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REVIEW ARTICLE

Contribution of ^{18}F-FDG PET in the diagnostic assessment of fever of unknown origin (FUO): a stratification-based meta-analysis

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Abstract
Purpose The aim of this study was to quantify the contribution of FDG PET to the diagnostic assessment of fever of unknown origin (FUO), taking into account the diagnostic limitations resulting from the composite nature of this entity.
Methods The PubMed/MEDLINE database was searched from 2000 to September 2015. Original articles fulfilling the following criteria were included: (1) FUO as the initial diagnosis, (2) no immunosuppressed or nosocomial condition, (3) final diagnosis not based on PET, (4) a follow-up period specified, (5) adult population, and (6) availability of adapted data for calculation of odds ratios (ORs). ORs were computed for each study and then pooled using a random effects model. Stratification-based sensitivity analyses were finally performed using the following prespecified criteria: (a) study design, (b) PET device, (c) geographic area, and (d) follow-up period.
Results A meta-analysis of the 14 included studies showed that normal PET findings led to an increase in the absolute final diagnostic rate of 36 % abnormal PET findings to an increase of 83 %, corresponding to a pooled OR of 8.94 (95 % CI 4.18 – 19.12, $Z = 5.65$; $p < 0.00001$). The design of the studies influenced the results (OR 2.92, 95 % CI 1.00 – 8.53 for prospective studies; OR 18,57, 95 % CI 7.57 – 45.59 for retrospective studies; $p = 0.01$), whereas devices (dedicated or hybrid), geographic area and follow-up period did not.
Conclusion Abnormal PET findings are associated with a substantially increased final diagnostic rate in FUO. Consequently, FDG PET could be considered for inclusion in the first-line diagnostic work-up of FUO. Further randomized prospective studies with standardized FDG PET procedures are warranted to confirm this first-line position.

Keywords FUO · FDG PET · FDG PET/CT · Meta-analysis

Introduction

High glucose consumption through aerobic glycolysis (the so-called Warburg effect) is characteristic of tumour cells [1, 2]. However, inflammatory cells (e.g. neutrophils and monocytes) have also been shown to be high glucose consumers [3–6]. As a nonspecific glucose analogue, ^{18}F-fluorodeoxyglucose (FDG) may thus identify both malignancy and inflammatory processes. FDG PET is now a reference standard in cancer imaging [7]. Recently, interest in FDG PET has been rapidly increasing, particularly in the field of inflammation and infection [8]. Fever of unknown origin (FUO) is currently defined as a fever higher than 38.3 °C lasting more than 3 weeks and remaining undiagnosed after appropriate inpatient and outpatient investigations [9]. FUO is typically classified as classical, nosocomial, immunocompromised or HIV-related [10]. In clinical practice, the accurate identification of one of the aetiological categories of FUO, i.e. infection, neoplasm, noninfectious inflammatory disease (NIID) and "miscellaneous", affects the management of patients.

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Such a heterogeneous composite entity often requires an extensive diagnostic work-up. The first-line strategy includes clinical, biological and radiological standard tests. The use of FDG PET has thus instead been proposed in the second phase of the diagnostic process after failure of the first-line strategy. Several qualitative reviews highlight the potential value of FDG PET in the diagnostic work-up of FUO [11–13]. Two quantitative reviews have also been performed [14, 15]. However, the classical statistical approach used is unsuitable in FUO, a composite entity without a diagnostic gold standard and with a high rate of undiagnosed cases [16–18] that lead to artificial definitions of true-negative and false-negative cases.

In the absence of a structured diagnostic work-up, the usefulness of FDG PET in FUO remains quantitatively undetermined. Our aim was to quantify the contribution of FDG PET in the diagnostic assessment of FUO, taking into account the diagnostic limitations resulting from the composite nature of this entity.

Materials and methods

The study was conducted in accordance with the Preferred Reported Items for Systematic Reviews and Meta-Analyses guidelines [19].

Study objective and outcome definition

The objective of this meta-analysis was to quantify the impact of FDG PET in the diagnostic work-up of FUO. The outcome measure was the final diagnosis established during the follow-up period.

Search strategy

We conducted a comprehensive literature search of the PubMed/MEDLINE database from 2000 to September 2015 for studies in English using FDG PET in the diagnostic work-up of FUO. We used the search terms “fever of unknown origin” and “positron emission tomography”. Reference lists of original complete studies or reviews were carefully checked to identify articles missed by the database searches. Studies by the same single author were carefully checked to ensure that there were no overlapping data.

Study selection and data extraction

All original articles with patients fulfilling the following criteria were included: (1) FUO as the initial diagnosis, according to the standard criteria [9]; (2) no immunosuppression or nosocomial conditions; (3) a final diagnosis that was not based on PET data; (4) the follow-up period for the final diagnostic assessment reported; (5) adult population; and (6) availability of adapted quantitative data for calculation of odds ratios (ORs). Case reports and original studies with fewer than ten participants were excluded from this meta-analysis, as well as studies that were not written in English.

Two reviewers (F.B. and M.P.) independently extracted the following data from all included studies: first author, year of publication, inclusion period to avoid potential overlapping data, country, study design, population characteristics (sample size, gender, age, follow-up period, aetiological category and number of final diagnoses obtained, number of undiagnosed cases), and PET technical characteristics (device, number of patients with abnormal PET findings). Discrepancies were resolved by consensus between the two reviewers.

Data synthesis and statistical analysis

For each study, two subgroups of patients were defined based on the PET findings: an “abnormal PET” subgroup and a “normal PET” subgroup based on the visual distribution of the ^{18}F-FDG radiopharmaceutical. A PET finding related to nonphysiological uptake was considered abnormal. Other findings were considered normal. For each subgroup, the number of events (e.g. definitive diagnosis) and the total number of PET scans in the subgroup of interest allowed computation of study-related ORs. ORs from all individual studies were then pooled to globally quantify the strength of association between the outcome measure (final diagnosis) and the PET data. The results are presented as forest plots with study-specific ORs, their 95 % confidence intervals (CIs), and the relative weighted contribution of each study, as well as the estimated OR pooled across all studies.

We used a Mantel-Haenszel random-effects model, which is indicated when variations in sampling schemes could introduce heterogeneity in the results. Statistical significance was set at the two-tailed 0.05 level. Publication bias was assessed visually by examination of funnel plots. Between-study heterogeneity was assessed with chi-squared and I^2 statistics. Significant heterogeneity was set at the level of $p < 0.10$ and $I^2 > 50$ %.

A stratification-based sensitivity analysis was finally performed to investigate discrepancies among studies. Sensitivity analyses were performed using the following prespecified criteria: (a) study design, (b) PET device (dedicated or hybrid), (c) geographic area, and (d) follow-up period. All statistical computations were performed with Review Manager (RevMan) software, version 5.2 (The Cochrane Collaboration, 2012; The Nordic Cochrane Centre, Copenhagen).

Results

Literature search

Figure 1 shows the selection process in detail. The literature search found 241 references. Among them, 127 records not directly related to FUO were excluded. Of the remaining studies, 71 were excluded because they were case reports, small sample studies (fewer than ten patients), reviews, editorials or comments, and 43 full-text articles were assessed for eligibility. Of these 43 articles, 29 did not fulfil the selection criteria. Thus, 14 full-text articles were retained for the meta-analysis.

Included studies: main characteristics

Among the 14 included studies, ten patients were excluded from the analysis because they did not fulfil our inclusion criteria: one 5-year-old patient [20], seven HIV patients [21], and two patients who died before the end of the diagnostic work-up [22].

Tables 1 and 2 summarize the characteristics of the 712 included patients. Among them, 446 had abnormal PET findings (mean 63.5 %, range between studies 43–84 %), and 11–69 % (mean 48 %) of the PET findings were considered to have contributed to the final diagnosis. The follow-up periods ranged from 3 to 29 months. At the end of follow-up, 466 patients had a final diagnosis, including infections (198 patients, 42 %), NIID (153 patients, 33 %), malignancy (80 patients, 17 %), and "miscellaneous" (35 patients, 8 %). The majority of studies (9 of the 14) were retrospective [20–28], and in 7 of the 14 PET/CT was used [20–22, 25–29], including a PET and PET/CT case-mixed study [21].

Statistical analysis

The random-effects model revealed an increases in the absolute final diagnosis rate of 36 % if the PET findings were normal and 83 % if the PET findings were abnormal. This corresponds to an overall pooled OR of 8.94 (95 % CI 4.18–19.12; Fig. 2). Although the overall effect was highly significant ($Z=5.65$; $p<0.00001$), heterogeneity across studies was high ($p=0.0002$, $I^2=67$ %), justifying the use of a random-effects model. Funnel plots were relatively symmetrical, indicating the absence of major publication bias (Fig. 3).

Sensitivity analyses

The sensitivity analysis showed a significant difference between prospective and retrospective studies ($p=0.01$; Fig. 4). Retrospective designs led to a significantly higher final diagnostic rate if the PET findings were abnormal (OR 18.57, 95 % CI 7.57–45.59) compared with prospective designs (OR 2.92, 95 % CI 1.00–8.53). The effect was as much as four times higher for hybrid PET/CT studies (OR 18.17, 95 % CI 5.86–

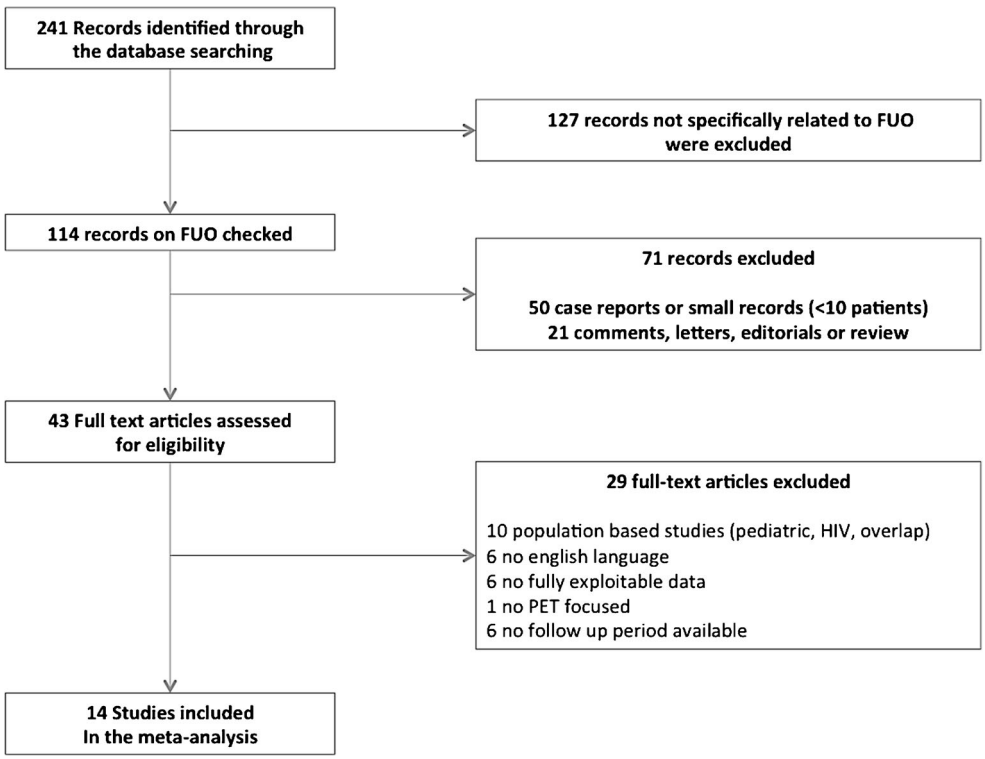

Fig. 1 The selection process

Table 1 Details of the 14 included studies

Reference	Inclusion period	Country	Design	Follow-up (months)	Sex ratio (M/F)	Age of patients (years), mean (SD)
[23]	1998 – 2000	Germany	Retrospective	3	9/7	44 (17 – 78)[a]
[24]	1999 – 2002	Netherlands	Retrospective	22	15/20	50.5 (18 – 82)[b]
[17]	1999 – 2001	Belgium	Prospective	29	40/34	53.5 (34 – 68)[b]
[37]	2001 – 2003	Denmark	Prospective	4	12/7	49 (27 – 82)
[18]	2003 – 2005	Netherlands	Prospective	22	32/38	53 (26 – 87)
[25]	2005 – 2008	Netherlands	Retrospective	4 – 24	33/35	NA (23 – 91)
[20]	NA	Turkey	Retrospective	3	17/6	54 (18 – 77)[a]
[21]	2006 – 2007	Japan	Retrospective	3	NA	NA
[29]	2007 – 2009	China	Prospective	10	34/14	57 (24 – 82)
[22]	2005 – 2010	Denmark	Retrospective	>12	11/11	53 (17 – 87)[a]
[34]	2007 – 2010	UK	Prospective	6	17/6	NA (33 – 83)
[26]	NA	India	Retrospective	6	NA	NA
[28]	2008 – 2012	Turkey	Retrospective	12	11/14	59 (16 – 88)[a]
[27]	2008 – 2012	Israel	Retrospective	6	57/55	58 (19 – 94)[b]

NA not available

[a] Recomputed

[b] Estimated from median and range values [38]

56.34) compared with dedicated PET studies (OR 4.52, 95 % CI 1.33 – 15.36). However, the difference was not significant ($p = 0.1$; Fig. 5). Finally, the sensitivity analyses based on geographic area (Fig. 6) and follow-up period (Fig. 7) criteria showed no significant difference in pooled ORs between the groups ($p = 0.59$ and $p = 0.70$, respectively), revealing no impact of these factors on the results.

Table 2 Contribution of PET to the final diagnosis in the 14 included studies

Reference	No. of patients undergoing PET	Abnormal PET findings, *n* (%)	PET contribution (%)	Modality	Final diagnosis assessed				
					Malignant	NIID	Infection	Miscellaneous	Total
[23]	16	12 (75)	69	PET	1	8	4	0	13
[24]	35	15 (43)	37	PET	4	6	6	3	19
[17]	74	53 (72)	26	PET	4	12	7	16	39
[37]	19	9 (47)	11	PET	1	5	6	0	12
[18]	70	33 (47)	33	PET	5	16	12	2	35
[25]	68	41 (60)	56	PET/CT	2	14	25	3	44
[20]	23[a]	18 (78)	52	PET/CT	5	3	3	2	13
[21]	74[b]	45 (61)	32	Mixed	2	25	25	3	55
[29]	48	40 (83)	67	PET/CT	12	9	15	0	36
[22]	22[c]	12 (55)	46	PET/CT	3	7	1	1	12
[34]	23	14 (61)	52	PET	1	8	6	0	15
[26]	103	63 (61)	60	PET/CT	22	13	31	3	69
[28]	25	21 (84)	60	PET/CT	3	10	8	0	21
[27]	112	69 (62)	67	PET/CT	15	17	49	2	83

[a] One 5-year-old patient excluded

[b] Seven HIV patients excluded

[c] Recomputed because only 24 of the 52 mentioned patients underwent FDG PET/CT, and two patients without a diagnosis died before the end of follow-up

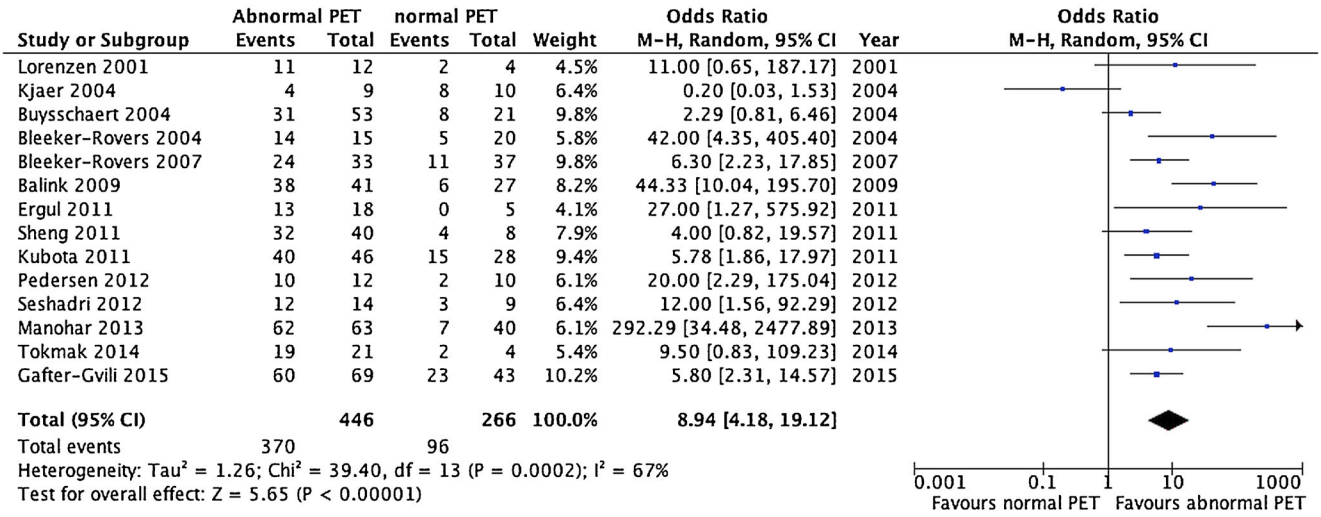

Fig. 2 The forest plot shows the strength of the association between PET findings (abnormal versus normal) and the final diagnostic assessment. The pooled OR is 8.94. For Kubota et al. [21], grade 2 (uptake visually higher than background uptake) was considered positive

Discussion

Summary of the results

We present here the first attempt to quantify the contribution of PET findings to the diagnostic work-up of FUO, taking into account the diagnostic limitations resulting from the composite nature of this entity. Abnormal PET findings, which represented two thirdsof the PET data, were strongly associated with a higher rate of definitive diagnosis. Infections were the most frequent diagnosis (42 %), and NIID the second most frequent diagnosis (33 %), whereas malignancy was identified in 17 % and miscellaneous diseases in 8 % of patients. Sensitivity analyses failed to indicate the superiority of PET/CT over dedicated PET (OR 18.17 vs. 4.52, $p = 0.1$). Previous studies have indicated that geographic area [30] and follow-up period [31] are factors affecting the diagnostic variability in FUO. In our stratified pooled analyses, these criteria had no statistically significant impact and could not explain the heterogeneity of the results.

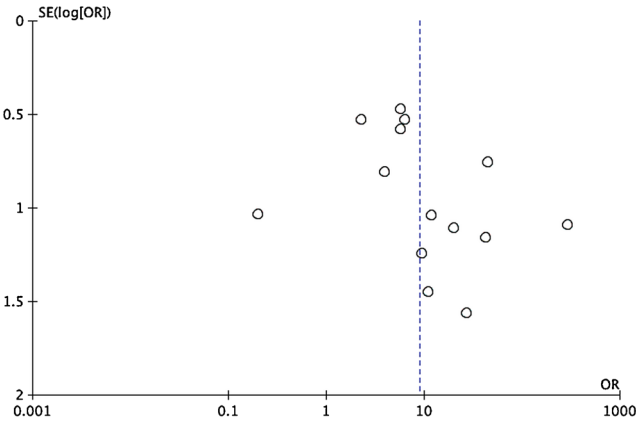

Fig. 3 The funnel plot (effect size of individual studies versus the OR from each study) indicates absence of major publication bias

Performance and position of FDG PET in FUO

Two studies formally assessed the diagnostic performance of FDG PET in FUO [14, 15]. In a meta-analysis by Dong et al., five FDG PET studies including 214 patients provided a pooled sensitivity and specificity of 83 % (95 % CI 0.73–0.90) and 58 % (95 % CI 0.49–0.67), respectively, and four FDG PET/CT studies including 174 patients provided a pooled sensitivity and specificity of 98 % (95 % CI 0.936–0.998) and 86 % (95 % CI 0.750–0.934), respectively [14]. Hao et al. performed a sensitivity analysis of FDG PET/CT in FUO including 595 patients (combining the results in adults and children), and found a pooled sensitivity of 85 % (95 % CI 81–88 %, AUC = 0.88) [15]. More than 200 aetiologies for FUO have been described [16], and 10–60 % of patients remain undiagnosed despite follow-up [18, 31–33]. Such considerations associated with the lack of reference standards significantly affect the relevance of sensitivity and specificity in FUO, as well as of their derived parameters (positive and negative predictive values, likelihood ratios). Consequently, these performance measures are potentially unsuitable for use in FUO. For these reasons, we propose an original approach that does not depend on these diagnostic limitations.

Beyond a different methodological approach and a twofold larger data sample, the findings of our study corroborated those of Dong et al. [14] in failing to show significant differences between PET and PET/CT. This is surprising because accurate attenuation correction, precise anatomical localization and better characterization of metabolic foci make PET/CT currently the best procedure. Interestingly, the recent study of FUO by Gafter-Gvili et al. showed that contrast-enhanced

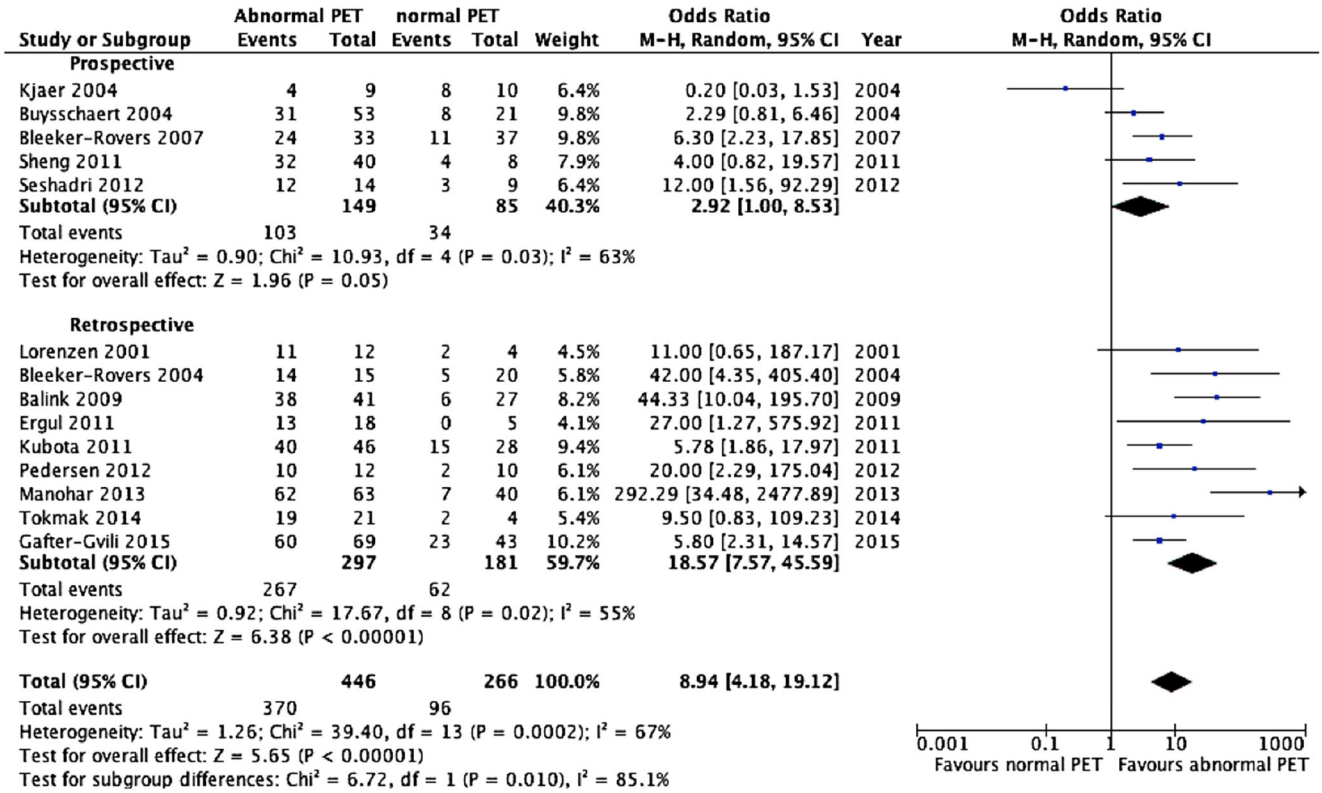

Fig. 4 Sensitivity analysis: study design. The forest plot shows the strength of association of between PET findings (abnormal versus normal) and the final diagnostic assessment with the analysis stratified based on the study design (prospective versus retrospective)

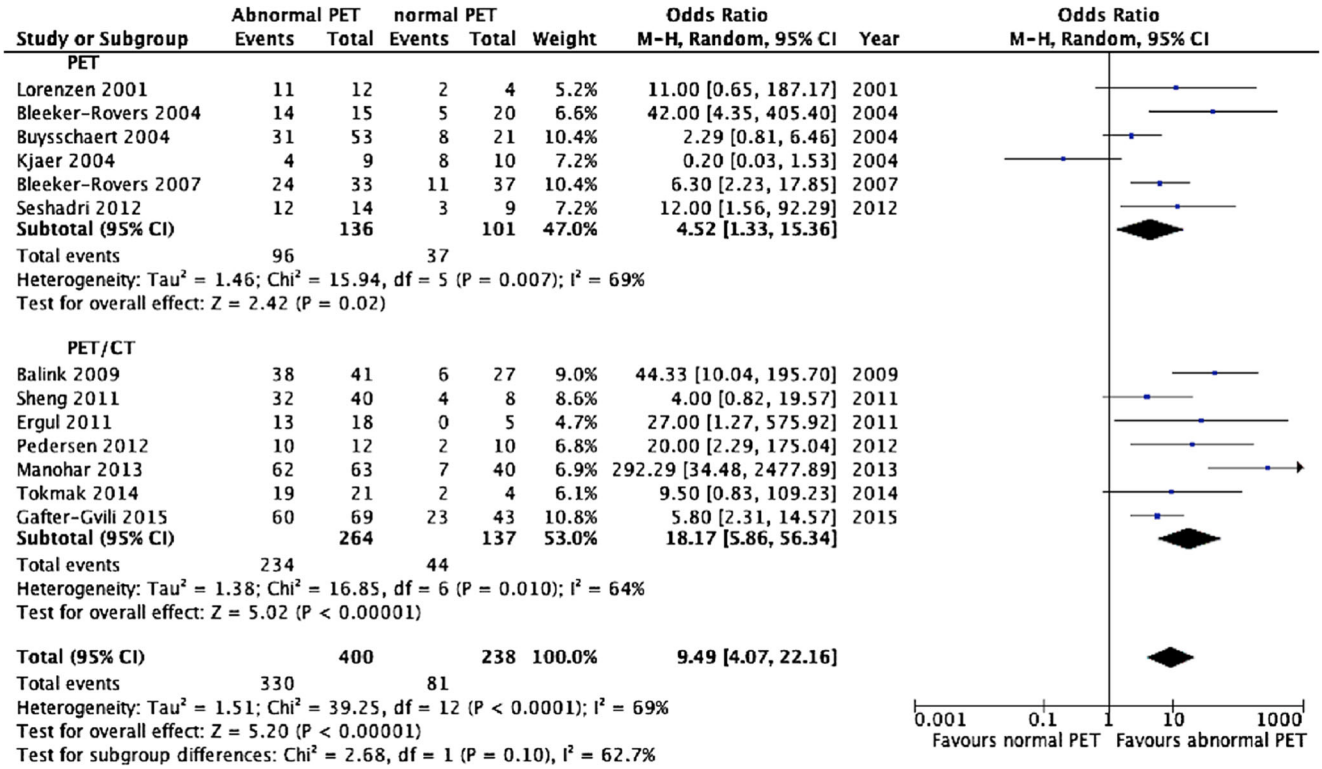

Fig. 5 Sensitivity analysis imaging device. The forest plot shows the strength of association of between PET findings (abnormal versus normal) and the final diagnostic assessment with the analysis stratified based on the PET device (PET versus PET/CT). The study by Kubota et al. [21] was excluded because it was a PET and PET/CT mixed case study

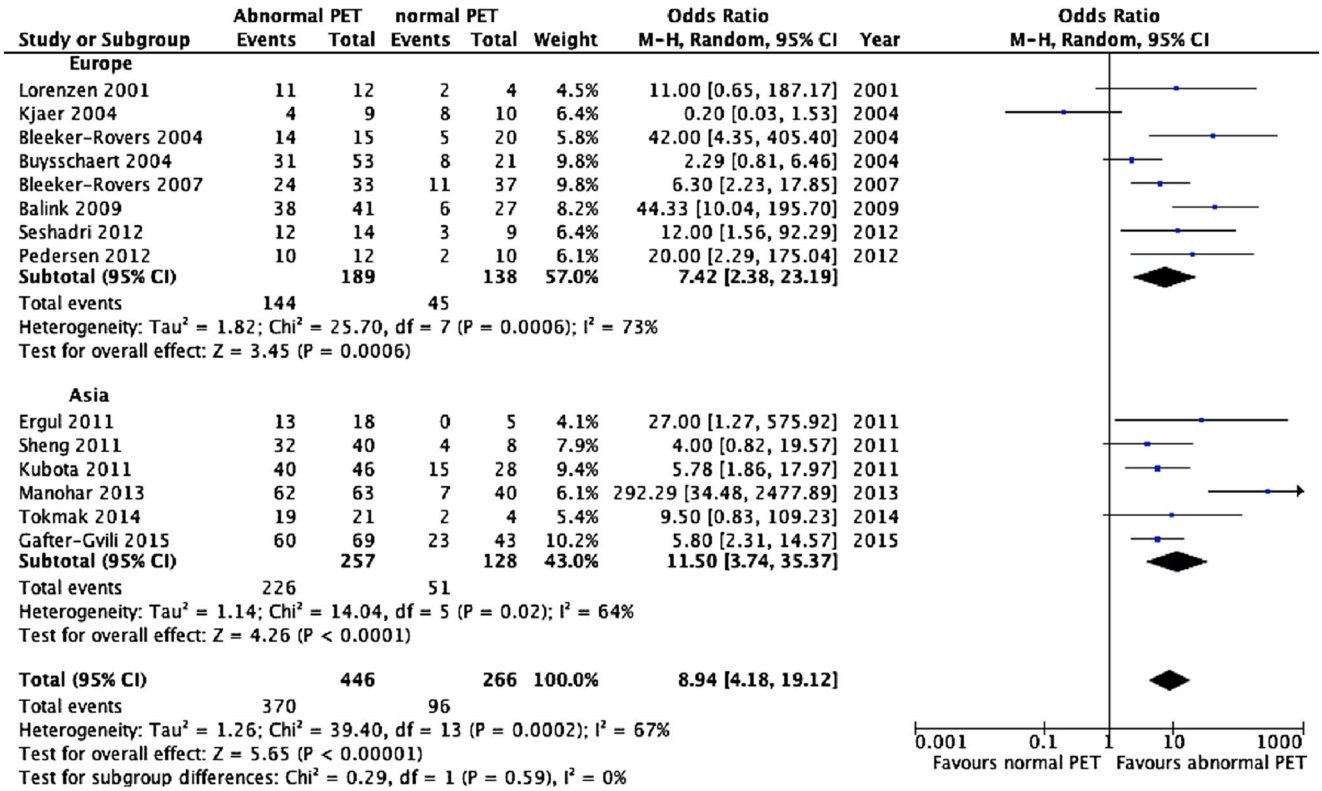

Fig. 6 Sensitivity analysis: geographic area. The forest plot shows the strength of association of between PET findings (abnormal versus normal) and the final diagnostic assessment with the analysis stratified based on geographic area (Europe versus Asia)

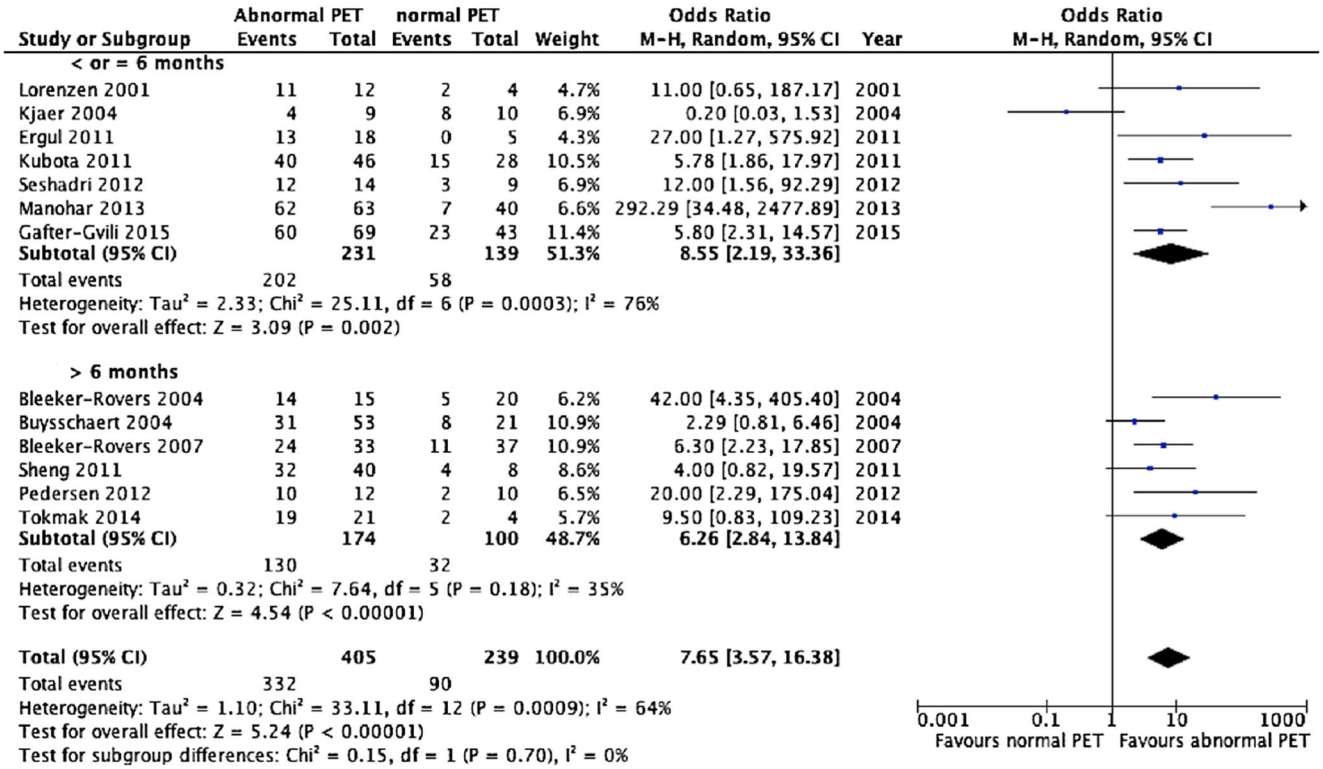

Fig. 7 Sensitivity analysis: follow-up period. The forest plot shows the strength of association of between PET findings (abnormal versus normal) and the final diagnostic assessment with the analysis stratified based on the follow-up period ≤6 versus >6 months). The study by Balink et al. [25] was excluded because the threshold at the 6-month follow-up was unavailable

PET/CT is more effective than PET/CT without contrast enhancement [27]. In our study, the majority of PET/CT procedures were performed without contrast enhancement, and the low "CT diagnostic quality" of the PET/CT could partially explain the lack of statistically significant superiority of PET/CT over PET, despite higher ORs. Nevertheless, the benefit of contrast-enhanced CT versus CT without contrast enhancement in PET/CT is still a matter of controversy, and this point should be investigated in further prospective studies of FUO. Additionally, it is important to note that currently there are no structured guidelines for the diagnostic work-up of FUO. The diagnostic strategy typically includes first-line procedures (general examination, laboratory tests and standard conventional imaging modalities including CT) and second-line procedures (advanced imaging techniques such as FDG PET and invasive analyses such as tissue biopsy).

One major problem concerns the definition of "helpful" FDG PET in the literature. In the majority of studies, only positive PET foci that directly led to a final diagnosis were considered "helpful". Thus, the fact that abnormal FDG PET findings may indirectly stimulate other diagnostic procedures (imaging methods, biology, biopsy or surgery) was rarely considered. In our meta-analysis, two studies explicitly considered negative PET findings as clinically "helpful" when no final diagnosis was obtained at the end of the follow-up period [27, 34]. This discrepancy in the definition of the value of PET can be explained by the fact that FDG PET, in the majority of cases, arises as a part of the second-line strategy. Beyond these considerations, limiting the number of useless imaging procedures is of great interest in FUO. Recently, FDG PET/CT has been shown to be cost effective in the diagnostic work-up of inflammation of unknown origin by limiting the number of diagnostic procedures [35]. In our study, two thirds of the PET examinations were considered abnormal, and these findings were significantly associated with a greatly increased rate of agreement with the final diagnosis. All these results strongly suggest the value of FDG PET as part of the first-line diagnostic strategy in FUO. These findings should be considered in future prospective studies to improve the global strategy for exploring FUO.

Potential limitations of the study

FUO is a composite entity that includes a wide variety of heterogeneous conditions. We attempted to control for this intrinsic heterogeneity by excluding HIV-related and nosocomial FUO, as their management and prognosis are specific [36]. The use of a random-effects model contributed to limiting the impact of heterogeneity. Additionally, we performed stratification-based analyses to incorporate the risk of bias assessment. However, the lack of a structured diagnostic work-up may have been led to the presence of selection bias in the screened populations, but, to date, only in one prospective study has the strategic integration of PET/CT in a structured diagnostic work-up been proposed [18]. Another point, as mentioned above, is that the usefulness of FDG PET in FUO does not consider as potentially helpful positive PET findings that are not directly related to the final diagnosis. By quantifying the strength of the association between PET findings and final diagnosis, our approach integrated the potential contributions of both direct and indirect FDG PET. Even if the notion of an indirect contribution is a limitation of the study, this approach has the major advantage that it does not suffer from a lack of reference standards or unsuitable true-negative or false-negative definitions.

Conclusion

Abnormal FDG PET findings are associated with a substantial increase in the rate of agreement with the final diagnosis in FUO. Regarding these results, FDG PET could be considered for inclusion in the first-line diagnostic work-up of FUO. Further randomized prospective studies with first-line versus second-line standardized optimized FDG PET procedures are warranted to confirm this position.

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Compliance with ethical standards This article does not describe any studies with human participants performed by any of the authors.

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Conflicts of interest None.

References

1. Gillies RJ, Robey I, Gatenby RA. Causes and consequences of increased glucose metabolism of cancers. J Nucl Med. 2008;49 Suppl 2:24S–42. doi:10.2967/jnumed.107.047258.
2. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science. 2009;324:1029–33. doi:10.1126/science.1160809.
3. Mochizuki T, Tsukamoto E, Kuge Y, Kanegae K, Zhao S, Hikosaka K, et al. FDG uptake and glucose transporter subtype expressions in experimental tumor and inflammation models. J Nucl Med. 2001;42:1551–5.
4. Yamada S, Kubota K, Kubota R, Ido T, Tamahashi N. High accumulation of fluorine-18-fluorodeoxyglucose in turpentine-induced inflammatory tissue. J Nucl Med. 1995;36:1301–6.
5. Gamelli RL, Liu H, He LK, Hofmann CA. Augmentations of glucose uptake and glucose transporter-1 in macrophages following thermal injury and sepsis in mice. J Leukoc Biol. 1996;59:639–47.
6. Fukuzumi M, Shinomiya H, Shimizu Y, Ohishi K, Utsumi S. Endotoxin-induced enhancement of glucose influx into

murine peritoneal macrophages via GLUT1. Infect Immun. 1996;64:108–12.
7. Boellaard R, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging. 2015;42:328–54. doi:10.1007/s00259-014-2961-x.
8. Jamar F, Buscombe J, Chiti A, Christian PE, Delbeke D, Donohoe KJ, et al. EANM/SNMMI guideline for 18F-FDG use in inflammation and infection. J Nucl Med. 2013;54:647–58. doi:10.2967/jnumed.112.112524.
9. Petersdorf RG. Fever of unknown origin. An old friend revisited. Arch Intern Med. 1992;152:21–2.
10. Durack DT, Street AC. Fever of unknown origin – reexamined and redefined. Curr Clin Top Infect Dis. 1991;11:35–51.
11. Nazar AH, Naswa N, Sharma P, Soundararajan R, Bal C, Malhotra A, et al. Spectrum of 18F-FDG PET/CT findings in patients presenting with fever of unknown origin. AJR Am J Roentgenol. 2012;199:175–85. doi:10.2214/AJR.11.7570.
12. Kouijzer IJ, Bleeker-Rovers CP, Oyen WJ. FDG-PET in fever of unknown origin. Semin Nucl Med. 2013;43:333–9. doi:10.1053/j.semnuclmed.2013.04.005.
13. Sioka C, Assimakopoulos A, Fotopoulos A. The diagnostic role of (18)F fluorodeoxyglucose positron emission tomography in patients with fever of unknown origin. Eur J Clin Invest. 2015;45:601–8. doi:10.1111/eci.12439.
14. Dong MJ, Zhao K, Liu ZF, Wang GL, Yang SY, Zhou GJ. A meta-analysis of the value of fluorodeoxyglucose-PET/PET-CT in the evaluation of fever of unknown origin. Eur J Radiol. 2011;80:834–44. doi:10.1016/j.ejrad.2010.11.018.
15. Hao R, Yuan L, Kan Y, Li C, Yang J. Diagnostic performance of 18F-FDG PET/CT in patients with fever of unknown origin: a meta-analysis. Nucl Med Commun. 2013;34:682–8. doi:10.1097/MNM.0b013e328361cd0e.
16. Arnow PM, Flaherty JP. Fever of unknown origin. Lancet. 1997;350:575–80. doi:10.1016/S0140-6736(97)07061-X.
17. Buysschaert I, Vanderschueren S, Blockmans D, Mortelmans L, Knockaert D. Contribution of (18)fluoro-deoxyglucose positron emission tomography to the work-up of patients with fever of unknown origin. Eur J Intern Med. 2004;15:151–6. doi:10.1016/j.ejim.2004.01.018.
18. Bleeker-Rovers CP, Vos FJ, Mudde AH, Dofferhoff AS, de Geus-Oei LF, Rijnders AJ, et al. A prospective multi-centre study of the value of FDG-PET as part of a structured diagnostic protocol in patients with fever of unknown origin. Eur J Nucl Med Mol Imaging. 2007;34:694–703. doi:10.1007/s00259-006-0295-z.
19. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535. doi:10.1136/bmj.b2535.
20. Ergul N, Halac M, Cermik TF, Ozaras R, Sager S, Onsel C, et al. The diagnostic role of FDG PET/CT in patients with fever of unknown origin. Mol Imaging Radionucl Ther. 2011;20:19–25. doi:10.4274/MIRT.20.04.
21. Kubota K, Nakamoto Y, Tamaki N, Kanegae K, Fukuda H, Kaneda T, et al. FDG-PET for the diagnosis of fever of unknown origin: a Japanese multi-center study. Ann Nucl Med. 2011;25:355–64. doi:10.1007/s12149-011-0470-6.
22. Pedersen TI, Roed C, Knudsen LS, Loft A, Skinhoj P, Nielsen SD. Fever of unknown origin: a retrospective study of 52 cases with evaluation of the diagnostic utility of FDG-PET/CT. Scand J Infect Dis. 2012;44:18–23. doi:10.3109/00365548.2011.603741.
23. Lorenzen J, Buchert R, Bohuslavizki KH. Value of FDG PET in patients with fever of unknown origin. Nucl Med Commun. 2001;22:779–83.
24. Bleeker-Rovers CP, de Kleijn EM, Corstens FH, van der Meer JW, Oyen WJ. Clinical value of FDG PET in patients with fever of unknown origin and patients suspected of focal infection or inflammation. Eur J Nucl Med Mol Imaging. 2004;31:29–37. doi:10.1007/s00259-003-1338-3.
25. Balink H, Collins J, Bruyn GA, Gemmel F. F-18 FDG PET/CT in the diagnosis of fever of unknown origin. Clin Nucl Med. 2009;34:862–8. doi:10.1097/RLU.0b013e3181becfb1.
26. Manohar K, Mittal BR, Jain S, Sharma A, Kalra N, Bhattacharya A, et al. F-18 FDG-PET/CT in evaluation of patients with fever of unknown origin. Jpn J Radiol. 2013;31:320–7. doi:10.1007/s11604-013-0190-z.
27. Gafter-Gvili A, Raibman S, Grossman A, Avni T, Paul M, Leibovici L, et al. [18F]FDG-PET/CT for the diagnosis of patients with fever of unknown origin. QJM. 2015;108:289–98. doi:10.1093/qjmed/hcu193.
28. Tokmak H, Ergonul O, Demirkol O, Cetiner M, Ferhanoglu B. Diagnostic contribution of (18)F-FDG-PET/CT in fever of unknown origin. Int J Infect Dis. 2014;19:53–8. doi:10.1016/j.ijid.2013.10.009.
29. Sheng JF, Sheng ZK, Shen XM, Bi S, Li JJ, Sheng GP, et al. Diagnostic value of fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography in patients with fever of unknown origin. Eur J Intern Med. 2011;22:112–6. doi:10.1016/j.ejim.2010.09.015.
30. Tabak F, Mert A, Celik AD, Ozaras R, Altiparmak MR, Ozturk R, et al. Fever of unknown origin in Turkey. Infection. 2003;31:417–20. doi:10.1007/s15010-003-3040-6.
31. de Kleijn EM, Vandenbroucke JP, van der Meer JW. Fever of unknown origin (FUO). I A. prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. The Netherlands FUO Study Group. Medicine (Baltimore). 1997;76:392–400.
32. Mourad O, Palda V, Detsky AS. A comprehensive evidence-based approach to fever of unknown origin. Arch Intern Med. 2003;163:545–51.
33. de Kleijn EM, van der Meer JW. Fever of unknown origin (FUO): report on 53 patients in a Dutch university hospital. Neth J Med. 1995;47:54–60.
34. Seshadri N, Sonoda LI, Lever AM, Balan K. Superiority of 18F-FDG PET compared to 111In-labelled leucocyte scintigraphy in the evaluation of fever of unknown origin. J Infect. 2012;65:71–9. doi:10.1016/j.jinf.2012.02.008.
35. Balink H, Tan SS, Veeger NJ, Holleman F, van Eck-Smit BL, Bennink RJ, et al. (18)F-FDG PET/CT in inflammation of unknown origin: a cost-effectiveness pilot-study. Eur J Nucl Med Mol Imaging. 2015;42:1408–13. doi:10.1007/s00259-015-3010-0.
36. Knockaert DC, Vanderschueren S, Blockmans D. Fever of unknown origin in adults: 40 years on. J Intern Med. 2003;253:263–75.
37. Kjaer A, Lebech AM, Eigtved A, Hojgaard L. Fever of unknown origin: prospective comparison of diagnostic value of 18F-FDG PET and 111In-granulocyte scintigraphy. Eur J Nucl Med Mol Imaging. 2004;31:622–6. doi:10.1007/s00259-003-1425-5.
38. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13. doi:10.1186/1471-2288-5-13.