of PET-CT scans have been noted to be 81%–86% and 52%–88%, respectively, in meta-analyses.[11,44-46] PET-CT scans have high false positive rates for FUO, which imply that patients might be subjected to unnecessary invasive procedures.

Classical FUO patients with negative PET-CT results are likely to have spontaneous regression of symptoms (relative risk 5.6, $P < 0.001$).[47] In a study at a South Korean hospital that included FUO patients with non-diagnostic PET-CT scans, 83.3% (5/6) were documented to have favorable outcome at follow-up.[48]

PET-CT can detect high tracer uptake in vessel-walls in those with large vessel vasculitis.[49] In a study by Singh *et al*. that included 47 FUO subjects from north India, three had aortoarteritis. CT scans were normal in these patients, and PET-CT was the diagnostic test.[35] However, in our study,

Table 5: Infectious and Non-infectious inflammatory diseases (NIID) as etiology of Fever of Unknown Origin in Europe, Asia and the Middle East (selected studies published during the last 15 years)

Continent/region	First author, year of publication	Country	Infectious diseases (% of diagnosed patients)	NIID (% of diagnosed patients)	Patients with a final diagnosis, *n* (%)
Europe	Bleeker-Rovers, 2007[28]	Netherlands	32.4	44	36/73 (49)
Europe	Efstathiou, 2009[29]	Greece	38.2	41.6	89/112 (79.4)
Europe	Pedersen, 2012[24]	Denmark	32	55	31/52 (59.6)
Europe	Robine, 2014[2]	France	23.5	61	51/103 (49.5)
Europe	Pereira, 2016[30]	Switzerland	34.8	19.6	46/76 (60.5)
Europe	Garcia-Vicente, 2018[31]	Spain	55.6	44.4	45/67 (67.2)
Europe	Bosilkovski, 2019 (2011-2015 cohort)[21]	North Macedonia	36.5	31.8	85/106 (80.2)
Europe	Mulders-Manders, 2019[13]	Netherlands	47	47	68/104 (65.4)
Asia	Hu, 2008[13]	China	41.8	37.7	122/142 (86)
Asia (tropical)	Kei, 2010[32]	Singapore	57.1	14.3	7/12 (58.3)
Asia (tropical)	Manohar, 2011[33]	India	51.4	18.9	37/58 (63.8)
Asia (tropical)	Bandyopadhyay, 2011[26]	India	62.5	12.5	144/164 (87.8)
Asia	Kim, 2012[34]	South Korea	29.3	19.5	41/48 (85.4)
Asia (tropical)	Mir, 2014[27]	India	60.6	16.7	66/91 (72.5)
Asia	Naito, 2013[3]	Japan	23.1	30.6	93/121 (76.9)
Asia (tropical)	Singh, 2015[35]	India	36	40	25/47 (53.2)
Asia	Yang, 2015[36]	China	43.3	29.9	67/175 (38.3)
Middle East	Kucukardali, 2008[37]	Turkey	40.8	36.2	130/154 (84.4)
Middle East	Abdelbaky, 2011[37]	Egypt	56.2	27	89/100 (89)
Middle East	Ali-Eldin, 2011[38]	Egypt	48	17.3	81/93 (87.1)
Middle East	Gafter-Gvili, 2015[39]	Israel	59	20.5	83/112 (74)
Middle East	Montasser, 2015[40]	Egypt	71.9	15.7	345/374 (92.5)
Middle East	Kabapy, 2016[41]	Egypt	80.5	17.7	961/979 (98.2)

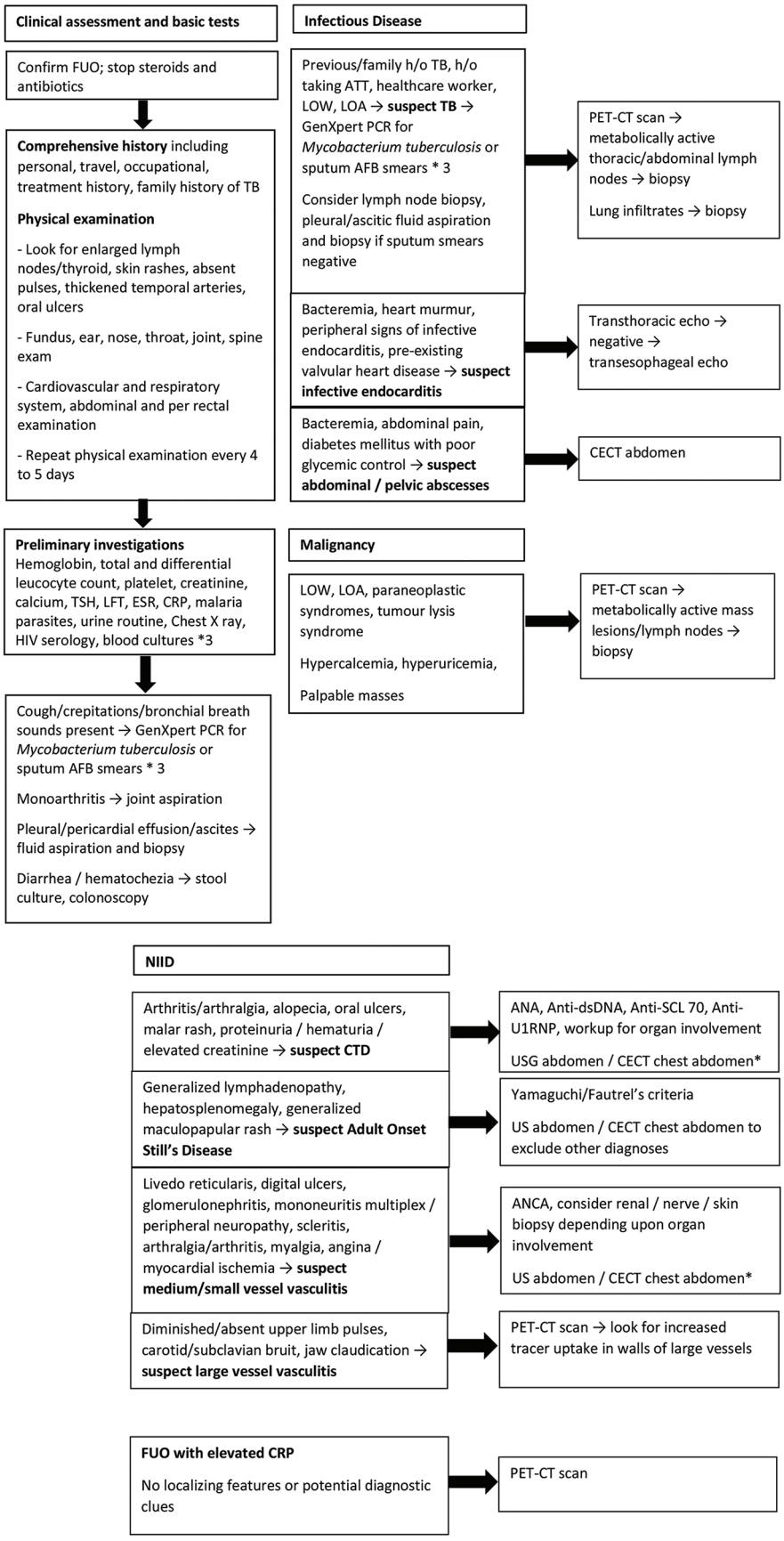

Figure 4: Algorithm for workup of classical fever of unknown origin in tropical regions

we did not find any patients with large vessel vasculitis. PET-CT scans are unable to detect small and medium vessel vasculitis. PET-CT scans may miss renal pathology as ^{18}FDG is excreted by the kidneys.[50] Limitations of our study include retrospective nature and unavailability of long-term follow-up data for some patients.

PET-CT should be considered in FUO patients when a comprehensive history and physical examination, first- and second-tier investigations, workup toward potential diagnostic clues have not yielded a diagnosis [Figure 4]. A detailed clinical assessment and tests guided by potential diagnostic clues is of paramount importance in FUO workup, and PET-CT is not a substitute for the same.

CONCLUSIONS

Tuberculosis was the most common diagnosis among FUO patients in this study. High CRP and AST were associated with contributory PET-CT scans. PET-CT scans leading to diagnostic biopsy were associated with final diagnosis of infectious disease in our study. PET-CT scans, though a useful imaging technique in FUO, should be used judiciously in evaluation of FUO. Protocol for FUO workup should be modified based on geographical region and prevalence of diseases. Physical examination findings, diagnostic clues, probable diagnosis, and feasibility of tests should be taken into account prior to performing imaging tests for patients with FUO.

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Conflicts of interest
There are no conflicts of interest.

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