

Association of ^{18}F -FDG PET or PET/CT results with spontaneous remission in classic fever of unknown origin

A systematic review and meta-analysis

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Abstract

Background: Spontaneous remission is common in patients with undiagnosed classic fever of unknown origin (FUO). Although identifying reliable predictors of spontaneous remission in such diagnostically challenging cases could improve their management strategies, few studies have assessed such clinical factors. Recently, studies have reported that ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG PET) alone and integrated with computed tomography (PET/CT) were useful in localizing the source of FUO. In this systematic review and meta-analysis, we assessed the association of results of these imaging modalities with spontaneous remission in patients with classic FUO.

Methods: We searched PubMed and Scopus from inception until June 30, 2018, and studies that evaluated the PET or PET/CT results of ≥ 10 adult or adolescent patients with classic FUO who were followed up for at least 3 months were included. At least 2 investigators extracted data and rated quality using the QUIPS-2 tool. We used a random-effects meta-analysis to calculate summary risk ratios (RRs) with 95% confidence intervals (CIs).

Results: Nine studies of PET/CT results (418 patients) and 4 studies of standalone PET results (128 patients) were eligible. None explicitly specified the incidence of spontaneous remission as the primary or secondary outcomes of interest. The risk of bias was considered high in all studies because patients received subsequent diagnostic workup based on imaging results. Patients with negative PET/CT results were significantly more likely to present with spontaneous regression than those with positive results (summary RR=5.6; 95% CI: 3.4–9.2; $P < .001$; $I^2 = 0\%$). In contrast, no significant association was found between standalone PET results and spontaneous remission. The random-effects study-level meta-regression found that PET/CT results [relative RR (rRR)=7.4; 95% CI: 2.5–21.3; $P = .002$], compared with standalone PET results, and publication year (rRR=1.2 per 1 year; 95% CI: 1.0–1.3; $P = .013$) were significantly associated with spontaneous remission.

Conclusion: Limited data suggest that undiagnosed classic FUO patients with negative PET/CT results had a high likelihood of spontaneous remission after a series of unsuccessful investigations for fever workup. Prospective studies should validate these results.

Abbreviations: ^{18}F -FDG = ^{18}F -fluorodeoxyglucose, CI = confidence interval, CT = computed tomography, FUO = fever of unknown origin, NIID = non-infectious inflammatory disease, PET = positron emission tomography, RR = risk ratio, rRR = relative risk ratio.

Keywords: fever of unknown origin, meta-analysis, positron emission tomography, prognosis, spontaneous remission

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1. Introduction

Classic fever of unknown origin (FUO) is defined as community-acquired fever of $\geq 38.3^{\circ}\text{C}$ (101°F) lasting ≥ 3 weeks in immunocompetent individuals and explicitly excludes fever among hospitalized patients or patients with human immunodeficiency virus infection or neutropenia.^[1] In developed countries, with advances in diagnostic technology, including sophisticated imaging tests, improved culture techniques, and molecular diagnostics, there has been a decrease in cases of infectious and malignant diseases, the 2 most common classic causes, and cases remaining undiagnosed after extensive diagnostic workup have become more prevalent.^[2,3] In such diagnostically challenging cases, up to 75% are reported to remit spontaneously during clinical follow-up, and watchful waiting is a common approach for clinically stable patients.^[4] However, how clinicians identify patients with a high likelihood of spontaneous remission and manage such patients remains unclear. Therefore, identifying reliable predictors of spontaneous remission may improve management strategies, which can potentially reduce unnecessary invasive investigations, such as tissue biopsy or empiric treatments with antibiotics or steroids.

¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG PET) and its combined modality with computed tomography (PET/CT) are established functional imaging tests used in the clinical management of malignant tumors.^[5] Because the common causes of classic FUO, such as infectious diseases, noninfectious inflammatory diseases (NIIDs), and neoplasms, are often FDG-avid, several studies have investigated the clinical role of PET or PET/CT in patients with classic FUO, and a recent meta-analysis has reported that PET and PET/CT successfully localized the source of fever in 44% and 58% of the patients with classic FUO, respectively, after a series of unsuccessful investigations for fever workup.^[6] However, these primary studies did not specifically focus on whether PET or PET/CT is also useful in identifying cases of subsequent spontaneous remission. On the basis of the high diagnostic yield attributable to FDG-avidity in several life-threatening causes of classic FUO,^[6] we formulated a clinical hypothesis that an absence of abnormal FDG uptakes in standalone PET or PET/CT, in contrast, is a good predictor of spontaneous remission. To test this hypothesis, we conducted a systematic review and meta-analysis to evaluate the associations between PET and PET/CT results and spontaneous remission in diagnostically challenging cases of classic FUO.

2. Materials and methods

This study is a systematic review and meta-analysis of data from already published studies; thus, it was exempted from ethical review.

2.1. Data sources and search strategy

We performed an in-depth extended systematic review and meta-analysis based on our previous research and literature searches. We searched PubMed and Scopus from inception until June 30, 2018, with no language restrictions. We used search terms for the target condition (e.g., “fever of unknown origin” or “FUO”) and the tests of interest (e.g., “PET,” or “PET/CT”) and their synonyms. The exact search strategies can be found in the Appendix (Supplemental Table 1, <http://links.lww.com/MD/C560>). We then perused the reference lists of eligible primary studies, relevant reviews, and meta-analyses. We also tracked citations of eligible papers through Scopus, Web of Science, and Google Scholar.

2.2. Study selection

Two reviewers independently screened abstracts and examined the full-text of potentially eligible citations. We included studies that evaluated PET or PET/CT for ≥ 10 adult patients (≥ 18 years of age) with classic FUO and experienced at least 1 case of spontaneous remission. After retrieving full-text articles, we operationally expanded the original inclusion criterion from “adult patients (≥ 18 years of age)” to “adult and adolescent patients (≥ 16 years of age)” because the studies adopted different age cutoffs. The eligible studies had to have followed up the patients for ≥ 3 months after PET or PET/CT scans and report whether a patient remitted spontaneously or not along with the scan results.

We contacted the authors of potentially eligible studies to obtain unpublished data when relevant information, including whether the symptoms of FUO in undiagnosed patients spontaneously remitted during follow-up after PET or PET/CT and subsequent diagnostic interventions that were provided to the patients based on the scan results, was not explicitly reported. We excluded studies that exclusively evaluated patients ≤ 15 years old and studies that jointly analyzed both pediatric and adult patients but did not report separate data on patients ≥ 16 years old. We also excluded studies that jointly analyzed the results for PET and PET/CT or classic FUO and FUO in nonclassic settings because from these studies, separate data on PET or PET/CT for classic FUO only were not extractable.

2.3. Data extraction

One investigator (MT) extracted descriptive information, and at least 1 of the senior investigators (TN, TT) confirmed all of the data. Discrepancies were resolved by consensus. We extracted study design characteristics, including pre-imaging workup strategies and follow-up methods and durations after imaging; patient characteristics, such as age and causes of FUO identified through additional tests and follow-up; and test characteristics, such as PET or PET/CT protocols, diagnostic criteria of positive results, and details on the interpreters. Two reviewers (MT, TT) independently extracted quantitative data for the numbers of total patients, and patients who remitted spontaneously during follow-up by scan results (i.e., either positive or negative). We defined a patient with spontaneous remission as a patient in whom FUO symptoms were reported to have regressed spontaneously without a therapeutic intervention before reaching a diagnosis during the clinical follow-up. We only considered the continuous disappearance of symptoms during the follow-up as spontaneous remission and excluded patients with recurrent FUO or those who had relapsing fever even if spontaneous remission was temporarily observed. Moreover, we did not specify the required diagnostic tests for the workup of individuals with FUO or the minimum follow-up duration after spontaneous remission was observed. We counted patients for whom a cause of fever was diagnosed (regardless of FUO causes), deaths from any causes, and losses to follow-up as zero events. We explicitly excluded from spontaneous remission the patients who remitted after they were administered any cause-specific therapeutic intervention, including empirical treatments with antibiotics or corticosteroids. We contacted the authors by e-mail or postal mail to obtain unpublished data when information on spontaneous remission was not explicitly described. We considered the request to be rejected when there was no response after 2 e-mail correspondences that were sent 2 weeks apart.

2.4. Assessments of risk of bias

Two independent reviewers assessed the risk of bias for each eligible study by using a revised version of the Quality in Prognosis Studies tool (the QUIPS-2),^[7] which is an established tool to address 6 important domains that pertain to validity and bias in studies of prognostic factors: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account, and analysis and reporting. We did not evaluate domains 5 and 6 because no studies accounted for confounding factors or performed statistical adjustments for spontaneous remission. Discrepancies were resolved by discussion to arrive at a consensus. At least 1 of the 3 senior authors (NT, MI, TT) adjudicated the unresolved results.

2.5. Data synthesis

Our primary outcome of interest was the association of negative PET or PET/CT with spontaneous remission. For each study, we calculated the risk ratio (RR) of spontaneous remission and its 95% confidence interval (95% CI) by dividing the cumulative incidence in patients with a negative scan result (defined as the negative scan group) by the cumulative incidence in those with a positive scan result (defined as the positive scan group). We then performed the Knapp–Hartung-corrected restricted maximization likelihood random-effects meta-analysis to obtain the summary RRs^[8]; random-effects model was selected because of the possibility of a cross-study clinical and methodological heterogeneity.^[9] In the main analysis, we applied the standard continuity corrections by adding 0.5 for each cell in the 2 by 2 contingency table for studies that reported zero spontaneous remission events in either of the 2 groups. To test the effects of the zero-cell corrections, we performed stability analysis by meta-analyzing only studies with at least 1 spontaneous remission event in both (i.e., the positive and negative scan) groups. We estimated the I^2 statistic as a measure of statistical heterogeneity and considered I^2 to be suggestive of intermediate or high heterogeneity when it was $>50%$ or $>70%$, respectively.^[10] Moreover, we indirectly compared the associations of scan results with spontaneous remission between PET and PET/CT by calculating the relative RR (rRR) by modeling RRs and the imaging modality (i.e., either PET or PET/CT as 0 or 1, respectively) in each study as a covariate in the random-effects study-level meta-regression analysis. We also performed univariable study-level meta-regressions on publication year as the surrogate for improvement of technologies and incidence of spontaneous remission as the surrogate for disease spectrum of the assessed cases. We did not perform tests for funnel plot asymmetry because no recommended approach was established to provide an appropriate test statistic with adequate power for assessing the extent and impact of missing data for the systematic reviews of diagnostic and prognostic accuracy studies.^[11]

Several causes of FUO spontaneously regress and thus can be considered “benign.” Examples include viral infections; acute crystal arthritis, such as gout or pseudogout; subacute thyroiditis; and drug-induced fever (in the case of successful cessation). However, the extent to which these studies have investigated these “benign” causes or whether the studies rigorously differentiated the successfully diagnosed “benign” causes from *bona fide* spontaneous remissions with no diagnosable cause was not explicitly reported. For example, viral infections that were accurately diagnosed could have been categorized as “diagnosed” disease in some studies because they were specifically investigated and thus successfully diagnosed, whereas similar

cases could have been considered as patients with “undiagnosed FUO” who experienced spontaneous remission because of unsuccessful diagnosis (or simply classified so because diagnosable “benign” causes were not even investigated). In the latter case, a patient categorized as “undiagnosed FUO” could have been reported as spontaneous remission if the clinical course was eventually benign. To perform a uniform assessment for stability analysis, we considered the cases of diagnosed “benign” causes as spontaneous remissions in addition to the reported cases of spontaneous remission based on the operational criteria that were previously reported (Supplemental Table 2, <http://links.lww.com/MD/C560>).^[6] We again excluded the patients from spontaneous remission who remitted after receiving any cause-specific therapeutic interventions as long as the pertinent information was explicit.

3. Results

3.1. Selection of eligible studies

We screened 9384 abstracts and evaluated 93 full-text articles. Unpublished data from 5 studies were provided by the authors. Finally, after excluding 84 citations, a total of 13 publications met our eligibility criteria,^[12–24] including 4 studies (128 patients) on PET results and 9 studies (418 patients) evaluating PET/CT results (Fig. 1). A full list of the excluded publications with their reasons can be found in the Appendix, <http://links.lww.com/MD/C560>.

3.2. Study and patient characteristics

The 13 eligible studies were conducted in Europe (9 studies), the Middle East (3 studies), and North Africa (1 study). Studies of PET were conducted between 1996 and 2003, whereas PET/CT was conducted after 2005 (Table 1). The sample size was small; the number of study participants ranged from 10 to 112 (mean: 45; median: 35). Only 4 studies (2 for PET and 2 for PET/CT) had a prospective design. Nine (69%) of 13 studies retrospectively reviewed data obtained from clinical practice and used nonuniform pre-imaging workup strategies and follow-up methods. The minimum follow-up duration after PET or PET/CT assessment for undiagnosed FUO ranged from 3 to 16 months. No study explicitly specified primary outcomes, and the 2 most commonly reported outcomes were “diagnostic accuracy” ($n=7$) and “diagnostic contribution” ($n=6$), the latter of which described how often the study authors considered PET or PET/CT results contributory to identifying the FUO causes. None explicitly specified the incidence of spontaneous remission as the primary or secondary outcomes of interest.

Overall, the studies evaluated relatively young patients (min–max average age: 42–60 years). Infections, NIIDs, and malignancies were the 3 most commonly diagnosed causes of fever (Table 2). The average proportions of these causes were similar between studies of PET (infections: 21%; NIID: 26%; malignancies: 9%; and miscellaneous: 7%) and PET/CT (infections: 31%; NIID: 25%; malignancies: 14%; and miscellaneous: 3%). The average spontaneous remission rate in the studies was 20% (min–max: 6–45%).

3.3. Assessment of risk of bias

Reporting in general lacked adequate details on key methodologies in prognostic studies, including consecutive sampling of all eligible patients, reasons for exclusions and losses to follow-up, and explicit diagnostic criteria used for negative results (Table 3).

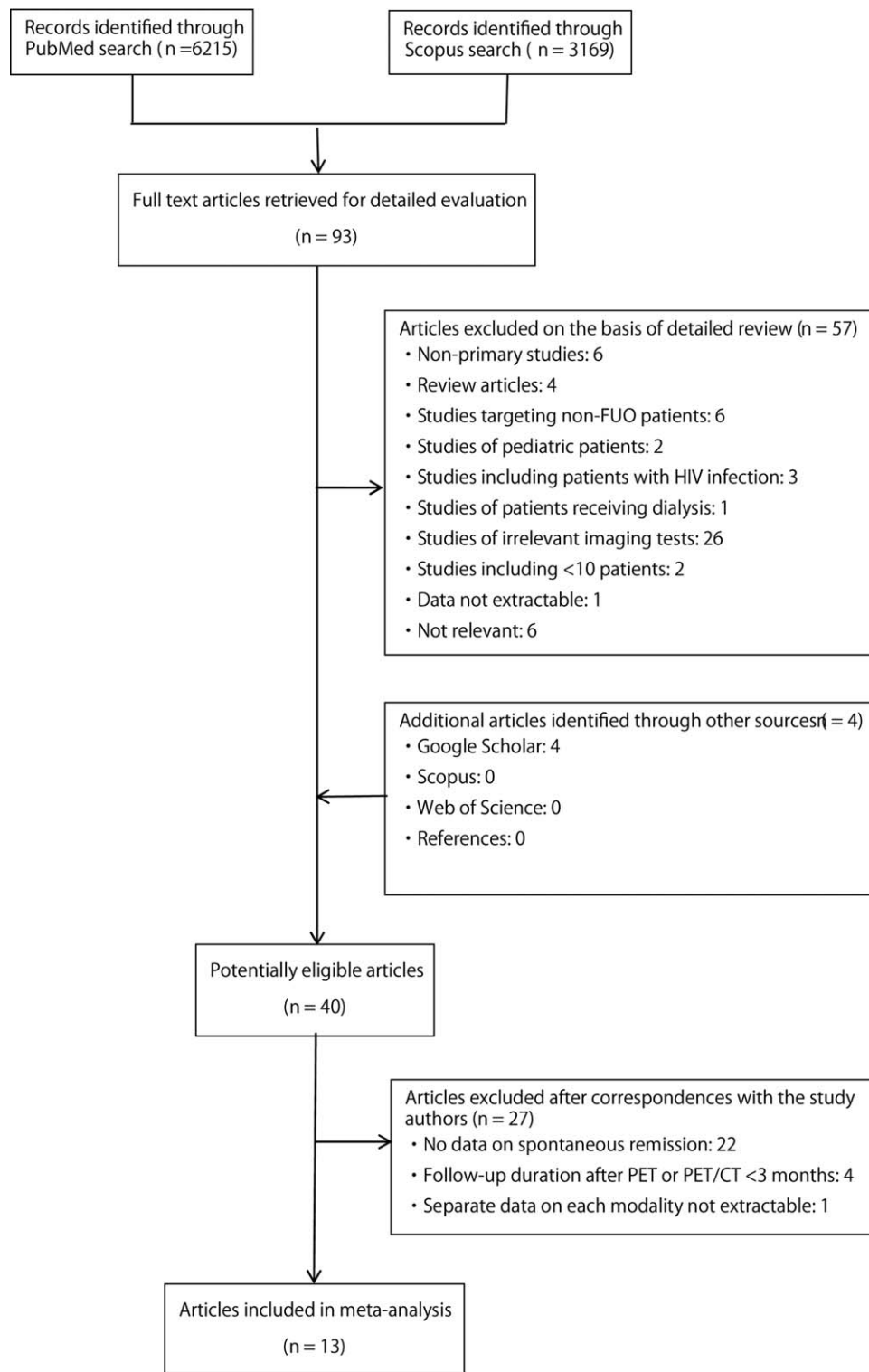


Figure 1. PRISMA flow diagram. CT=computed tomography, FUO=fever of unknown origin, HIV=human immunodeficiency virus, PET=positron emission tomography.

These limitations precluded reliable assessment of the study validity. Further, the risk of bias due to differential verification was deemed high in all studies because investigators selected more specific add-on diagnostic investigations targeting at PET or PET/CT-positive sites, and patients with a negative result were clinically less aggressively followed.

3.4. Incidence of spontaneous remission

The cumulative incidence of spontaneous remission ranged from 20% to 78% in patients with negative PET/CT results and from 0% to 48% in those with positive results. Overall, patients with negative PET/CT results had a significantly higher probability of spontaneous regression than those with positive results (summary

Table 1
Study characteristics of association of FDG-PET or PET/CT results with spontaneous remission in classic FUO.

Study ID	Country, city	Period of recruitment	Design	Type of centers (number)	Patient enrollment	Definition of FUO	Follow-up duration, mo	Obligatory test										
								ESR/CRP	CBC	Chemistry*	Urinalysis	ANA/RF	Ferritin	PEP	BCX	UCX	CXR	AUS
FDG-PET/CT																		
Abdelrahman et al ^[2]	Egypt, Cairo	ND	Prospective	University hosp. (1)	Consecutive	Petersdorf	3	—	—	—	—	—	—	—	—	—	—	No data on obligatory tests
Bainik et al ^[3]	Netherlands, Leeuwarden	Jun 2005–Oct 2008	Retrospective	Community hosp. (1)	ND	ND	Up to 24	—	—	—	—	—	—	—	—	—	—	No data on obligatory tests
Crouzet et al ^[4]	France, Nîmes	Jan 2007–May 2009	Retrospective	University hosp. (1)	ND	Durack-Street	≥12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	Thoracoabdominal CT
Federici et al ^[5]	France, Strasbourg	Jan 2005–July 2006	Retrospective	University hosp. (1)	Inconsecutive	Custom [†]	≥6 [†]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	(93% of patients only)
Gaffar-Ghili et al ^[6]	Israel, Petah Tikva	2008 - 2012	Retrospective	Community hosp. (1)	ND	Durack-Street; Petersdorf	≥6	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	Serology; US [‡] ; CT [‡] ; UCG ^{§,}
García-Gomez et al ^[7]	Spain, Sevilla	Mar 2010–Sep 2013	Retrospective	ND	Consecutive	Modified Durack-Street	Mean 16	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Keidar et al ^[8]	Israel, Haifa	ND	Prospective	Community hosp. (1)	Consecutive	Petersdorf	12–36 in case of no diagnosis	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	Abdominal CT [¶]
Pedersen et al ^[9]	Denmark, Copenhagen	May 2005–Apr 2010	Retrospective	University hosp. (1)	Inconsecutive	Durack-Street	Mean 30; IQR, 17–43	—	—	—	—	—	—	—	—	—	—	No data on obligatory tests
Tokmak et al ^[6]	Turkey, Istanbul	2008–2012	Retrospective	Community hosp. (1)	ND	Petersdorf	12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	ND
FDG-PET																		
Bleeker-Rovers et al ^[21]	Netherlands, Nijmegen	Jan 1999–Dec 2002	Retrospective	University hosp. (1)	ND	Petersdorf	≥6 for negative PET	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	Serology
Blockmans et al ^[22]	Belgium, Leuven	Mar 1996–Oct 1998	Prospective	University hosp. (1)	Consecutive	Durack-Street	≥6 [†]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	Serology
Kjaer et al ^[22]	Denmark, Copenhagen	Mar 2001–Jun 2003	Prospective	University hosp. (1)	Inconsecutive	Petersdorf	≥4	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	Not reported
Lorenzen et al ^[24]	Germany, Hamburg	Feb 1998–Mar 2000	Retrospective	University hosp. (1)	ND	ND	≥3	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	UCG; CT (abdomen, chest, brain); endoscopy (upper GI, colon); bronchoscopy; BX (bone marrow, liver, muscle); MRI

ALP = alkaline phosphatase; ANA = antinuclear antigen, ANCA = anti-neutrophil cytoplasmic antibody; AUS = abdominal ultrasound; BCX = blood culture; BX = biopsy; CBC = complete blood count; CPK = creatine phosphokinase; CRP = C-reactive protein; CT = computed tomography; CXR = chest x-ray; ESR = erythrocyte sedimentation rate; FDG = fluorodeoxyglucose; FUO = fever of unknown origin; GI = gastrointestinal; IQR = interquartile range; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PEP = protein electrophoresis; RF = rheumatoid factor; TST = tuberculin skin test; UCG = ultrasound cardiography; UCX = urine culture; US = ultrasound.

*The basic laboratory tests included renal and hepatic function tests, electrolytes, CPK, LDH, and ALP.

[†] At least 6 for patients with spontaneous remission confirmed by the study authors.

[‡] Fever of > 38.3°C for > 3 weeks after 1 week of investigations in hospital or outpatient setting.

[§] Selective patients only.

^{||} When these tests were performed was not explicitly reported.

[¶] These tests were performed as part of FUO work-up.

** FDG-PET/CT was performed as part of FUO work-up in selected patients only in addition to the following tests: CBC; ESR; renal and hepatic function tests; electrolytes; CPK; LDH; urinalysis; CXP; AUS; Brucella serum tube agglutination; Gruber–Widal agglutination; peripheral blood smear; ANA; ANCA; RF; BCX; UCX; cultures other than blood and urine; serologic tests for cytomegalovirus (IgM); Epstein–Barr virus; Salmonella; Brucella; Cowiella Burnetii; Toxoplasma; rubella; herpes; and hepatitis A, B, and C viruses; UCG; CT; MRI; histopathological examination; and peripheral smear for malaria.

Table 2

Patient characteristics and final diagnosis of patients in studies of association of FDG-PET or PET/CT results with spontaneous remission in classic FUO.

Study ID	Patient, n	Mean/median age (range), y	Final diagnosis, n (%)					
			Infection	NIID	Neoplasm	Miscellaneous	No diagnosis	Spontaneous remission
FDG-PET/CT								
Abdelrahman et al ^[12]	27	44 (18–70)	6 (22)	9 (33)	9 (33)	1 (4)	2 (7)	2 (7)
Balink et al ^[13]	68	ND (23–91)	25 (37)	14 (21)	2 (3)	3 (4)	0 (0)	24 (35)
Crouzet et al ^[14]	79	54 (ND)	23 (29)	20 (25)	12 (15)	6 (8)	0 (0)	18 (23)
Federici et al ^[15]	10	53 (25–74)	4 (40)	3 (30)	0 (0)	0 (0)	2 (20)	1 (10)
Gafter-Gvili et al ^[16]	112	60 (19–94)	49 (44)	17 (15)	15 (13)	2 (2)	6 (5)	23 (21)
Garcia-Gomez et al ^[17]	28	54 (23–85)	6 (21)	7 (25)	10 (36)	1 (4)	2 (7)	2 (7)
Keidar et al ^[18]	48	57 (24–88)	9 (19)	16 (33)	3 (6)	1 (2)	0 (0)	19 (40)
Pedersen et al ^[19]	22	52 (17–87)	1 (5)	8 (36)	3 (14)	0 (0)	3 (14)	7 (32)
Tokmak et al ^[20]	25	59 (16–88)	8 (32)	10 (40)	3 (12)	0 (0)	1 (4)	3 (12)
FDG-PET								
Bleeker-Rovers et al ^[21]	35	51 (18–82)	6 (17)	6 (17)	4 (11)	3 (9)	12 (34)	4 (11)
Blockmans et al ^[22]	58	ND	10 (17)	17 (29)	6 (10)	5 (9)	6 (10)	14 (24)
Kjaer et al ^[23]	19	49 (27–82)	7 (37)	3 (16)	1 (5)	1 (5)	0 (0)	7 (37)
Lorenzen et al ^[24]	16	42 (17–78)	4 (25)	8 (50)	1 (6)	0 (0)	2 (13)	1 (6)

CT=computed tomography, FDG=fluorodeoxyglucose, FUO=fever of unknown origin, NIID=noninfectious inflammatory disease, PET=positron emission tomography.

Table 3

Risk of bias assessment of studies of association of FDG-PET or PET/CT results with spontaneous remission in classic FUO.

Study ID	Risk of bias			
	DOMAIN 1 Study participation	DOMAIN 2 Study attrition	DOMAIN 3 Prognostic factor measurement	DOMAIN 4 Outcome measurement
<i>FDG-PET/CT</i>				
Abdelrahman 2018 ^[12]	⊖	☺	?	⊖
Balink 2009 ^[13]	⊖	☺	?	⊖
Crouzet 2012 ^[14]	⊖	?	⊖	⊖
Federici 2010 ^[15]	⊖	☺	⊖	⊖
Gafter-Gvili 2014 ^[16]	⊖	?	?	⊖
Garcia-Gomez 2015 ^[17]	⊖	?	⊖	⊖
Keidar 2008 ^[18]	☺	☺	?	⊖
Pedersen 2012 ^[19]	⊖	☺	⊖	⊖
Tokmak 2014 ^[20]	?	☺	⊖	⊖
<i>FDG-PET</i>				
Bleeker-Rovers 2004 ^[21]	☺	☺	⊖	⊖
Blockmans 2001 ^[22]	☺	?	⊖	⊖
Kjaer 2004 ^[23]	⊖	☺	⊖	⊖
Lorenzen 2001 ^[24]	⊖	?	⊖	⊖

Key

- ☺ Low risk of bias or concern about applicability
- ⊖ High risk of bias or concern about applicability
- ? Unclear risk of bias or concern about applicability

CT=computed tomography, FDG=fluorodeoxyglucose, FUO=fever of unknown origin, PET=positron emission tomography.

RR=5.6; 95% CI: 3.4–9.2; $P < .001$; $I^2=0\%$) (Fig. 2). The results of the stability analysis were not materially different, in which only 6 of 9 PET/CT studies that observed at least 1 spontaneous remission event in both groups were meta-analyzed (summary RR=5.3; 95% CI: 3.0–9.4; $P = .001$; $I^2=0\%$). Sparse data from only 4 studies precluded a reliable analysis on whether the positive or negative result of standalone PET was associated with a higher incidence of spontaneous remission (summary RR=0.83 favoring positive result; 95% CI: 0.14–5.0; $p=0.77$; $I^2=32\%$) (Fig. 2). The results were similar when only 3 of 4 standalone PET studies that observed at least 1 spontaneous remission event in both groups were meta-analyzed (summary RR=0.62; 95% CI: 0.09–4.3; $P = .40$; $I^2=0\%$).

The random-effects study-level meta-regression analysis found that PET/CT results (rRR=7.4; 95% CI: 2.5–21.3; $P = .002$), compared with standalone PET results, and publication year (rRR = 1.2 per 1 year; 95% CI: 1.0–1.3; $P = .013$) were significantly associated with spontaneous remission. Similar positive findings were obtained for the use of PET/CT compared with standalone PET (rRR=8.5; 95% CI: 2.6–27.9; $P = .004$)

and publication year (rRR=1.2 per 1 year; 95% CI: 1.0–1.4; $P = .031$) when meta-analysis was performed in the stability analysis for only studies that observed at least 1 spontaneous remission event in both groups: The use of PET/CT remained significant when both the assessed modality and publication year were simultaneously modeled in the bivariate study-level meta-regression analysis (rRR=7.0; 95% CI: 1.0–48.3; $P = .049$ in the main analysis; rRR=12.1; 95% CI: 1.3–114.8; $P = .035$ in the stability analysis), compared with standalone PET.

Six studies of PET/CT and 3 studies of PET provided the relevant data amenable to the stability analysis, where a total of 9 patients diagnosed as “benign” causes (4 in the negative PET/CT group, 1 in the positive PET/CT group, 3 in the negative PET group, and 1 in the positive PET group) were additionally counted as spontaneous remissions. The summary results were not materially different from those in the main analysis. The summary RR for negative PET/CT results was 6.5 (95% CI: 3.1–13.4; $P < .001$; $I^2=0\%$) and that for negative PET results was 1.1 (95% CI: 0.14–8.1; $P = .91$; $I^2=19\%$).

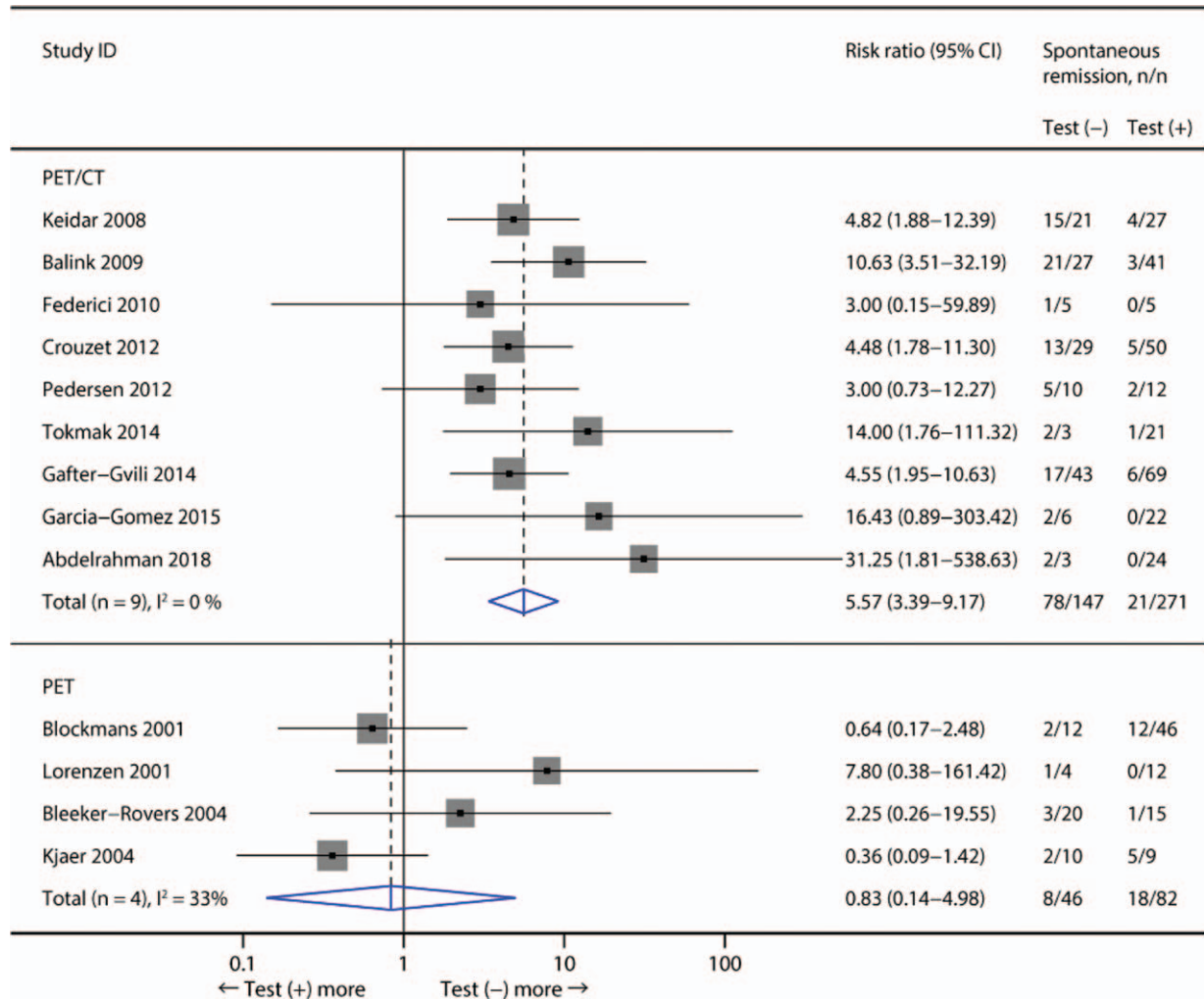


Figure 2. Association of FDG-PET or PET/CT results with spontaneous remission in classic FUO. The diamond depicts the summary risk ratio and extending 95% CI. Each square and horizontal line indicates the risk ratio and corresponding 95% CI, respectively, for each study. The size of the squares is proportional to the weight of each study in the meta-analysis. Studies are ordered by publication year. CI=confidence interval, CT=computed tomography, FDG=fluorodeoxyglucose, FUO=fever of unknown origin, PET=positron emission tomography.

4. Discussion

In the present study, we systematically reviewed the associations of PET and PET/CT results with spontaneous remission in approximately 550 patients with classic FUO from 13 studies. Our meta-analysis found that after a series of unsuccessful investigations for fever workup, patients with negative PET/CT results have approximately 6 times higher average chance of spontaneous remission than those with positive PET/CT results. These findings were stable in the stability analysis, suggesting that a negative PET/CT result can be a good predictor of favorable prognosis in patients with undiagnosed classic FUO after a series of unsuccessful investigations. Evidence was limited as to whether standalone PET results were associated with spontaneous remission. Our naive indirect comparison using study-level meta-regression suggested that studies that evaluated PET/CT reported an approximately 7 times higher average association between negative scan results and spontaneous remission than studies that evaluated standalone PET.

Our previous work found that positive PET/CT results helped to identify sources of FUO by successfully localizing the vast majority of infectious and malignant lesions.^[6] PET/CT also frequently failed to detect lesions caused by other noninfectious or nonmalignant conditions, including NIIDs. Because infectious diseases and malignancies are the 2 most life-threatening causes of classic FUO, PET/CT should be useful in identifying cases with lesions deemed to have worse prognoses. For this reason, it is theoretically understandable that FUO patients unsuccessfully screened with PET/CT would have a lower likelihood of having infections or malignancies than those with positive results, and thus be more likely to have a cause that remits spontaneously.

Anatomical information from a CT image is widely believed to provide additional accuracy for localization of pathological conditions visualized by a PET image alone, which has been further strengthened by technological improvements in the hybrid imaging system over the past 2 decades. In this line of reasoning, one may speculate that the stronger associations between scan results and spontaneous remission reported in the PET/CT studies than those of the standalone PET studies could be explained at least in part by the association between CT results and spontaneous remission. Unfortunately, studies failed to assess the CT findings of remitted patients systematically, which precluded the pertinent exploration. Nevertheless, this comparative information may no longer be clinically relevant at least in developed countries, where PET/CT has almost replaced standalone PET scanners, and thus is the only available technology in routine clinical practice.

Our meta-analysis has several limitations. First, our results are mostly based on retrospective observations that relied on the data derived from clinical practice; the sample size of the included studies was small and the follow-up period was short and based on nonuniform methods. The definition of spontaneous remission was generally unclear and most likely nonstandardized across studies. This is not surprising because published studies focused on the diagnostic role of these imaging modalities, typically whether the nuclear imaging tests helped localize the cause of FUO. No study explicitly specified spontaneous remission as the target outcome of interest. Although we did not formally perform the pertinent assessment, including funnel plot asymmetry testing, the possibility of bias from selective reporting cannot be ruled out. Further, the risk of bias due to differential verification can be substantial; patients with a positive test would take immediate and perhaps aggressive and potentially

more accurate diagnostic interventions, such as biopsy, whereas those with a negative result might be less intensively worked-up or even not investigated. Given the reported short follow-up period, these differences in the intensiveness of succeeding diagnostic managements would have further impaired the accurate diagnosis of spontaneous remission in patients with negative results. Our results should thus be viewed as a retrospective exploration of available information, and the quality of the data is limited.

Second, because of the designs adopted in the primary studies, the imaging results had to be assessed as the standalone predictor, which did not account for other factors. Identification of predictors of good prognosis in diagnostically challenging cases of FUO is, however, only an emerging clinical question. For example, prognostic ability of other commonly performed tests in clinical practice, such as white blood cell (WBC) counts, C-reactive protein levels (CRP), or erythrocyte sedimentation rate (ESR) test have not yet been systematically assessed.

PET/CT for predicting spontaneous remission is still under investigation and should not be used by itself other than for research purposes. The prognostic ability of PET/CT in clinically challenging cases of classic FUO, together with its diagnostic usefulness, should be rigorously assessed in prospective studies in settings where pre-imaging workup and post-imaging management strategies, including prophylactic therapies, are standardized. Watchful waiting may be recommended for those with negative PET/CT results, particularly if undiagnosed patients are clinically stable.^[2] However, any test-based interventions, including watchful waiting, should be protocol oriented; it remains uncertain as to how often we can reliably expect spontaneous remission as an intermediate outcome for those with negative PET/CT, let alone more patient-relevant ultimate outcomes, such as mortality from FUO. For example, our previous meta-analysis found that PET/CT failed to localize several important or potentially life-threatening causes, such as adult onset Still disease, polymyalgia rheumatica, tuberculosis, and several hematological malignancies.^[6] The impact of failure to diagnose these conditions in a timely manner can be substantial. Prospective studies of predictive markers of spontaneous remission in undiagnosed classic FUO are necessary to validate the prognostic ability of negative PET/CT scan results. Future studies should evaluate other candidate predictors simultaneously to build a more reliable predictive model of spontaneous remission.

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