Review Article
[18F]FDG PET/CT for identifying the causes of fever of unknown origin (FUO)

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Abstract: Fever of unknown origin (FUO) continues to be a challenging diagnosis in clinical medicine. It has more than 200 known causes, including infections, autoimmune diseases, neoplasia, and other miscellaneous disorders. Despite the development of a wide range of diagnostic tools, a specific diagnostic algorithm for FUO is not yet available. However, [18F]FDG PET/CT, which yields information on cellular metabolism, in addition to details of organ anatomy, has been shown to be successful in the FUO investigation. This study highlights the uses of [18F]FDG PET/CT in diagnosing various causes of FUO. [18F]FDG PET/CT has been increasingly used to detect septic infections, sterile inflammatory processes, and malignancies, occupying a significant portion of the known causes of FUO. It has led to a more definitive identification of the etiology of FUO and accurate clinical management. However, more in-depth studies are crucial to understanding if [18F]FDG PET/CT can be used in the work-up of FUO.

Keywords: Fever of unknown origin (FUO), positron emission tomography (PET), [18F]FDG, infection, malignancy

Introduction

The definition of fever of unknown origin (FUO) has changed over time. As per its first definition in 1961, FUO refers to fever (> 38.3°C) measured for at least 3 times over 3 weeks duration, with no diagnosis reached despite of a week of in-hospital evaluation [1]. The criteria were later changed in 1991 to include a minimum of 3 outpatient visits or 3 days in-hospital assessment [1]. Another update in 2003 brought forward the idea of qualitative criteria, i.e., instead of a three-day period, it shifted the attention to the completion of appropriate intelligent standard investigations, which was proposed to decrease observer bias and variations in diagnostic facilities in different countries and hospitals [2].

The cause of FUO can be related to a number of causes, and thus, the diagnosis seems rather elusive. The underlying etiologies of FUO can be grouped into five categories: infection, neoplasia, inflammation, miscellaneous, and idiopathic illness; infection remains a major contributor [3]. The etiologies of FUO depend in large part on the type of population, their socioeconomic status, and the healthcare facilities available in their area [4, 5]. Based on data from a study published recently in 2023, which included 788 subjects from 21 countries with different

economic developments, the causes of FUO were infection in 51.6%, neoplasm in 11.4%, collagen vascular disease in 9.3%, miscellaneous in 7.7%, and 20.1% of cases were undiagnosed [5].

Although FUO was defined more than 60 years ago, no specific diagnostic strategy guidelines have yet been established. Moreover, since there are > 200 listed etiologies of FUO, their diagnoses remain a challenge despite the development of a wide range of diagnostic tools [6]. Due to the varied number of causes, most studies recommend some essential steps when approaching patients with FUO; these include confirming that the patient actually has a fever, a thorough history, systemic physical examinations, excluding drug fever as a side effect of drugs, or the presence of underlying immunosuppression before proceeding to noninvasive and invasive tests [7]. Currently, there is no consensus on the standard FUO evaluation, so investigations are usually individualized as per the patient's characteristics & clinical findings. Some of the common investigations performed in FUO include complete blood count (hemoglobin, platelet, and leukocyte count), CRP, ESR, blood chemistry, urine tests (microscopic, culture, and sensitivity), and chest x-rays [8, 9]. According to Arnow and Flaherty, additional laboratory tests should be performed for this condition to meet the

Figure 1. [18F]FDG PET/CT image of a patient with Infective coxitis. This figure represents the case of a 60-year-old male who satisfied the criteria for FUO. Whole body [18F]FDG PET/CT scan indicated abnormal activity at the right hip joint (indicated by the arrow). While earlier clinical assessments had hinted at activated osteoarthrosis, biopsy, and blood tests done after [18F]FDG PET/CT confirmed an infection in the hip joint (Infective coxitis) due to Staphylococcus aureus. Following an extended intravenous antibiotic regimen, the patient made a complete recovery (with permission from reference [14]).

minimal diagnostic evaluation criteria and qualify as FUO [10]. Any abnormalities detected in those tests are investigated in detail [10]. However, the absence of any established cut-off value related to laboratory parameters limits the clinical usefulness of these investigations for the evaluation of FUO.

In addition to laboratory investigations, the FUO work-up also involves various imaging studies depending on the patient's symptoms. 2-deoxy-2-[18F]fluoro-D-glucose ([18F]FDG) PET/CT is used for whole body imaging when targeted body part imaging techniques such as radiographs, ultrasound, CT scan, and MRI are inconclusive for diagnosing FUO [8]. [18F]FDG PET/CT can play a substantial role in determining the source of FUO, including malignancies, infections, and inflammatory conditions [11, 12]. With the growing evidence on the early use of [18F]FDG PET/CT to avoid unnecessary interventions in subjects with FUO, our aim is to review the potential of [18F]FDG PET/CT as a routine imaging test for an early diagnostic evaluation to identify the cause of FUO.

The role of [18F]FDG PET/CT in FUO

[18F]FDG PET scan yields information on the glucose metabolism within the cells, while the CT scan offers detailed information on organ structure/anatomy [13]. The effectiveness of [18F]FDG PET/CT in assessing FUO is enhanced by the lack of significant morphological changes in the preliminary stages of many infectious and inflammatory conditions. Hence, when other imaging techniques are not conclusive, this hybrid imaging technique constitutes a primary modality due to its high sensitivity (**Figure 1**) [14].

[18F]FDG is a glucose-analog, which is internalized in cells through glucose transporters available on the membrane of the cell [15]. After phosphorylation by hexokinase (in most instances), [18F]FDG then accumulates in cells such as activated leukocytes and malignant cells with high rates of glycolysis (having GLUT1, GLUT3, and hexokinase activity). The presence of inflammatory mediators in inflamed tissues, local up-regulation of glucose transporters by inflammatory mediators, and high glucose metabolism of leukocytes make them detectable by [18F]FDG PET/CT [16]. The higher uptake of [18F]FDG by activated leukocytes is not specific but covers many causes of FUO, such as infections, inflammations, and malignancies [15, 17-19].

The diverse clinical presentations and a range of probable etiologies of FUO make identifying the origin of FUO challenging, time-consuming, and expensive. There always remains the possibility of missing causes. In fact, the causes of 10% to 50% of FUO remain undiagnosed [20]. With the benefits of increased resolution of whole-body PET, relatively lower exposure to radiation (around 15 mSv, compared to 20-25 mSv due to high-dose CT scan), and high sensitivity, [18F]FDG PET/CT is a useful tool for evaluating FUO [21]. To comprehensively identify the uses of [18F]FDG PET/CT for the evaluation of FUO, we have reviewed seven meta-analysis studies published in this context; two of them were related to pediatric patients and are discussed later in a separate section.

In the 2017 meta-analysis, Bharucha et al. analyzed the diagnostic yield of [18F]FDG PET/CT in FUO [22]. Based on the analysis of 18 studies published from 15 countries in Asia and Europe and encompassing 905 patients, the diagnostic efficacy of [18F]FDG PET/CT in FUO was 56% (95% CI was 50-61% and I^2=61%). When exclusive analysis of the five studies that presented the findings of previous imaging was performed, the diagnostic efficacy beyond CT was 32% (95% CI was 22-44% and I^2=66%) [22]. Seven studies (39%) reported elevated inflammatory markers, but correlation with [18F]FDG PET/CT contribution was not found. Overall, 69% of [18F]FDG PET/CT scans were abnormal, with 9% false positives. The methods for the final diagnosis varied, including biopsies, serology, and autopsy. Of the 73% of patients who received a final diagnosis, 32% had infectious diseases, 20% had inflammatory causes, and 12% had malignancy [22]. The authors reported increased availability and possible applications of [18F]FDG PET/CT for assessing FUO; however, its implementation exhibits significant variability [22]. The existing evidence then was insufficient to provide robust support for the application of [18F]FDG PET/CT as a diagnostic tool in the FUO investigation algorithm. The 18 studies in this meta-analysis were observational case series without any comparison groups; Most were retrospective studies (89%) and showed high chances of bias. Thus, future research should emphasize prospective studies, include revised definitions, and specify measures of the outcome. Evaluation of the possible risks and expenses associated with [18F]FDG PET/CT in comparison to its potential advantages may require broad collaboration across various centers [22].

Another meta-analysis by Hao et al. studied the diagnostic power of [18F]FDG PET/CT in FUO [23]. It included 15 studies, encompassing 595 people with FUO. The utilization of [18F]FDG PET/CT exhibited a notable degree of sensitivity in accurately diagnosing individuals with FUO. [18F]FDG PET/CT had a sensitivity of 85% for identifying the etiology of FUO by per-patient evaluation, with a 95% confidence interval ranging from 81% to 88% [23]. The ROC curve analysis resulted in an AUC of 0.88. Therefore, [18F]FDG PET/CT was found to be a reliable method to achieve this objective; nonetheless, it is crucial to con-

sider the possible occurrence of false-positive outcomes [23]. The limitation of using [18F]FDG PET/CT for evaluating FUO was found to be due to its limited availability and high cost, especially in underdeveloped nations [23]. It should be noted that, among the 15 papers incorporated in this particular meta-analysis, only one originated from a developing country. This emphasizes the lack of accessibility to [18F]FDG PET/CT in developing nations and, therefore, the difficulties in general extrapolation of the results of other meta-analyses to patients from developing countries.

A meta-analysis by Dong et al. compared [18F]FDG PET vs [18F]FDG PET/CT in FUO who had previous unsuccessful conventional diagnostic testing [24]. Nine studies involving 388 patients were analyzed for specificity, sensitivity, and AUC [24]. [18F]FDG PET had a pooled sensitivity of 0.826, a specificity of 0.578, and an AUC of 0.810. However, the results were heterogeneous among [18F]FDG PET studies. [18F]FDG PET/CT had a superior sensitivity of 0.982, a specificity of 0.859, and an AUC of 0.947. There were no differences between the AUCs of [18F]FDG PET and [18F]FDG PET/CT. Of the 388 patients, [18F]FDG PET resulted in a final diagnosis in 32.2% of cases, while the results of [18F]FDG PET/CT contributed to 62.1% of cases. Despite the heterogeneity in [18F]FDG PET studies, it was a sensitive tool for detecting FUO causes [24]. [18F]FDG PET/CT showcased sensitivity and specificity higher than [18F]FDG PET alone, suggesting its importance in early diagnosis [24]. The study also highlighted the cost-benefits of [18F]FDG PET and [18F]FDG PET/CT. In conclusion, by providing an accurate early diagnosis, these methods can reduce unnecessary tests, accelerate diagnosis time, and potentially decrease hospital stays for diagnostic purposes [24].

A stratification-based meta-analysis by Besson et al. quantified the contributions of [18F]FDG PET for the diagnostic evaluation of FUO [25]. Abnormal PET findings were found to significantly improve the diagnostic success rate in the FUO [25]. Most (two-thirds) of the abnormal PET findings were related to a higher probability of reaching a definite diagnosis [25]. Of 14 selected studies involving 712 patients, the findings indicated that normal PET results increased the final diagnostic rate by 36%, while abnormal results did so by 83%, resulting in a combined odds ratio of 8.94 [25]. Factors such as study design influenced the results, but the type of PET device, the geographic location, and the duration of follow-up did not. Thus, [18F]FDG PET may enhance the primary diagnostic evaluation for FUO but requires more standardized studies for validation. In particular, sensitivity analyses revealed there were no additional advantages to using [18F]FDG PET/CT over the dedicated [18F]FDG PET [25].

Spontaneous remission is often observed in classic FUO patients. However, there are limited credible predictors of spontaneous recovery in such instances. Takeuchi et al. looked at the correlation between [18F]FDG PET (or [18F]

FDG PET/CT) findings and spontaneous recovery in FUO [26]. Of the total of 13 studies that qualified for consideration, the majority (nine) were from Europe, three from the Middle East, and one from North Africa. Of these, nine studies, which included 418 patients, concentrated on the results of PET/CT scans, while the remaining four studies examined the results of standalone PET scans involving 128 patients. No study directly mentioned spontaneous remission as a result, and all studies had a high risk of bias, as patients underwent further diagnostic procedures based on imaging findings. Overall, negative PET/CT results were associated with a higher likelihood of spontaneous recovery compared to positive PET/CT results, in such a way that cases with negative PET/CT results had a spontaneous recovery rate of 20-78%, and cases with positive PET/CT results had a spontaneous recovery rate of 0-48% [26]. The association between independent PET findings and spontaneous recovery was not conclusive. It might be possible that patients whose PET/CT comes out to be negative, especially those who are clinically stable, may be advised to adopt a cautious waiting approach. However, every action taken after testing, such as the cautious observation approach, should be guided by a protocol and supported by empirical evidence [26]. Among the included studies, the imaging results were reviewed as the only predictor without considering other factors. For example, the prognostic abilities of other tests, such as WBC counts, CRP levels, and ESR tests, have not been systematically assessed. Hence, future studies in this perspective should ideally be set in environments with standardized pre- and post-imaging management perspectives, inclusive of preventive treatments [26].

[18F]FDG PET/CT for establishing the probable causes of FUO

[18F]FDG PET/CT in infectious diseases

In the last 10 years, the utilization of [18F]FDG PET/CT has increased to detect septic infections and sterile inflammatory conditions and enhance the precision of therapeutic management. Although MRI remains the preferred method for detecting spine infections due to its high sensitivity, [18F]FDG PET/CT could be useful in these conditions, particularly during the earlier stages. It is especially considered when there is some contraindication to MRI. It has a high sensitivity for paravertebral and psoas abscesses and is highly recommended in these contexts as it helps to detect early, prevents irreversible complications of spine infections, and evaluates response to treatment in both conditions [17].

[18F]FDG PET/CT has been recommended in tuberculosis for evaluating inflammatory activity, diagnosing extrapulmonary pathologies, and evaluating the response to treatment [21]. A patient experiencing FUO for four months had an [18F]FDG PET/CT, which detected unusual & variable [18F]FDG activity in the renal cortex bilaterally. A urine GeneXpert test was conducted, which identified the presence of mycobacterium tuberculosis [27]. In prospective research conducted in China, [18F]FDG PET/CT was used to diagnose FUO patients, revealing that infections were the predominant diagnosis among these cases, and tuberculosis was identified as the most frequent infectious cause [28]. [18F]FDG PET/CT scans are highly effective in showing the progression and the response to treatment in patients with HIV and fungal infections. Moreover, it is advantageous for detecting infections early and determining the exact location of the lesion [21].

[18F]FDG PET/CT was done on a subject with the aim of therapeutic control of liver metastases of colorectal cancer. However, the scan suggested a lung abnormality not related to cancer metastases. The patient then developed a fever and was admitted to the hospital with a positive RT-PCR for COVID-19, increased CRP, lymphocytopenia, and leukopenia. This shows the potential application of [18F]FDG PET/CT for monitoring the progression of lung disease and early detection of COVID-19. While [18F]FDG PET/CT may have potential uses in the context of COVID-19, currently, it is not approved/recommended for routine testing for COVID-19 due to the risk of spreading the virus [29].

[18F]FDG PET/CT is becoming popular as a sensitive but nonspecific method for identifying infections in cardiac implantable electronic devices (CIED). Research involving 30 patients, ten as controls suspected of having a CIED infection, revealed a 90% sensitivity and 73% specificity rate in diagnosing CIED infections, particularly for devices implanted remotely. Elevated [18F]FDG uptake was noted in patients who had undergone CIED placement or intervention eight weeks before and who showed clinical signs of infection, such as erythema, pain, and possible endocarditis. Furthermore, it was also able to show increased lead uptake in an individual with FUO without any symptoms in the CIED area, as seen in **Figure 2**. Later, the removed device culture yielded Staphylococcus epidermidis [30].

[18F]FDG PET/CT in inflammatory diseases

Among the four most common causes of FUO are noninfective inflammatory conditions that could also be diagnosed with [18F]FDG PET/CT (**Figure 3**) [14]. As metabolic changes typically precede morphologic changes in inflammatory diseases, [18F]FDG PET/CT should have the potential benefits of detecting involved vascular regions at an earlier stage than with other diagnostic modalities [31].

In 2017, Schönau et al. studied 240 patients, 72 with FUO and remaining with infection of unknown origin (IUO) or who had or were treated for FUO/IUO [32]. [18F]FDG PET/CT established a diagnosis in 56.7% of cases. Furthermore, among those who received a definitive diagnosis, the primary conditions identified were vasculitis of large vessels in 21.1%, polymyalgia rheumatica in 18.3%, and
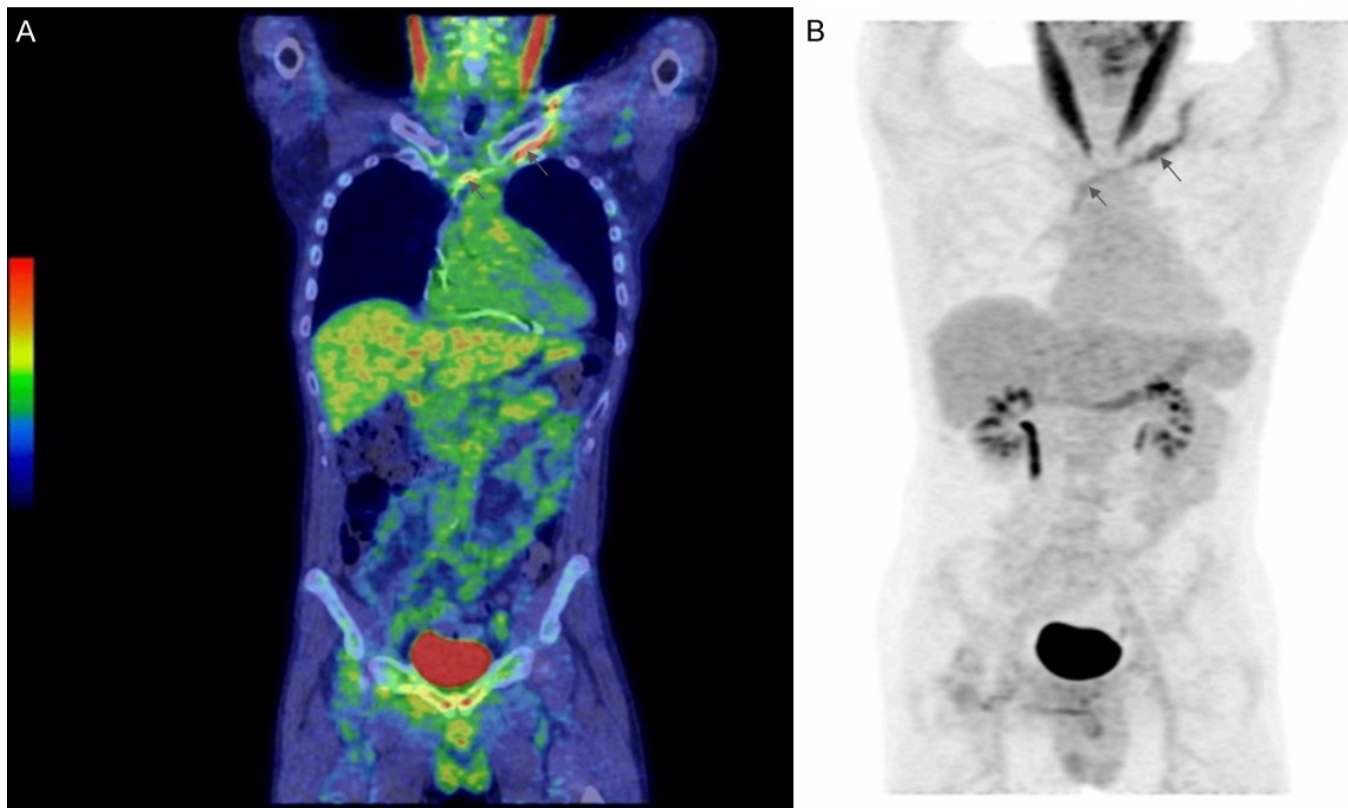
Figure 2. [18F]FDG PET/CT image of a patient with cardiac implantable electronic device infection (CIED). Patient with FUO and no symptoms in the CIED area. His generator had been changed one and a half years ago. Increased uptake in the lead was shown by [18F] FDG PET/CT with an SUVmax of 5.2 (A and B). Staphylococcus epidermidis was isolated later in a removed CIED system (modified with permission from reference [30]).

adult-onset Still's disease in 15.3% [32]. Similarly, [18F]FDG PET/CT can diagnose vasculitis of medium vessels, such as vasculo-Behcet's disease [33].

In detecting signs of large vessel vasculitis (LVV) in untreated patients with high levels of inflammation markers, [18F]FDG PET/CT had a sensitivity of 77-92% and a specificity of 89-100% [34]. While [18F]FDG PET/CT demonstrated 90% sensitivity and 98% specificity in identifying giant cell arteritis (GCA), it does not prove to be particularly valuable in monitoring the progression of vasculitis [21]. Moreover, its usefulness in GCA remains limited if temporal arteries are involved due to its relatively small size and concealed location [34]. Still, [18F]FDG PET/CT is a valuable method to detect increased tracer uptake in the aorta and major proximal branches, which are commonly affected by giant cell arteritis in as many as 45% of patients [35]. However, even in patients with normal vessels in CECT, PET/CT was diagnostic by showing abnormal [18F]FDG uptake in the aorta and the large vessels [31]. [18F]FDG PET/CT is also notably useful for delineating the extent and monitoring disease activity in patients with active Takayasu arteritis, with a sensitivity of 87-93% and a specificity of 73%-92% [34, 36].

Similarly, a case report by Furuya et al. highlighted the benefits of using [18F]FDG PET/CT for early detection of medium-vessel vasculitis in patients with Behçet's dis-

ease patients [33]. The report described a 22-year-old woman patient who had symptoms such as fever, pain in the right foot, a deformity in the left foot, and numbness in her extremities after a recent diagnosis of tonsillitis. She tested positive for HLA B51 and the pathergy test and had elevated CRP levels. An MRI identified swelling in the muscles of her left leg, and [18F]FDG PET/CT showed pronounced [18F]FDG uptake in the left popliteal artery, which was indicative of active vasculitis. These findings led to the diagnosis of vasculo-Behçet's disease. The patient was treated with corticosteroids, colchicine, and infliximab, which markedly improved the MRI results and decreased CRP levels [33].

Relapsing polychondritis, although rare, is another inflammatory condition that can present with FUO. Liu et al. published a case report of a 54-year-old male patient who had been experiencing moderate to severe fever for three months. [18F]FDG PET/CT revealed intense symmetric [18F]FDG uptake in cartilages of the larynx, trachea, and bronchia, in addition to lymph nodes of the hilum, mediastinum, and axilla, eventually leading to the diagnosis of relapsing polychondritis [37].

[18F]FDG PET/CT in malignancies

Other common causes of FUO include malignancies. Among the malignancies presenting with FUO, [18F]FDG
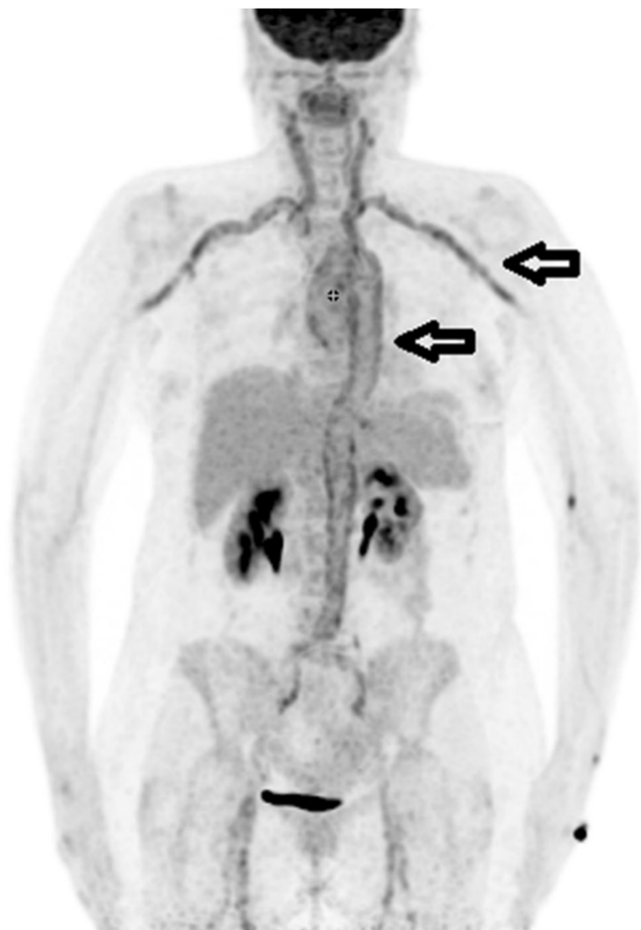
Figure 3. [18F]FDG PET/CT image of a patient with giant cell arteritis. A 68-year-old female patient who met the FUO criteria underwent [18F]FDG PET/CT. Although the patient had only a few clinical signs of vasculitis, the aorta and other major vessels exhibited longitudinal uptake in [18F]FDG PET/CT imaging (indicated by arrows), which is pathognomonic for giant cell arteritis. The patient responded effectively to the anti-inflammatory therapy with oral cortisone (with permission from reference [14]).

PET/CT is most useful in detecting lymphomas [38]. [18F]FDG PET/CT is now an essential tool for staging and PET-guided therapies for the management of lymphoma [38].

Suzuki et al. conducted a study among 50 patients with difficult-to-diagnose FUO who were evaluated with [18F]FDG PET/CT. Eighteen of 50 had malignancy; 6 of 18 had a known history of cancer and the diagnosis was unknown in the remaining cases. For patients who had positive [18F]FDG PET/CT findings suggestive of malignancy, the type of malignancy was determined by biopsy and histopathological evaluation, in addition to clinical information. [18F]FDG PET/CT localized malignancy in 17 of the 18 (94%) patients, identifying cases of lymphoma (9/9), colorectal carcinoma (3/3), chronic lymphocytic leukemia (1/1), testicular tumor (1/1), metastatic uterine cancer (1/1), Castleman's disease (1/1), and pseudomyxoma peritonei (1/1). However, it was unable to locate a case of lymphoma (peripheral T cell type) [39]. Similarly, another study evaluated 47 patients, in which a definitive diagno-

sis was reached in 25 patients (53.2%) and remained undiagnosed in 22 (46.8%) [31]. Among the patients who received a definitive diagnosis, 5 (10.6%) were diagnosed with malignant neoplasms, including 4 cases of lymphoma and one prostate carcinoma [31]. Thus, [18F]FDG PET/CT can diagnose various kinds of malignancies that can manifest with FUO.

[18F]FDG PET/CT has other advantages in FUO evaluation with respect to reducing the cost and duration of hospital stay. A Spanish study on 20 patients concluded that if [18F]FDG PET/CT was done relatively earlier during FUO work-up, £5471 could have been saved for each patient, along with fewer days of hospital admission [31]. These benefits are primarily due to the avoidance of unnecessary and costly invasive procedures and shortening the length of hospital stays [17, 20, 32]. However, the limited availability of PET/CT in many centers has contributed to the inability to incorporate PET/CT in FUO algorithms [31].

[18F]FDG PET/CT in other causes of FUO

Miscellaneous causes of FUO include cirrhosis, drug fever, thyroiditis, pulmonary emboli, Crohn's disease, and familial periodic fever syndrome, to name a few [40]. A recently published article indicated that miscellaneous causes comprise 2-14% of all causes of FUO and showed that thyroiditis, histiocytosis, Crohn's disease, and macrophage activation syndrome are the most common miscellaneous causes of FUO [5]. There are limited studies related to the application of [18F]FDG PET/CT for detecting miscellaneous causes of FUO.

[18F]FDG PET/CT to identify causes of FUO in the pediatric population

Currently, the overall efficacy of [18F]FDG PET/CT for diagnosing pediatric FUO is unclear. This is mainly due to the limited number of research conducted to explore the utility of [18F]FDG PET/CT in diagnosing the causes of FUO in children [41]. The definition, causes, and assessment of FUO vary between adult and pediatric patients [41], and the results achieved from the application of [18F]FDG PET/CT for assessing FUO in adults may not be extrapolated to children [42-44]. Although there is a clear definition of FUO for adults, a consensus is lacking for children. The range of diseases that cause FUO in children varies significantly with age and is classified into three primary age groups: newborns-1 month, 1-3 months, and 3 months-3 years [45]. Using [18F]FDG PET/CT for the assessment of FUO in children has advantages and limitations. Young children's inability to effectively communicate with healthcare professionals means that objective data from [18F]FDG PET/CT images can provide more insight into children's diagnoses than adults [41]. However, the higher sensitivity of children to radiation is a significant concern [41]. The initial analysis of eight journal articles and 3 abstracts related to the utilization of [18F]FDG PET/CT in

pediatric FUO suggested that abnormal PET results could lead to a more conclusive diagnosis among children compared to adults [41]. However, the studies analyzed had small sample sizes, a lack of comparative data, and retrospective study designs. Therefore, the authors suggested that more evidence should be collected from prospective studies with a large sample before drawing a conclusion [41]. In summary, while the application of [18F]FDG PET/CT for evaluating FUO among adults is well recognized, its use in children should be approached with caution due to differences in the definition, causes, evaluation method, and risk of radiation exposure between the two groups [41].

Multiple other research has established the valuable effects of [18F]FDG PET/CT in pediatric FUO [38, 46, 47]. A study done on 110 children found [18F]FDG PET/CT could determine underlying etiologies of FUO among 50% of them. Among the identified causes, endocarditis (5%), inflammatory bowel disease (5%), and juvenile systemic arthritis (5%) were found to be common etiologies. The same study reported an 85.5% sensitivity and 79.2% specificity for [18F]FDG PET/CT [46]. In another study, [18F]FDG PET/CT helped to conclude diagnosis in 85% of cases with suspected infection or inflammation (**Figure 4**) [48]. When it comes to evaluating children with FUO during immunosuppression, [18F]FDG PET/CT helped to diagnose 75% of them with 78% sensitivity and 67% specificity, respectively [38]. Similarly, another study conducted among immunocompromised children with fever showed that [18F]FDG PET/CT has a large impact clinically (79%) [47]. Moreover, it also played a crucial role in diagnosing suspected metastatic infections in pediatric patients [47].

Another meta-analysis, including six studies, examined [18F]FDG PET scans in children to assess the probability of reaching a definitive diagnosis by comparing abnormal with normal scan results, using the pattern of [18F]FDG uptake (where an abnormal PET image is characterized by unusual [18F]FDG accumulation in the targeted area) as a criterion [49]. The study revealed that children with abnormal PET scan results had approximately 17 times higher chance of obtaining a conclusive diagnosis compared to children with normal PET scan results [49]. Differences in sample size, causes of FUO, imaging technique, geographical distribution, and follow-up duration did not affect the results.

The probability of obtaining a conclusive diagnosis with an abnormal [18F]FDG PET scan is notably higher for children, with an odds ratio of 17, than for adults, who have an odds ratio of 8.9. Considering that the incidence of abnormal PET scans is almost the same for both children (58%) and adults (63%), and the proportion of cases where a diagnosis is not reached is similar (38% in children and 35% in adults), these figures imply, abnormal PET scans can lead to a higher outcome in identification of the etiology of fever in children compared to adults. The probability of obtaining a conclusive diagnosis with an abnormal [18F] FDG PET scan is notably higher for children, with an odds ratio of 17, than for adults, who have an odds ratio of 8.9 [25]. Considering that the incidence of abnormal PET scans is almost the same for both children (58%) and adults (63%), and the proportion of cases where a diagnosis is not reached is similar (38% in children and 35% in adults), these figures imply that abnormal PET scans could be more successful in identifying the cause of fever in children compared to adults [49]. This study also highlighted the fact that although negative [18F]FDG PET findings are usually considered non-contributory to the diagnosis of FUO, they can help rule out some of the differential diagnoses [49]. The observed instances of negative [18F]FDG PET outcomes may be attributable to etiologies that remain undetectable through [18F]FDG PET, for example, urinary tract infections, familial Mediterranean fever, Kawasaki arteritis, and drug-induced fever [46, 50].

In the above meta-analysis, Li et al. decided against computing sensitivity and specificity, citing the inaccessibility of a consistent reference standard for diagnosing FUO. In response to this, Lo et al. published a letter to the editor enforcing that the calculation of specificity and sensitivity remains valuable despite the absence of a perfect reference standard [51]. These measures help to understand the frequency of reaching a definitive diagnosis despite a normal [18F]FDG PET (false negatives) and the instances where an abnormal [18F]FDG PET might not identify the cause of fever (false positives) [51]. Lo et al. pointed out that only computing the odds ratio will not adequately address the concern related to the "lack of reference standard" [51]. Lo et al. filled the gap by calculating sensitivity, specificity, and summary ROC (SROC) curves for [18F]FDG PET [51]. Besides performing a diagnostic odds ratio meta-analysis similar to that of Li et al., they conducted a separate subgroup analysis on [18F]FDG PET/CT because of a scarcity of studies focused solely on [18F] FDG PET. In their meta-analysis, [18F]FDG PET - irrespective of combined with CT or not, had a sensitivity of 83.03% and a specificity of 77.60% [51]. A subgroup analysis focusing only on [18F]FDG PET/CT showed similar results. They found no evidence of variation between the studies, indicating consistent results across the board. The SROC curve further emphasized these findings [51].

Conclusion

[18F]FDG PET/CT has demonstrated encouraging results in diagnosing infectious, inflammatory, and neoplastic etiologies of FUO. During the past decade, studies have validated [18F]FDG PET/CT as a sensitive & effective diagnostic technique for FUO. This modality provides both cellular metabolic information and anatomical details, leading to a higher diagnostic yield than conventional FUO diagnostic methods. [18F]FDG PET/CT is crucial to detecting and localizing lesions and monitoring and evaluating treatment response. When utilized appropriately, [18F]FDG
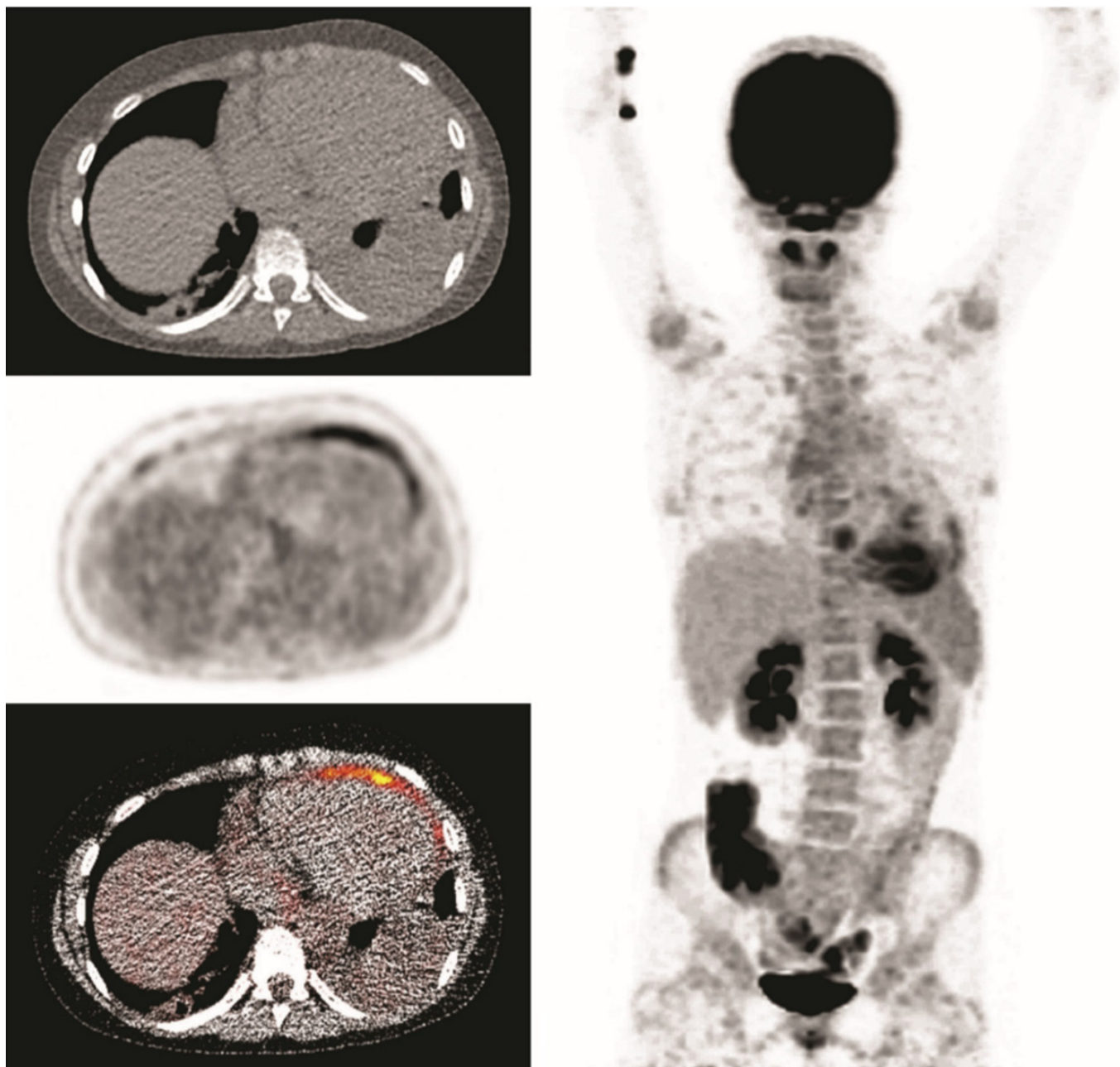
Figure 4. [18F]FDG PET/CT image of a patient with pericarditis. A 14-year-old female patient who had undergone a mitral valve annulo-plasty was admitted after experiencing a week-long fever and a maximal CRP of 290 mg/L. Endocarditis was suspected, but an accurate diagnosis could not be made by echocardiography. Hence, [18F]FDG PET/CT was performed, and it demonstrated pericardial [18F]FDG uptake, most obvious towards the anterior wall and apex, but no signs of endocarditis. Her symptoms subsided after receiving antibiotic treatment for six weeks, and microbiological tests remained negative. The fever returned later, and a second [18F]FDG PET/CT was done six weeks after the end of the antibiotic treatment, revealing similar pericardial uptake suggestive of persistent pericarditis. She success-fully responded to Colchicine, pointing to a non-infectious cause of pericarditis (with permission from reference [48]).

PET/CT can be cost-effective, minimize unnecessary inva-sive procedures, and reduce hospitalization time. How-ever, its use is limited by availability, the risk of radiation exposure, and cost considerations. Collaborative multi-centric studies are essential to potentially establish [18F] FDG PET/CT as a primary noninvasive modality for evalu-ating FUO. Thus, more research is required to fully inte-grate [18F]FDG PET/CT into the management algorithm of FUO.

Disclosure of conflict of interest

None.

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