Review

Role of 18F FDG-PET-CT in Fever and Inflammation of Unknown Origin

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Review

Role of 18F FDG-PET-CT in Fever and Inflammation of Unknown Origin

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Abstract

Fever of unknown origin (FUO) and inflammation of unknown origin (IUO) remain complex diagnostic challenges due to their heterogeneous presentations and broad differential diagnoses. FUO was first described by Petersdorf and Beeson in 1961 and later redefined by Durack and Street, while IUO was introduced more recently by Vanderschueren et al. in 2009. Despite thorough investigations, a significant proportion of patients remain without a clear diagnosis, often resulting in prolonged hospital stays and increased healthcare costs. In recent years, [^{18}F]FDG PET/CT has emerged as a valuable tool in the diagnostic workup of FUO and IUO, offering both metabolic and anatomical insights in a single scan. This review evaluates the diagnostic utility of [^{18}F]FDG PET/CT, based on an analysis of 55 studies encompassing 6681 patients. The scan was found to be clinically helpful in 59% of cases, with diagnostic contributions from both true-positive and true-negative findings. Negative scans were frequently associated with spontaneous symptom resolution and fewer unnecessary interventions. However, differences in study design and definitions of diagnostic value make it difficult to compare results across studies. Overall, [^{18}F]FDG PET/CT has proven to be a useful tool in the evaluation of FUO and IUO, and future research should focus on standardizing how its clinical benefit is measured and directly comparing its effectiveness with conventional imaging in well-designed prospective studies.

Keywords: infection; inflammation; FDG; PET/CT; FUO; IUO; fever of unknown origin; inflammation of unknown origin

1. Introduction

Fever of unknown origin (FUO) and inflammation of unknown origin (IUO) present significant diagnostic challenges in clinical practice.

FUO was first described by Drs. Petersdorf and Dr. Beesom in 1961 [1]; since then, the definition has undergone several revisions, with the latest widely accepted version proposed by Durack and Street in 1991, characterizing it as a fever of 101°F (38.3°C) or higher on more than 3 occasions, without a diagnosis despite 3 days of relevant inpatient workup or 3 outpatient visits [2].

IUO, on the other hand, has a more recent history, first described by Vanderschueren et al. in 2009, who outlined it as an illness lasting more than three weeks, during which the body temperature is ≤38.3°C on several occasions, the inflammatory markers are elevated (C-reactive protein (CRP) ≥ 30 mg/L or increase erythrocyte sedimentation rate), and for which no diagnosis could be established, despite minimal investigation, during at least three outpatient visits or 3 days of hospital investigation [3].

Despite thorough initial evaluations, many patients still remain undiagnosed, leading to prolonged workups, increased healthcare costs, and compromised outcomes.

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With a wide range of possible differential diagnoses, spanning from infectious to non-infectious diseases, from malignancies to miscellaneous disease, a systematic, multidisciplinary approach is essential to identify active disease early and to guide the right therapy.

In recent years, [^{18}F]FDG PET/CT has become a key tool in the diagnostic workup for FUO and IUO. Its use in everyday clinical settings—either as a first- or second-line modality—is getting increasingly common, particularly when conventional imaging fails to identify a cause. As set forth by the European Association of Nuclear Medicine (EANM), this imaging technique combines metabolic and anatomical information in a single scan, allowing for precise localization and characterization of pathological FDG uptake [4]. Moreover, recently published Delphi-generated consensus-based recommendations on FUO/IUO listed [^{18}F]FDG PET/CT in the strong consensus agreement as "an important diagnostic test (to perform) after a patient fulfills the FUO criteria with minimal diagnostic tests" and that "clinicians should consider earlier use of [^{18}F]FDG PET/CT, after plain radiography or CT, particularly in the absence of potential diagnostic clues" [5]. Recent studies, including work by Buchrits et al. [6], report a diagnostic contribution in over 75% of cases, highlighting its ability to both detect underlying disease and exclude focal pathology. As nuclear medicine advances, [^{18}F]FDG PET/CT is expected to further enhance diagnostic accuracy. Its integration into the diagnostic pathway helps optimize outcomes, reduce unnecessary interventions, and improve the overall management of patients with FUO and IUO.

This review aims to assess the role of [^{18}F]FDG PET/CT in the evaluation of FUO and IUO, as supported by current literature.

2. Methodology

A comprehensive search of existing literature was performed on PubMed and Cochrane library from 2001 up to May 2025, using the following search terms: (PET OR FDG OR fluorodeoxyglucose) AND (fever OR FUO OR PUO OR pyrexia OR inflammation OR IUO). We included prospective, retrospective and ambispective studies that examined the contribution of [^{18}F]FDG PET/CT to the investigation of "fever of unknown origin" as defined by Durack [2] and of "inflammation of unknown origin" as defined by Vanderschueren" [3]. The complete PubMed search string is presented in **Table 1** [7-61].

We excluded studies that assessed the contribution of [^{18}F]FDG PET alone without the component of CT and studies that assessed [^{18}F]FDG PET associated with MRI.

The primary goal was to assess the clinical helpfulness of [^{18}F]FDG PET/CT to the final diagnosis of fever of unknown origin or inflammation of unknown origin, which was defined, depending on the study, as True Positive or as True Positive summed to the True Negative (as reported in **Table 1**). We also reported, when available or possible to extract from known data, sensitivity and specificity, positive predictive value and negative predictive value of [^{18}F]FDG PET/CT, as shown in **Table 2** [7-61].

Table 1. Characteristics of included studies.

First author	Year	Patients n.	Population	Study type	Final diagnosis
Jaruskova[7]	2006	94	FUO	R	NR
Bleeker-Rovers[8]	2006	70	FUO	P	0.50
Keidar[9]	2008	48	FUO	P	0.60
Balink[10]	2009	68	FUO	R	0.65
Federici[11]	2010	14	FUO/IUO	R	0.71
Ferda[12]	2010	48	FUO	R	0.92
Kei[13]	2010	12	FUO	R	0.58
Ergül[14]	2011	24	FUO	R	0.54
Kubota[15]	2011	81	FUO	R	0.75
Pelosi[16]	2011	24	FUO	R	0.71

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Sheng[17]	2011	48	FUO	R	0.75
Rosenbaum[18]	2011	24	FUO	R	1.00
Becerra Nakayo[19]	2012	20	FUO	R	NR
Crouzet[20]	2012	79	FUO	R	0.77
Kim[21]	2012	48	FUO	R	0.85
Pedersen[22]	2012	22	FUO	R	0.60
Manohar[23]	2013	103	FUO	R	0.67
Balink[24]	2014	140	IUO	R	0.74
Buch-Olsen[25]	2014	57	FUO	R	0.91
Tokmak[26]	2014	25	FUO	R	0.92
Balink[27]	2015	498	FUO/IUO	R	0.66
Gafter-Gvili[28]	2015	112	FUO	R	0.74
Singh[29]	2015	47	FUO	P	0.53
Bouter[30]	2016	72	FUO/IUO	R	0.83
Pereira[31]	2016	76	FUO	R	0.93
Hung[32]	2017	58	FUO	P	0.79
Abdelrahman[33]	2018	27	FUO	P	0.92
Garcia-Vicente[34]	2018	67	FUO	R	0.88
Schönau[35]	2018	240	FUO/IUO	P	0.79
Wang[36]	2019	376	FUO/IUO	R	0.91
Wang[37]	2020	147	FUO/IUO	P	0.88
Georga[38]	2020	50	FUO	R	0.78
Zhu[39]	2020	89	FUO/IUO	R	0.74
Kubota[40]	2021	128	FUO	P	0.72
Letertre[41]	2021	44	FUO	R	0.70
MuldersManders[42]	2021	104	FUO/IUO	R	0.65
Bilici Salman[43]	2021	97	IUO	R	0.90
Mahajna[44]	2021	128	FUO	R	0.74
Das[45]	2021	43	FUO	R	0.74
Yadav[46]	2021	51	FUO	P	0.88
Buchritis[47]	2021	303	FUO	R	0.72
Chen[48]	2022	524	FUO	P	0.91
Chen[49]	2022	326	FUO/IUO	R	0.91
Holubar[50]	2022	317	IUO	R	0.72
Ogut[51]	2022	58	FUO/IUO	R	0.90
Ly[52]	2022	103	FUO/IUO	P	0.56
Weitzer[53]	2022	300	FUO/IUO	R	0.84
Becker KK[54]	2024	77	FUO/IUO	R	1.00
Fathala[55]	2024	105	FUO	R	1.00
Khan[56]	2024	573	FUO	A	0.38
Liu[57]	2024	40	FUO	R	1.00
Kobayashi[58]	2024	45	FUO/IUO	R	0.71
Koreli[59]	2025	30	FUO/IUO	R	0.50
Yu[60]	2025	284	FUO	R	0.69
Greuez[61]	2025	93	FUO/IUO	R	0.59

*FUO: fever of unknown origin; IUO: inflammation of unknown origin; R: retrospective; P: prospective; A: ambispective; NR: not reported.

Table 2. FDG PET-CT contributory results in examined studies.

First author	Clinical Helpfulness	Sensitivity	Specificity	PPV	NPV
Jaruskova[7]	0.36	NR	NR	NR	NR
Bleeker-Rovers[8]	0.33 (TP)	0.88	0.77	0.70	0.92
Keidar[9]	0.90 (TP+TN)	1.00	0.81	0.81	1.00

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Balink[10]	0.56 (TP)	1.00	0.90	0.93	1.00
Federici[11]	0.50 (TP)	0.70	0.75	0.88	0.5
Ferda[12]	0.77	0.97	0.75	NR	NR
Kei[13]	0.42 (TP)	NR	NR	NR	NR
Ergül[14]	0.63	0.92	0.45	0.63	1.0
Kubota[15]	0.54	0.81	0.75	NR	NR
Pelosi[16]	0.87 (TP+TN)	0.50	0.50	0.85	0.85
Sheng[17]	0.67	0.89	0.33	0.80	0.50
Rosenbaum[18]	1.00 (TP+TN)	NR	NR	NR	NR
Becerra Nakayo[19]	0.55 (TP)	0.78	0.83	0.92	0.62
Crouzet[20]	0.19	0.98	0.87	NR	NR
Kim[21]	0.56	0.92	0.23	NR	NR
Pedersen[22]	0.83	0.67	0.71	0.83	0.50
Manohar[23]	0.60	0.90	0.97	0.98	0.83
Balink[24]	0.51	0.94	0.83	0.93	0.77
Buch-Olsen[25]	0.75 (TP+TN)	NR	NR	NR	NR
Tokmak[26]	0.60 (TP)	0.94	0.80	NR	NR
Balink[27]	0.59 (TP)	0.89	0.89	0.94	0.80
Gafter-Gvili[28]	0.66	0.72	0.58	0.74	0.54
Singh[29]	0.38 (TP)	NR	NR	NR	NR
Bouter[30]	0.65 (TP)	0.81	0.86	NR	NR
Pereira[31]	0.61	0.77	0.31	0.61	0.50
Hung[32]	0.72	0.79	0.56	0.83	0.50
Abdelrahman[33]	0.85 (TP)	0.95	0.67	0.96	0.67
Garcia-Vicente[34]	0.52	0.84	0.31	NR	NR
Schönau[35]	0.57 (TP)	0.91	0.22	0.65	0.62
Wang[36]	0.90	NR	NR	NR	NR
Wang[37]	0.58	0.88	0.15	0.59	0.47
Georga[38]	0.72 (TP)	0.94	0.50	0.86	0.75
Zhu[39]	0.74 (TP+TN)	0.84	0.26	NR	NR
Kubota[40]	0.33 (TP)	0.45	0.40	0.67	NR
Letertre[41]	0.44	0.85	0.37	0.58	0.70
MuldersManders[42]	0.45	NR	NR	NR	NR
Bilici Salman[43]	0.61 (TP)	0.67	1.00	1.00	0.26
Mahajna[44]	0.48 (TP)	0.70	0.37	0.70	0.34
Das[45]	0.91 (TP+TN)	0.77	0.33	0.83	0.25
Yadav[46]	0.63	NR	NR	NR	NR
Buchritis[47]	0.26	0.89	0.81	NR	NR
Chen[48]	0.91	NR	NR	NR	NR
Chen[49]	0.96	NR	NR	NR	NR
Holubar[50]	0.75 (TP+TN)	0.84	0.62	0.77	0.72
Ogut[51]	0.72 (TP+TN)	0.88	0,37	0.79	0,55
Ly[52]	0.19 (TP)	0.36	0.81	NR	NR
Weitzer[53]	0.54 (TP)	0.80	0.90	NR	NR
Becker KK[54]	0.61 (TP+TN)	NR	NR	NR	NR
Fathala[55]	0.72 (TP+TN)	0.72	0.29	0.68	0.33
Khan[56]	0.16 (TP)	NR	NR	NR	NR
Liu[57]	0.98	0.93	0.62	0.83	0.80
Kobayashi[58]	0.64	0.91	0.38	0.78	0.62
Koreli[59]	0.50 (TP)	1.00	0.33	0.60	1.00
Yu[60]	0.48	0.79	0.61	0.76	0.63
Greuez[61]	0.31	NR	NR	NR	NR

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* PPV: positive predictive value; NPV: negative predictive value; TP: true positive; TN: true negative; NR: not reported.

3. Results

The literature search yielded 605 potentially pertinent publications. Among them, 549 articles were found to be unrelated to the subject or were the wrong study type. Ultimately, we included 55 studies, with a total of 6681 patients. We listed in **Table 1** the general features of each study: this review included mostly retrospective studies (78%), a few prospective studies (20%) and only 1 ambispective study. Of these, 36 studies focused on patients presenting with fever of unknown origin, 3 studies examined patients with inflammation of unknown origin, and 16 studies comprised both these populations. **Table 2** describes the main findings of the considered studies. Fifty-three studies out of the total fifty-five analysed reported the number of patients who received a final diagnosis: out of 6567 patients for whom the study reported a final diagnosis, the underlying cause of FUO or IUO was identified in 4917 of them (75%); in most of the remaining cases fever resolved spontaneously.

A precise definition for clinical helpfulness of [^{18}F]FDG PET/CT was not always reported in the analysed studies: it was specified, as a matter of fact, in only twenty-nine studies (53%). Among these twenty-nine studies, in nineteen works (65%) the diagnostic contribution of [^{18}F]FDG PET/CT scan was delineated as impactful exclusively when abnormal uptake was localized to a specific organ or tissue, and subsequent specific conventional diagnostic modalities confirmed a definitive diagnosis (true positive scans, TP). Ten studies defined [^{18}F]FDG PET/CT as a "valuable" test when the imaging either provided information that directly led to the final diagnosis (TP) or when it showed no focal FDG uptake (true negative, TN), consistent with the absence of disease in the final diagnosis.

Overall, [^{18}F]FDG PET/CT was found to be contributory to the diagnostic workup in 59% of all examined cases (it was considered as clinically helpful in a total of 3919 patients over the 6681 observed).

3. Discussion

The diagnostic evaluation of patients with FUO or IUO presents significant methodological challenges due to the heterogeneity of potential etiologies, the absence of universally accepted reference standards, and the considerable proportion of patients who remain without a definitive diagnosis. Timely and accurate diagnosis significantly influences the therapeutic approach in patients with FUO. Early identification of the underlying etiology can lead to the initiation of appropriate treatment, adjustment of ongoing therapies, or a complete change in the therapeutic regimen. Moreover, a precise diagnosis can guide targeted diagnostic interventions, both invasive and noninvasive—such as biopsy, drainage procedures, serological testing, and cultures of blood, urine, or tissues—with potential implications for cost-effectiveness and clinical efficiency [10]. [18F]FDG PET/CT plays a crucial role in the diagnostic work-up of FUO by directing the clinician toward the most suitable and accessible biopsy site, thereby facilitating histological confirmation of the underlying disease. Additionally, [18F]FDG PET/CT contributes indirectly by helping to rule out numerous potential causes, effectively narrowing the differential diagnosis [38].

Most existing studies only take in consideration [^{18}F]FDG PET/CT as a useful tool when it directly correlates to the final diagnosis (true positive), while true negative studies are often underreported, despite their relevance in excluding significant pathology, predicting spontaneous clinical resolution, and potentially reducing unnecessary diagnostic procedures [9, 16, 34, 24, 40, 62]. Moreover, negative PET/CT scans have been significantly associated with spontaneous remission [63]. While true-positive (TP) findings are essential for establishing a definitive diagnosis, true-negative (TN) results are equally valuable in excluding potential causes. In the context of FUO and IUO, previous studies have reported that the absence of pathological [^{18}F]FDG PET/CT uptake on PET/CT is frequently associated with spontaneous resolution [28, 62]. This finding has important clinical implications, as supported by Takeuchi et al.'s recent meta-analysis [63], demonstrating that patients with negative PET-CT results are significantly more likely to experience spontaneous resolution of symptoms compared to those with positive findings. These results emphasize the utility of a negative PET-CT not only as a diagnostic exclusion tool but also as a means to guide clinical

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management. Specifically, it may help avoid unnecessary invasive diagnostic procedures and limit the use of potentially inappropriate treatments, such as empirical antibiotic therapy [64].

However, a substantial proportion of FUO/IUO patients—ranging from 7% to 62% in the studies taken into consideration in our literature search—remained undiagnosed after [^{18}F]FDG PET/CT. In light of these limitations, the more general concept of "clinical helpfulness"—defined as the proportion of scans that inform subsequent clinical decision-making—offers a more comprehensive assessment of [^{18}F]FDG PET/CT's value in this population with respect to more classical parameters like specificity and sensitivity [65-67]. The analysed studies reported an overall clinical helpfulness ranging from 16% to 100% (with a mean value of 60%), with higher values observed when both true-positive and true-negative results were considered: indeed, studies that counted PET/CT scans as helpful when they showed either true positive or true negative results reported an overall usefulness of 61% to 100%. In contrast, studies that only considered true positive results showed a usefulness ranging from 16% to 85%.

A sizable prospective study [48] by Chen's group, that examined 524 patients over the course of 5 years, found [^{18}F]FDG PET/CT to be positive in 91% of patients (477/524; diffuse or focal high uptake of FDG in various organs and tissues), and the model demonstrated excellent discrimination for infection (AUC = 0.88), malignancy (AUC = 0.93), and NIID (AUC = 0.95). Notably, several studies included in this analysis only unacknowledged focal uptake as impactful, while excluding other "nonspecific" uptake from consideration (such as diffuse uptake in the spleen, bone marrow, or symmetrical lymphadenopathy) [9, 14, 28, 35-36].

In conclusion, while the accuracy of [^{18}F]FDG PET/CT in evaluating FUO/IUO can be affected by a range of factors—including patient complexity, definitions of FUO/IUO, timing, and variability in reference standards—most studies agree that it often provides useful information for clinical decision-making. A positive scan can be key to making a diagnosis, and sometimes it's even essential. Positive scans frequently contribute to, and occasionally are indispensable for, establishing a diagnosis. Conversely, negative scans can rule out focal disease and are associated with a high likelihood of spontaneous remission, thus serving as valuable prognostic tools. Moving forward, well-designed prospective studies are needed to further refine its diagnostic role in FUO/IUO workup.

4. Conclusions and future Directions

FUO and IUO continue to present significant diagnostic challenges due to the heterogeneity of clinical presentations, a wide range of potential underlying etiologies, and the lack of a standardized diagnostic approach. The existing literature mirrors this complexity, making it challenging to compare or combine study results. [^{18}F]FDG PET/CT has shown a valuable role in this setting, with positive scans often helping to establish a diagnosis, while negative scans may also be clinically relevant by excluding localized disease and suggesting a better prognosis. For future research, the contribution of PET/CT should be defined as the sum of true positives and true negatives to improve accuracy and consistency. Additional studies, especially randomized controlled trials comparing PET/CT to conventional CT, are needed to determine the most effective first-line imaging modality in the evaluation of FUO/IUO.

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Abbreviations

The following abbreviations are used in this manuscript:

FUO	Fever of unknown origin

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IUO	Inflammation of unknown origin
FDG	Fluorodeoxyglucose
PET-CT	Positron emission tomography/computed tomography
PPV	positive predictive value
NPV	negative predictive value
NR	not reported
TP	True Positive
TN	True Negative
R	Retrospective
P	Prospective
A	Ambispective

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