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Value of Positron Emission Tomography Coupled With Computed Tomography for the Diagnosis of Inflammatory Syndrome of Unknown Origin in an Internal Medicine Department

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Abstract

Objective: To evaluate the usefulness of positron emission tomography (PET) coupled with computed tomography (CT) in the diagnostic workup for inflammatory syndrome of undetermined origin (IUO) and to determine the diagnostic delay in an internal medicine department.

Patients and methods: We retrospectively studied a cohort of patients for whom a PET/CT scan had been prescribed in an indication of IUO in an internal medicine department (Amiens University Medical Center, Amiens, France) between October 2004 and April 2017. The patients were grouped according to the PET/CT findings: very useful (enabling an immediate diagnosis), useful, not useful, and misleading.

Results: We analyzed 144 patients. The median (interquartile range) age was 67.7 years (55.8-75.8 years). The final diagnosis was an infectious disease in 19 patients (13.2%), cancer in 23 (16%), inflammatory disease in 48 (33%), and miscellaneous diseases in 12 (8.3%). No diagnosis was made in 29.2% of the cases; half of the remaining had a spontaneously favorable outcome. Fever was observed in 63 patients (43%). Positron emission tomography coupled with CT was determined to be very useful in 19 patients (13.2%), useful in 37 (25.7%), not useful in 63 (43.7%), and misleading in 25 (17.4%). The median diagnostic delay (ie, the time interval between the first admission and a confirmed diagnosis) was significantly shorter in the useful (71 days [38-170 days]) and very useful (55 days [13-79 days]) groups than that in the not useful group (175 days [51-390 days]; P<.001). The median time interval between the PET/CT scan and the diagnosis was twice as long in the not useful group than that in the pooled misleading, useful, or very useful groups (P=.03). In a univariate analysis, the poor overall condition (P=.007) and the absence of fever (P=.005) were predictive of usefulness of PET/CT.

Conclusion: Positron emission tomography coupled with CT seems to be useful in the diagnosis of IUO and might shorten the diagnostic delay.

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The inflammatory syndrome of undetermined origin (IUO) is a frequent situation in the internal medicine departments, and many differential diagnoses must be considered. The management of cases of IUO is often complex, time-consuming, and nonstandardized.

The concept of fever of unexplained origin (FUO) was introduced by Petersdorf and Beeson[1] in 1961. Since then, several classifications for FUO have been published by experts and have been adapted to reflect the changes in practice and the expansion of ambulatory medicine.[2-5] Furthermore, de Kleijn et al,[3] followed by Vanderschueren et al,[6] specified IUO as a disease lasting more than 3 weeks, with the absence of fever (a temperature <38.3 °C), elevated blood levels of markers of systemic inflammation (C-reactive protein [CRP] of >30 mg/L or an accelerated sedimentation

rate) on at least 3 occasions, and no obvious explanation after a battery of investigations over 3 visits or 3 days in the hospital.

In routine clinical practice, it is common to prescribe positron emission tomography (PET) coupled with computed tomography (CT) when investigating FUO and IUO. According to the literature, the diagnostic contribution of PET/CT to FUO varies greatly from one study to another (from 16% of cases to 69%) (Table 1).[7-36] However, it must be borne in mind that the corresponding study populations, diagnostic criteria for FUO and/or IUO, and the regional or national prevalence of infectious disease also varied markedly.[37] Empirically, we considered that the diagnostic value of PET/CT appears to be ill-defined and overestimated.

The FUO study group considers that the diagnostic strategy for IUO is probably the same as for FUO.[38] However, there are few comparative studies of these 2 entities and limited published data on the diagnostic strategy for IUO (particularly on the effect of PET/CT on the diagnostic delay).

Therefore, the objective of this study (performed in the internal medicine department of a French university medical center) was to assess: (i) the diagnostic value of PET/CT in the workup for FUO and IUO and (ii) the technique's effect on the diagnostic delay (ie, the time interval between the admission to the internal medicine department and a confirmed diagnosis).

PATIENTS AND METHODS

We performed a retrospective cohort study in the Department of Internal Medicine at the Amiens University Medical Center (Amiens, France). First, all patients having undergone PET/CT (regardless of the indication) in the department between October 2004 and April 2017 were identified; the list of patients was obtained from the Department of Nuclear Medicine. The corresponding medical records were reviewed individually to check that patients met the inclusion criteria. Data were extracted from the medical records, using a predefined grid. The use and role of PET/CT in the diagnostic workup were left to the clinicians' discretion.

Inclusion Criteria

Patients were included if the PET/CT had been prescribed for the investigation of an IUO in the Department of Internal Medicine at the Amiens University Medical Center. The term IUO was used if the serum CRP level was more than 15 mg/L on 2 or more occasions at least 3 weeks apart, with or without fever (ie, meeting the criteria by de Kleijn et al[3]). Patients were not selected if the serum CRP level was less than 15 mg/L, if the inflammatory syndrome had a nosocomial cause, if chronic neutropenia was present (neutrophil count $<500/mm^3$) or if they had AIDS. Each patient's medical records were reviewed to confirm the origin of the IUO, that is, even after a thorough diagnostic workup that included clinical examinations, routine laboratory tests (including blood cultures, serology assessments for viral or bacterial pathogens, and screens for autoantibodies), and medical imaging (a chest X-ray and/or ultrasound of the abdomen).

Outcomes and Data Collected

The diagnostic value of PET/CT was determined by the investigator (XB) after the analysis of the patient electronic medical record. The results were grouped as follows:

- Very useful: the PET/CT scan found abnormal hypermetabolic zones and, when considered in isolation, prompted a diagnosis directly (eg, aortitis).
- Useful: the PET/CT scan found abnormal hypermetabolic zones but had to be combined with other findings (such as biopsies) before a diagnosis could be made.
- Not useful: the PET/CT scan did not find any abnormal hypermetabolic zones and did not contribute to the diagnosis.
- Misleading: the PET/CT scan found abnormal hypermetabolic zones, but these were misleading regarding the final diagnosis.

We recorded the patients' demographic characteristics (age, sex, and body mass index[kg/m^2]); clinical characteristics (eg, fever, weight loss, asthenia, and anorexia); laboratory results (eg, blood counts, CRP levels, liver function tests, and tumor markers); and imaging and other findings before the PET/CT scan

TABLE 1. The Usefulness of PET and PET/CT in the Diagnostic Workup for FUO or IUO in the Literature

Reference, year	Study design (number of patients)	Diagnostic criteria	Usefulness rate (%)	False-positive rate (%)
Meller et al,[7] 2000	Prospective (20)	Not specified	55	-
Blockmans et al,[8] 2001	Prospective (58)	Durack-Street	41	38
Lorenzen et al,[9] 2001	Retrospective (16)	Petersdorf-Beeson	69	6.2
Buysschaert et al,[10] 2004	Prospective (74)	Durack-Street	49	45
Kjaer et al,[11] 2004	Prospective (21)	Petersdorf-Beeson	16	37
Bleeker et al,[12] 2004	Retrospective (35)	Durack-Street	37	6
Bleeker et al,[13] 2007	Prospective (73)	de Kleijn et al	33	14
Keidar et al,[14] 2008	Prospective (48)	Durack-Street	46	10
Girard et al,[15] 2008	Retrospective (100)	Durack-Street	21	-
Balink et al,[16] 2009	Retrospective (68)	Petersdorf-Beeson	56	4.4
Ferda et al,[17] 2010	Retrospective (48)	de Kleijn et al	77	22
Sheng et al,[18] 2011	Retrospective (48)	de Kleijn et al	67	16
Pelosi et al,[19] 2011	Retrospective (24)	Durack-Street	46	25
Benesser Alaoui et al,[20] 2012	Retrospective (13)	Not specified	69	0
Crouzet et al,[21] 2012	Retrospective (79)	Durack-Street	57	2.5
Becerra Nakayo et al,[22] 2012	Retrospective (20)	de Kleijn et al	55	5
Manohar et al,[23] 2013	Retrospective (103)	Durack-Street	60	1.5
Reffad et al,[24] 2014	Retrospective (49)	Not specified	48	25
Tokmak et al,[25] 2014	Retrospective (50)	de Kleijn et al	60	28
Buch-Olsen et al,[26] 2014	Retrospective (57)	Not specified	53	21
Singh et al,[27] 2015	Retrospective (47)	Petersdorf-Beeson	38	36
Gafter-Gvili et al,[28] 2015	Retrospective (112)	Not specified	46	-
Pereira et al,[29] 2016	Retrospective (76)	Durack-Street	60	13
Hung et al,[30] 2017	Retrospective (58)	Petersdorf-Beeson	57	44
Schönau et al,[31]2017	Prospective (240)	Vanderschueren et al	56.7	30
Mulders-Manders et al,[32] 2019	Retrospective (104)	Not specified	21	-
Mahajna et al,[33] 2021	Retrospective (128)	Petersdorf-Beeson	48	20
Ly et al,[34] 2022	Prospective (103)	de Kleijn et al	28.2	8.7
Holubar et al,[35] 2022	Retrospective (317)	Not specified	49.8	15.1
Betrains et al,[36] 2023	Retrospective (439)	de Kleijn et al	25	31

FUO, fever of unknown origin; IUO, inflammatory syndrome of undetermined origin; PET/CT, positron emission tomography coupled with computed tomography.

(eg, a CT scan of the chest, abdomen, and pelvis; fibroscopy of the esophagus, stomach, and duodenum; colonoscopy; echocardiography; temporal artery biopsy; bone marrow biopsy; a dental X-ray; and examination of the sinuses).

Finally, we calculated the time interval between the admission to the internal medicine department and a confirmed diagnosis and the time interval between PET/CT and a confirmed diagnosis. We also assessed the diagnostic workup after the PET/CT (especially the invasive procedures).

The final diagnosis was determined by the investigator (XB) based on the patient's medical records (including follow-up data recorded after the PET/CT scan).

If a final diagnosis had not been made, the date of the last follow-up (according to the medical records) was used to calculate the diagnostic delay.

In line with the literature methods, we grouped the final diagnoses into 5 categories: infectious diseases, inflammatory diseases, cancer, miscellaneous diseases, and the persistent absence of a diagnosis.

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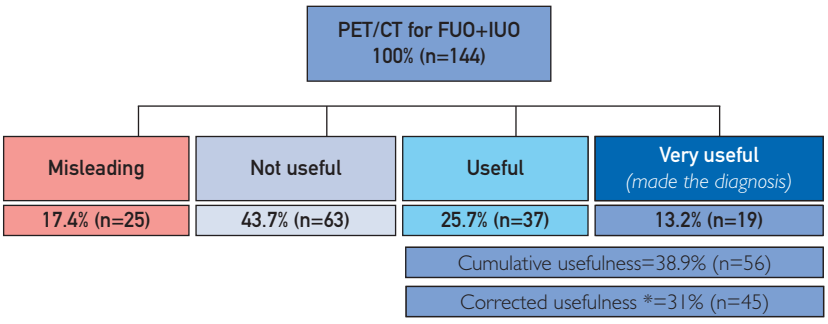

FIGURE. The usefulness of PET/CT at the end of follow-up, by all groups. FUO, fever of unknown origin; IUO, inflammatory syndrome of undetermined origin; PET/CT, positron emission tomography coupled with computed tomography.

The Protocol for PET/CT Imaging

To avoid a false-negative result, we checked whether the patient's capillary blood glucose level was less than 11 mmol/L. A 3-5 MBq/kg dose of 18F-fluorodeoxyglucose was administered, and the patient rested for 60 minutes. Afterward, a low-dose CT scan and PET images were acquired (from the base of the skull to the hip joints) on a Siemens Biograph 6 (Siemens Healthineers).

Statistical Analyses

Using a predefined grid, the study data were extracted from each set of medical records by the investigator and recorded in an EpiData database (version 3.1, EpiData Association). Statistical analyses were performed using the SAS software (version 9.4; SAS Institute Inc.). In a descriptive analysis, quantitative variables were expressed as the mean ± SD (when normally distributed) or as the median (interquartile range [IQR]), and qualitative variables were expressed as the frequency (percentage). Quantitative variables were compared using a Wilcoxon test, and qualitative variables were compared with a χ^2 test or (as appropriate) Fisher exact test. All tests were 2-sided. The threshold for statistical significance was set at $P<.05$. The sensitivity, specificity, positive predictive value, and negative predictive value of PET/CT were determined, along with the corresponding exact binomial CI. The study was conducted in compliance with the Declaration of Helsinki and the French legislation on retrospective studies of routine clinical practice. Furthermore, the study database was registered with the French National Data Protection Commission (Commission nationale de l'informatique et des libertés [Paris, France]; reference DRCI T172).

RESULTS

The Study Population

Between October 2004 and April 2017, 763 PET/CT scans were prescribed by clinicians in the internal medicine department and performed in the nuclear medicine department. Of the 763, 144 scans met the study's inclusion criteria. Most of the exclusions were owing to the prescription of PET/CT in an indication other than IUO.

The median (IQR) age of the study population was 67.7 years (55.8-75.8 years; range, 16-91 years). There were 82 men (56%) and 62 women (44%).

Fever was recorded in 63 patients (43%), weight loss in 55 (38%), asthenia in 59 (41%), and anorexia in 30 (21%). The median serum CRP level was 103 mg/L (46-152 mg/L; range, 15-683 mg/L). The CRP level was more than 20 mg/L in 96% of the patients.

The final diagnoses corresponded to an infectious disease in 19 patients (13.2%), cancer in 23 (16%), inflammatory disease in 48 (33%), and miscellaneous diseases (mostly thrombosis, overweight, and foreign bodies) in 12 patients (8.3%).

Forty-two patients (29.2%) did not receive a confirmed diagnosis. Twenty-one of the 42

TABLE 2. Usefulness of Imaging and Other Investigations Before PET/CT in the Study Population (n=144)

Imaging and other investigations	Number of prescriptions (percentage of patients included)	Number of findings in agreement with the final diagnosis (the usefulness rate, in %)	Median (IQR) times after admission
Tumor markers	64 (44.4)	4 (6.2)	-
CT of the chest, abdomen, and pelvis	117 (81.2)	36 (30.7)	7 (1-27.5)
Fibroscopy of the esophagus, stomach, and duodenum	44 (30.5)	7 (15.9)	-
Colonoscopy	42 (29.2)	9 (21.4)	-
Bone marrow biopsy	34 (23.6)	3 (8.8)	32 (13.5-71.5)
Echocardiography with negative blood cultures	62 (43)	5 (8)	-
Temporal artery biopsy	39 (27)	4 (10.2)	-
Dental X-ray	64 (44.4)	0 (0)	-

IQR, interquartile range; PET/CT, positron emission tomography coupled with computed tomography.

cases (50%) experienced a positive outcome after a median follow-up period of 45 days (12-191 days). In the other 21 cases, inflammation was still present after a median follow-up period of 150 days (14-384 days).

The Diagnostic Contribution of PET/CT

Positron emission tomography coupled with CT was very useful in 13.2% of the cases (n=19), useful in 25.7% (n=37), not useful in 43.7% (n=63), and misleading in 17.4% (n=25) (Figure). Overall, the median time interval between the first contact in our department and performance of the PET/CT scan was 34.5 days (17-85 days). The median (IQR) time interval was shorter in the pooled useful or very useful groups than that in the not useful group (26 days [13.5-64.5 days] vs 42.5 days [20-133 days]; P=.03). Furthermore, PET/CT had been more useful since 2010 (44.1%) than that between 2004 and 2010 (26.2%; P=.02).

When considering PET/CT for the diagnosis of IUO, we found a sensitivity of 68.63% (95% CI, 0.58-0.77), a specificity of 73.81% (95% CI, 0.57-0.86), a positive predictive value of 86.42% (95% CI, 0.77-0.93), and a negative predictive value of 50.79% (95% CI, 0.36-0.62).

The Diagnostic Necessity of PET/CT

To refine the usefulness of the PET/CT and determine whether the diagnosis could have been made without the PET findings (ie, with CT only), we reviewed the 37 sets of medical records from the useful group. The CT scan results were consistent with the final diagnosis in 14 of the 37 patients. Then, 2 internists independently reviewed these 14 cases and judged that the PET/CT was indisputably useful in only 3 cases (all of whom were diagnosed with cancer). In the other 11 cases, CT results alone would probably still have led to the diagnosis.

Therefore, the usefulness rate was corrected downward from 38.9% (n=56, corresponding to the patients in the very useful and useful groups) to 31% (n=45, after subtraction of the 11 patients with nonessential PET/CT findings).

Comparison of PET/CT With Other Evaluations

A CT scan was performed before the PET/CT in 81% of cases (Table 2). In retrospect, the CT findings agreed with the final diagnosis in 30.7% of cases (n=36). However, 57 patients (48%) presented with abnormal CT findings that were not associated with the final diagnosis. The median time between the admission to the internal medicine department and the CT scan was 7 days (1-27.5 days).

A temporal artery biopsy was performed before the PET/CT scan in 27% of the cases (n=39). The mean ± SD age of the biopsied patients was 73±9.1, which is consistent

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TABLE 3. Diagnostic Delay, According to the Usefulness of PET/CT

	Median (IQR) diagnostic delay (d)		Median (IQR) time interval between the PET/CT and the confirmed diagnosis (d)	
Very useful	55 (13-79)	P<.001	0 (0-21)	P<.001
Useful	71 (38-170)		32 (11-52)	
Not useful	175 (51-390)		50 (9-236)	
Misleading	109 (34-414)		44 (9-253)	

IQR, interquartile range; PET/CT, positron emission tomography coupled with computed tomography

with the epidemiology of giant cell arteritis. Moreover, 15% of the patients underwent a dental X-ray or sinus CT scan, 30% a colonoscopy, 43% echocardiography, and 27% a bone marrow biopsy (Table 2).

The Diagnostic Delay and the Association With PET/CT

Overall, the median diagnostic delay (ie, the time between the admission to the internal medicine department and a confirmed diagnosis) was 82 days (42-280 days) (Table 3).

The median diagnostic delay was significantly shorter in the useful (71 days [38-170 days]) and very useful (55 days [13-79 days]) groups than that in the not useful group (175 days [51-390 days]; P<.001).

The median time interval between the PET/CT and a confirmed diagnosis was 30.5 days (6-144 days). This median time interval was also significantly shorter in the useful (32 days [11-52 days]) and very useful (0 day [0-21 days]) groups than that in the not useful group (50 days [9-236 days]; P<.001).

The median time interval between the PET/CT and a confirmed diagnosis after PET/CT was 25 days (6-55 days) in the pooled misleading, useful, or very useful groups and 50 days (9-236 days) in the not useful group (P=.03).

Factors Associated With the Usefulness of PET/CT

In a univariate analysis, poor overall condition (P=.007) and the absence of fever (P=.005) were predictive of PET/CT's usefulness. In the very useful group, most of the final diagnoses were inflammatory diseases (63.16%, including 7 cases of noninfectious inflammatory aortitis and 5 cases of large-vessel vasculitis). In the useful group, the final diagnosis was more likely to be cancer (32.43%; P<.001). When the PET/CT was of no value, a diagnosis was not made in 49.21% of the cases.

Using a contingency table (Table 4), we compared the usefulness of CT with the PET/CT and confirmed that the various groups did not overlap.

DISCUSSION

We retrospectively studied the usefulness of PET/CT for the diagnostic workup of IUO. The PET/CT was useful for making a diagnosis in 38.9% of the cases and decisive in 13.2% (mainly cases of inflammatory disease). The usefulness rate reduced to 31% when we retrospectively selected the diagnoses for which the PET/CT was not essential and when the CT scan findings would probably have been sufficient. The latter analysis found that PET/CT was essential for the detection of 3 cases of cancer. Positron emission tomography coupled with CT was useful in 21.5% of the cases in which the CT findings alone did not contribute to the diagnosis. The PET/CT findings were misleading (false-positives) in 17.4% of the cases.

The median diagnostic delay was significantly shorter when the PET/CT findings were useful. Finally, when the PET/CT findings were not useful, half of the patients had not received a diagnosis at the end of the follow-up period.

Comparison With the Literature Data

In this study, we sought to study real-life practice in a university medical center's internal

TABLE 4. CT Scan vs a PET/CT Scan

		CT scan		
		Normal or irrelevant result, n (%)	Useful result for diagnosis, n (%)	Total, n (%)
PET/CT	Misleading and not useful groups	56 (46.3)	21 (17.3)	77 (63.6)
	Useful and very useful groups	26 (21.5)	18 (14.9)	44 (36.4)
	Total	82 (67.8)	39 (32.2)	121 (100)

PET/CT, positron emission tomography coupled with computed tomography.

medicine department. We considered that including solely the cases of FUO that met the Durack-Street criteria would not be representative of our patient population. Hence, we adopted a more pragmatic definition of IUO (regardless of the presence or absence of fever: 43% of our patients presented with fever) that complied with the diagnostic criteria by de Kleijn et al.[3]

The distribution of the diagnosis groups was roughly in line with the literature data. The observed proportion of cases of IUO without a final diagnosis was also in line with the literature data (29.2% in this study, vs 20.8% in the study by Schönau et al,[31] and 28.1% in the recent French cohort [described by Holubar et al[35]]). Only the proportion of patients with inflammation remaining unexplained appeared to be slightly higher (11.8% in this study, vs 2%-9% in the literature series[39]); however, this disparity might have been owing to the differences in the length of the follow-up.

We decided to stratify usefulness into subgroups because value is not always precisely defined in the literature. This enabled us to analyze the diagnostic contributions in a more detailed manner. It is noteworthy that a broad range of usefulness has been reported in the literature since 2002 (from 16%-70%) (Table 1).

In this analysis, patients in the useful and very useful groups recorded a significantly shorter diagnostic delay and a significantly shorter time interval between the PET/CT scan and a confirmed diagnosis. This might result in shorter hospital stays, fewer diagnostic procedures, more rapid treatment, and (perhaps) cost savings. In fact, these potential benefits must be balanced against the significant cost of the PET/CT scan itself. Few other published studies provided data on the diagnostic delay (a median of 53 days[13] and 55 days[10]). We consider that the diagnostic delay should be considered while choosing a diagnostic strategy.

Positron emission tomography coupled with CT found a high positive predictive value for the identification of an active inflammatory disease: 86.4% in this study and 76.7% in a report by Holubar et al[35] However, this advantage was counterbalanced by a high false-positive rate (17.4%), which appeared to be associated with a longer diagnostic delay. In the literature, the false-positive rate ranged from 0%-45%.[20] The economic and clinical effects of these false-positive results were not detailed.

We noticed that the diagnostic usefulness of PET/CT appears to have grown over the past decade. This probably reflects not only the technological progress (the coupling of PET to the CT increases the diagnostic usefulness[36]) but also the speed of prescription; in retrospect, our most helpful PET/CT scans were prescribed sooner after a patient's admission. We expect that the upcoming technological innovations (eg, PET/magnetic resonance imaging and artificial intelligence[40]) will increase the technique's sensitivity and negative predictive value.

A univariate analysis found a nonsignificant trend toward more severe disease when the PET/CT found abnormal hypermetabolism. One can reasonably hypothesize that PET can detect the abnormal hypermetabolism associated with cachexic, inflammatory disease. Positron emission tomography coupled with CT was more likely to be useful in patients without fever. Schönau et al[31] made a similar observation.

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Strengths and Weaknesses of the Study

Our study's strengths included the relatively large study population and easily reproducible definition of IUO, which facilitated comparisons with the literature data from few other cohorts of an equivalent size. A large proportion of our patients met the criteria for FUO, which facilitated comparisons with older studies that studied FUO and not just IUO. Our results were reported for a selected minimum CRP threshold of 15 mg/L—a threshold that is not always used in other classifications.

Each file was analyzed individually, and a patient's history was summarized; this enabled us to accurately calculate the time intervals involving the diagnostic procedures and imaging. The quality of the diagnostic workup is also a study strength. The high proportion of patients with imaging and laboratory investigations performed before the PET/CT scan enabled us to assess the investigations' respective values and to compare them with those of the PET/CT.

The 13-year inclusion period enabled a satisfactory follow-up of patients without a definitive diagnosis but might also have induced a bias. Indeed, the prescribers and their habits changed over time, and the PET/CT review was not centralized.

The integration of PET/CT into the diagnostic workup (ie, early or late) has not previously been studied. The diagnostic usefulness of PET/CT might vary owing to a lack of reproducibility or standardization. Finally, our single-center study might have been subjected to a center effect, being difficult to measure.

CONCLUSIONS

In this retrospective analysis, a PET/CT scan was found to be useful for the diagnostic workup in 31% of cases of IUO (with or without fever) and was more useful than other imaging and laboratory investigations. However, it did not provide the same information as a dedicated CT scan.

A PET/CT scan was associated with a shorter diagnostic delay. However, these advantages were counterbalanced by a high false-positive rate, the clinical and economic consequences of which remain to be determined.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

Abbreviations and Acronyms: **CRP,** C-reactive protein; **CT,** computed tomography; **FUO,** fever of unexplained origin; **IUO,** inflammatory syndrome of undetermined origin; **IQR,** interquartile range; **PET,** positron emission tomography

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