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DOI:

[10.1016/j.crad.2017.04.014](https://doi.org/10.1016/j.crad.2017.04.014)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Bharucha, T., Rutherford, A., Skeoch, S., Alavi, A., Brown, M., Galloway, J., Miller, R., Llewelyn, M., Jenkins, N., Lambourne, J., Cosgrove, C., Moore, E., Conlon, C., NicFhogartaigh, C., Agranoff, D., Ustianowski, A., Parker, B., Gullick, N., Snowden, N., ... Marks, D. (2017). Diagnostic yield of FDG-PET/CT in fever of unknown origin: a systematic review, meta-analysis, and Delphi exercise. *Clinical Radiology*, 72(9), 764-771.
<https://doi.org/10.1016/j.crad.2017.04.014>

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Clinical Radiology

Diagnostic Yield of FDG-PET/CT in Fever of Unknown Origin: A Systematic Review, Meta-analysis and Delphi Exercise.

--Manuscript Draft--

| | |
|--|---|
| Manuscript Number: | CRAD-D-17-00145R1 |
| Full Title: | Diagnostic Yield of FDG-PET/CT in Fever of Unknown Origin: A Systematic Review, Meta-analysis and Delphi Exercise. |
| Article Type: | Original Paper |
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| Abstract: | <p>Aim: To perform a systematic review, meta-analysis and Delphi exercise to evaluate diagnostic yield of 2-[18F]-fluoro-2-deoxy-D-glucose-Positron-Emission-Tomography/Computed-Tomography (FDG-PET/CT) in Fever of Unknown Origin (FUO).</p> <p>Materials and Methods: Study-ID CRD42016032696. Four databases were searched for studies of FDG-PET/CT in FUO 1/1/2000-1/12/2015. Exclusions were non-English language, case reports, non-standard FDG-radiotracer and significant missing data. Quality was assessed by two authors independently using a standardised tool. Pooled diagnostic yield was calculated using a random-effects model. An iterative electronic and face-to-face Delphi generated interspeciality consensus.</p> <p>Results: Pooled diagnostic yield was 56% (95%CI 50-61%), I²=61%, 18 studies and 905 patients. Only 5 studies reported results of previous imaging, and sub-group analysis estimated diagnostic yield beyond conventional CT at 32% (95%CI 22-44%), I²=66%. Consensus was established that FDG-PET/CT is increasingly available with an emerging role, but there is prevailing variability in practice.</p> <p>Conclusion: There is insufficient evidence to support the value of FDG-PET/CT in investigative algorithms of FUO. We need a paradigm shift in research, involving prospective studies recruiting at diagnosis of FUO, with updated case definitions and hard outcome measures. While these studies will be a significant undertaking with multi-centre collaboration, their completion is vital for balancing both radiation exposure and costs against possible benefits of utilising FDG-PET/CT.</p> |

Title

Diagnostic Yield of FDG-PET/CT in Fever of Unknown Origin: A Systematic Review, Meta-analysis and Delphi Exercise.

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Acknowledgements

With sincere thanks to the FDG-PET/CT in FUO Working Group: Robert Miller, Martin Llewelyn, Neil Jenkins, John Lambourne, Catherine Cosgrove, Elinor Moore, Chris Conlon, Coaimh NicFhogartaigh, Daniel Agranoff, Andy Ustianowski, Benjamin Parker, Nicola Gullick, Neil Snowden, David Jayne, Marwan Bukhari, Kevin Davies, Wendy Stewart, Kirit Ardeshta, Mohamedbhai Sajir, Dr Jamshed Bomanji, Haroon Athar, Wai-lup Wong, Amy Eccles, Manil Subesinghe, Neel Patel, Fahmid Chowdhury, John Buscombe, Sabina Dizdeveric and Dan Marks.

We are also indebted to the Special Trustees of the Hospital of Tropical Diseases for their generous contribution, and the exceptional support of the late Dr Manek-Phiroz Eddie Bharucha.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The face-to-face meeting was supported by a grant from the Special Trustees of the Hospital of Tropical Diseases

Conflicts of Interest

No authors have any conflicts of interest

Authors Contributions

| | TB | AR | SS | AA | MB | JG |
|---|-----|-----|-----|-----|-----|-----|
| 1. Guarantor of integrity of the entire study | + | | | | | |
| 2. Study concepts and design | + | + | | | + | + |
| 3. Literature research | + | + | + | + | + | + |
| 4. Clinical studies | N/A | N/A | N/A | N/A | N/A | N/A |
| 5. Experimental studies / data analysis | N/A | N/A | N/A | N/A | N/A | N/A |
| 6. Statistical analysis | + | + | + | | + | + |
| 7. Manuscript preparation | + | + | + | | + | + |
| 8. Manuscript editing | + | + | + | + | + | + |

Aim: To perform a systematic review, meta-analysis and Delphi exercise to evaluate diagnostic yield of 2-[18F]-fluoro-2-deoxy-D-glucose-Positron-Emission-Tomography/Computed-Tomography (FDG-PET/CT) in Fever of Unknown Origin (FUO).

Materials and Methods: Study-ID CRD42016032696. Four databases were searched for studies of FDG-PET/CT in FUO 1/1/2000-1/12/2015. Exclusions were non-English language, case reports, non-standard FDG-radiotracer and significant missing data. Quality was assessed by two authors independently using a standardised tool. Pooled diagnostic yield was calculated using a random-effects model. An iterative electronic and face-to-face Delphi generated interspeciality consensus.

Results: Pooled diagnostic yield was 56% (95%CI 50-61%), I²=61%, 18 studies and 905 patients. Only 5 studies reported results of previous imaging, and sub-group analysis estimated diagnostic yield beyond conventional CT at 32% (95%CI 22-44%), I²=66%. Consensus was established that FDG-PET/CT is increasingly available with an emerging role, but there is prevailing variability in practice.

Conclusion: There is insufficient evidence to support the value of FDG-PET/CT in investigative algorithms of FUO. We need a paradigm shift in research, involving prospective studies recruiting at diagnosis of FUO, with updated case definitions and hard outcome measures. While these studies will be a significant undertaking with multi-centre collaboration, their completion is vital for balancing both radiation exposure and costs against possible benefits of utilising FDG-PET/CT.

1 **Key words**

2 Imaging, Nuclear Medicine, Fever of Unknown Origin, Diagnostics

3

4

5 **Abbreviations**

6

7 CI Confidence Intervals

8 FDG-PET/CT 2-[18F]-fluoro-2-deoxy-D-glucose - Positron Emission Tomography/Computed
9 Tomography

10 FUO Fever of Unknown Origin

11 IQR Interquartile Range

12 IUO Inflammation of Unknown Origin

13 KPI Key Performance Indicator

14 Introduction

15 Fever as an isolated clinical presentation has challenged clinicians for decades^{1,2}. In 1961 Petersdorf
16 and Beeson provided a case definition for 'fever (or pyrexia) of unknown origin': 1) a body
17 temperature above 38.3°C; 2) on several occasions; with 3) a duration of illness of at least three
18 weeks; and 4) no diagnosis within one week of hospital admission²⁻⁴. Fifty years on, definitions of
19 FUO and the spectrum of aetiologies have evolved, however the diagnostic challenges remain⁴. FUO
20 represents an estimated 2.9% of hospital admissions, with morbidity associated with prolonged
21 hospital stay, repeated cycles of invasive investigations and presumptive treatment, mortality rates
22 between 12-35%, and cost implications⁵.

23 2-[18F]-fluoro-2-deoxy-D-glucose (FDG)-Positron-Emission-Tomography/Computed-Tomography
24 (PET/CT) emerged at the end of the 20th century as an amalgamation between functional and
25 conventional anatomical imaging⁶. Its role in oncological staging has been well-defined, however in
26 other specialities there is less clarity⁷. Specifically, in the investigation of FUO the role of FDG-PET/CT
27 in clinical practice and diagnostic algorithms is inconsistent and unestablished. Existing guidelines
28 suggest that FDG-PET/CT *may* be used where conventional investigations have not revealed a
29 source⁸.

30 FDG-PET/CT is not associated with nephrotoxicity, and standard protocols expose patients to less
31 radiation than a conventional CT. An average FDG-PET/CT scan exposes a patient to 15mSv radiation,
32 approximately 5-6 years background radiation, rather than 20-25mSv in a contrast-enhanced chest-
33 abdomen-pelvis CT. Other advantages include imaging areas (e.g. head and neck, extremities) which
34 are beyond the range of most CT scans used in this context, and detection of vascular and truncal
35 musculoskeletal inflammation for which cross-sectional contrast CT imaging is insensitive. The main
36 caveats are cost and accessibility, FDG-PET/CT costing £800, compared to £250 for a contrast-
37 enhanced chest-abdomen-pelvis CT. However this could easily be remunerated by earlier definitive

38 treatment associated with additional diagnostic sensitivity. A marginally reduced length of inpatient
39 stay could mitigate the cost, with an average £400 for one night hospital admission⁹.

40 Current literature evaluating the role of FDG-PET/CT in FUO is based on observational data involving
41 small samples, outdated case definitions, and poor generalisability. Outcomes reported by existing
42 meta-analyses focus on sensitivity of FDG-PET/CT in FUO^{10, 11}. Sensitivity refers to the proportion of
43 cases with a diagnosis to explain the FUO for which FDG-PET/CT contributed to the diagnosis, or
44 $A/(A+B)$ (Table 1). This is statistically inappropriate as there is no reference standard for the
45 investigation of FUO to enable estimates of diagnostic accuracy¹². In comparison, 'diagnostic yield'
46 provides a more suitable outcome measure, calculated as the proportion of all FDG-PET/CT scans
47 (both normal and abnormal) that contribute to the diagnosis of FUO, $A/(A+B+C+D)$ (Table 1)¹³.
48 Strikingly, there has been limited analysis of diagnostic yield of FDG-PET/CT beyond that of
49 conventional CT. Further, previous meta-analyses have not studied individual patient data.

50

51 **Table 1**

52

53 We performed an up-to-date meta-analysis of the diagnostic yield of FDG-PET/CT in all patients with
54 FUO. Secondary outcomes included the proportion with an abnormal FDG-PET/CT, final diagnosis,
55 false positive results and mortality. The results of the meta-analysis were used to inform two rounds
56 of a Delphi survey and a half-day meeting, to develop a consensus on the current knowledge on the
57 role of FDG-PET/CT in FUO and inform future research.

58

59 **Materials and Methods**

60

61 Systematic Review and Meta-analysis

62 The protocol was prospectively registered with PROSPERO, an online international database of
63 systematic reviews (Study-ID CRD42016032696). It adhered to PRISMA guidelines. QUADAS-2,
64 STROBE, Cochrane guidelines and MOOSE guidelines were also utilised¹⁴⁻¹⁷.

65 Inclusion and Exclusion criteria: All patients were included irrespective of age, comorbidities or
66 immunocompromise. Inclusion criteria for FDG-PET/CT protocols were not defined, provided they
67 involved a standard [18]-FDG radiotracer. Exclusion criteria were case reports, significant missing
68 data such that the primary outcome could not be calculated and non-English studies.

69 Search strategy and study detection: See Table 2.

70

71 **Table 2**

72

73 Methodological quality assessment: Two authors (TB&AR) independently performed the quality
74 assessment and used this to identify studies to be included in the meta-synthesis. Disagreements
75 were resolved by a third author (SS). Existing research is restricted to case series and, in the absence
76 of comparison with a reference standard, these cannot be interpreted as diagnostic accuracy
77 studies. For this reason a specific quality assessment tool was utilised, with nine criteria scored as
78 'High', 'Unclear' or 'Low' risk of bias, see Supplement¹⁸. Each study is given a quality rating 'Poor',
79 'Fair' and 'Good', and quality assessment are summarised in Figure 3. The studies included in the
80 inter-rater agreement on the quality assessment is evaluated by a calculated kappa statistic, with

81 95% confidence intervals (CIs) ranging from zero (completely chance-explained agreement) and one
82 (perfect agreement)¹⁹.

83 Data extraction: A data extraction form was developed using Microsoft Excel, see Supplement, and
84 two authors (TB&R) independently piloted the form and subsequently performed the data
85 extraction. Disagreements were resolved by a third author (SS). Authors of included studies were
86 contacted for missing data.

87 Analysis: A qualitative synthesis and summary was performed. Results for studies included in the
88 quantitative analysis were calculated as proportions, with meta-analysis performed using a random-
89 effects model in Stata.13 to produce a summary outcome proportion with 95% CIs, and I² statistic for
90 heterogeneity. Sensitivity analyses was performed to exclude poor quality studies. Sub-group
91 analyses were performed for immunocompetent adults.

92

93 Delphi Consensus

94 The Delphi technique is an accepted method for generating consensus in a wide variety of
95 disciplines²⁰⁻²². It involves multiple iteration questionnaire surveys with anonymous and unbiased
96 methods. This study included 2-rounds of sequential pre-tested questionnaires, and a half-day face-
97 face meeting. The working-group included 30 UK-based clinicians with expertise in Epidemiology,
98 Research Methods, and Clinical Practice in the specialities of Nuclear Medicine, Radiology, Infectious
99 Diseases, Rheumatology, Haematology and General Medicine. The questionnaires were developed,
100 refined and administered, each consisting of single and multiple answer questions, free-text
101 comments, and 5-point Likert agreement scales. An initial survey was performed in 2015 before the
102 face-to-face meeting and consisted of 12 questions. After the meeting, a refined survey with 22
103 questions was performed. The surveys and discussion surrounded the current evidence and available
104 guidelines, availability of FDG-PET/CT, working case-definitions of FUO, position of FDG-PET/CT in

105 diagnostic algorithms of FUO, and potential factors involved in improving the outcomes in the
106 application of FDG-PET/CT. There was also a focus on the future direction of research. Consensus in
107 surveys (Supplement) was accepted if agreement (participants responding 'Strongly agree' or
108 'Agree') was over 60%.

109

110 **Results**

111

112 Systematic review and Meta-analysis

113 Study Selection: 22 studies were identified for the qualitative synthesis, and the quality assessment
114 selected 18 studies with a total of 905 patients for meta-analysis, see Figure 1. Interrater agreement
115 between reviewers was 91% with Kappa 0.85 and $P < 0.001$. Reasons for exclusions are displayed in
116 Supplementary Data²³⁻²⁶.

117

118 **Figure 1**

119

120 Quality Assessment and Study Design: The qualitative assessment demonstrated a high risk of bias
121 across all the included studies, see Figure 2. All the studies were observational case series with no
122 comparison group. They were largely (89%) retrospective, involving recruitment from the Nuclear
123 Medicine Department databases of patients referred for the indication of a FUO. The studies were
124 largely confined to tertiary care centres, and were geographically widely distributed across 15
125 different countries in Europe and Asia. The median sample size was 48 (Interquartile range, IQR 24-
126 74), with a median sample size per year 22 (IQR 8-29). The year of commencement of the studies
127 ranged from 2003-2010 (median 2007, IQR 2005-2007), with the year of publication ranging from
128 2008-2015 (median 2012, IQR 2010-2013). The median study duration was 35 (IQR 23-49) months.
129 There is insufficient data to report the proportion of children. Three studies included children and
130 none were exclusively performed in children. 50% of the over-all population was female. 10 (56%)
131 studies excluded immunocompromised patients.

132

133 **Figure 2**

134

135 Case definitions: The included studies largely reported standardised case definitions of FUO as a
136 fever for 3 weeks with at least one documented fever over 38°C (17, 94%). There was minimal
137 documentation on the duration of symptoms prior to admission or the length of inpatient stay.

138 Patients were referred to the nuclear medicine department for FDG-PET/CT at the discretion of the
139 responsible clinician. One study mandated discussion at a multidisciplinary meeting prior to referral.

140 Intervention: 17 (94%) studies reported details of their FDG-PET/CT protocols. The protocols
141 demonstrate the studies utilised the same radiotracer injected at a standard interval of 60-90 mins
142 prior to scan. 7 (39%) used IV and/or oral contrast. It was notable that at least 4 (28%) studies
143 utilised high-dose CT. One study incorporated a 24 hour carbohydrate restricted diet prior to the
144 scan to reduce non-specific cardiac uptake. No studies reported independent assessors interpreting
145 the scans, however 7 (39%) reported the involvement of discussion between two assessors, usually a
146 nuclear medicine physician and a radiologist.

147 Primary outcome: A meta-analysis of 18 studies suggest an overall diagnostic contribution of 56%
148 (95% CI 50-61%), I^2 61% of FDG-PET/CT in all patients with FUO, illustrated in the forest plot in Figure
149 3. Sub-group analysis for diagnostic contribution in 1) adults, 2) immunocompetent patients
150 ('classical FUO'), 3) immunocompetent adults and 4) immunocompetent adults without contrast
151 reduced the heterogeneity in the model, however the point estimate of diagnostic yield remained
152 largely unchanged, Forest Plots included in Supplementary Data.

153 Previous cross-sectional imaging and added contribution of FDG-PET/CT: There were sparse data on
154 the documentation or results of previous imaging. Previous investigations were reported in 12 (67%)
155 studies, with a median 51% (IQR 27-81%) receiving a CT prior to referral for FDG-PET/CT. Out of

156 these, 5 studies reported the results of previous imaging. A sub-group analysis of these data suggest
157 the diagnostic yield of FDG-PET/CT over CT is 32% (95% CI 22-44%), I^2 66%.

158

159 **Figure 3**

160

161 Secondary outcomes

162 Meta-analysis of the proportion with an abnormal FDG-PET/CT produced an overall result of 69%
163 (95% CI 63-75%), I^2 72. The higher proportion of abnormal scans was accounted for by a proportion
164 of 'false positives', abnormal scans with no contribution to the final diagnosis, with an overall result
165 of 9% (95% CI 5-14%), I^2 72. The overall estimate was low which is reassuring but there was striking
166 variation across individual studies, between 0 to 33% reported false positive scans.

167 73% (95% CI 68-78%) had a final diagnosis, mainly corresponding with three categories: infectious
168 diseases representing 30% (95% CI 26-35%), inflammatory causes 20% (95% CI 17-24%) and
169 malignancy 13% (95% CI 9-17%), data included in Supplementary Text. Individual patient data
170 extraction from 16/18 studies, totalling 749 patients facilitated stratification of diagnoses that did
171 and did not benefit from FDG-PET/CT, illustrated in Figures 4-6.

172 The presence of raised inflammatory markers were reported in 7 (39%) studies, and there were
173 insufficient data to suggest any association with contribution of FDG-PET/CT to diagnosis.

174 Methods for the establishment of the final diagnosis were not uniformly reported, however existing
175 data suggests a variety of methods including bone marrow, lymph node, tissue biopsy, serology,
176 microbiology cultures, immunology and autopsy.

177 There were limited data on the period of follow-up and final outcomes of patients. 12 (67%) studies
178 reported the length of follow-up, with median 6 (IQR 6-12) months.

179

180 **Figures 4-6**

181

182 Delphi Consensus

183 31/40 (78%) participants responded to the initial Delphi survey. 22/40 (55%) attended the face-to-
184 face meeting. 30/40 (75%) responded to the second Delphi. The initial Delphi survey consisted of
185 three parts aiming to assess 1) availability of FDG-PET/CT for FUO, 2) clinical practice in requesting of
186 FDG-PET/CT for FUO, and 3) decision-making in a hypothetical case of FUO, see Supplementary Data
187 for the full questionnaire. While 100% reported access to FDG-PET/CT, there was wide-variability in
188 reported time from referral to FDG-PET/CT ranging from 2 days to 2 weeks (UK Key Performance
189 Indicator, KPI 5 days), and time to reporting of scans ranging from 1 day to 1 week (UK KPI 2days).
190 There was widespread agreement (87% responders) that FDG-PET/CT does have a role in the
191 investigation of unknown origin (suggested to be 56%), however there was little consensus on sub-
192 groups or factors that might improve the diagnostic yield. There was also agreement in the value of
193 re-assessing patients for developing symptoms and signs, involving other specialities during the
194 investigation process, and involvement of nuclear medicine physicians in case discussions. The initial
195 survey demonstrated consensus of opinions that false positives needed to be taken into account in
196 the decision to refer, that FDG-PET/CT has a high negative predictive value and that false negatives
197 may arise due to empirical steroids.

198 The face-to-face meeting involved a presentation of the results of the systematic review, meta-
199 analysis and initial Delphi survey, with sufficient time for questions and discussion. There were
200 focussed debate surrounding the case-definition of FUO, investigations required and priority
201 outcomes. The meeting identified the variability in access and knowledge of FDG-PET/CT, the
202 heterogeneity and updated working definitions of FUO and dearth of evidence but encouraging

203 results in clinical practice. It highlighted the need for clinicians to be aware of the deficits of FDG-
204 PET/CT: not always imaging the brain, low sensitivity for cardiac and renal tract pathology and
205 reduced gastrointestinal uptake with certain medication. In contrast to previous opinions, there is no
206 evidence for poor glycaemic control as a contraindication to FDG-PET/CT. Further, the fact that low-
207 contrast imaging is incorporated into standard protocols does reduce the resolution as compared to
208 conventional contrast-CT. It was agreed that certain circumstances affect decision-making, e.g. renal
209 impairment, suitability for invasive tests and recent surgery. The meeting concluded with dialogue
210 on prospects and feasibility of future research. Current practice incorporates FDG-PET/CT late in
211 diagnostic algorithms, however there was acknowledgement that it may have a role as a 'front-
212 loaded' investigation in a subset of patients. This has potential to speed diagnosis, reduced radiation
213 exposure and shorten hospital stay, maybe reduce mortality.

214 The second Delphi aimed to develop agreement on a case definition of FDG-PET/CT, basic
215 investigations required and resolve disagreement to questions. The participants agreed that a febrile
216 illness for 2 weeks and without immediate diagnostic clues worked for their practice was a clinically
217 acceptable definition. They agreed the definition should incorporate 'Inflammation of Unknown
218 Origin', IUO, unexplained symptoms for 2 weeks with raised inflammatory markers. Specific
219 investigations prior to PET imaging were deemed important, including a cross-sectional CT, TTE and
220 specific serology (see supplementary data). However there was also agreement that a front-loaded
221 FDG-PET/CT prior to conventional imaging may have a role. There was indecision about whether
222 antibiotics should be delayed prior to FDG-PET/CT. Priorities in the outcome of a formal analysis of
223 the benefit of front-loaded PET/CT, in the order of importance (most to least important) were 1)
224 Time to diagnosis, 2) Time to treatment, 3) Mortality, 4) Side-effects of investigations/ treatment
225 and 5) Time to discharge.

226

227 **Conclusion**

228 PET is a functional imaging tool that provides added information about site and intensity of active
229 metabolism, and so unsurprisingly has found its way into the diagnostic pathway of the febrile
230 patient. However it is expensive, lacks specificity and needs adequate evidence for its diagnostic
231 role. This meta-analysis suggests that a diagnostic yield was achieved in 56% (95% CI 50-61%)
232 performed. The results are consistent with previous results of 54% 'overall helpfulness' (synonymous
233 with diagnostic yield) in a meta-analysis of 10 studies²⁷. Two meta-analyses reviewing sensitivity
234 reported 85% (95% CI 81-88%; 15 studies) and 98% (95% CI 94-99%; 9 studies).

235 The results are based on results of case series, involving convenience sampling of FUO patients
236 referred to Nuclear Medicine departments at the discretion of the responsible physician. Specifically,
237 recruitment is not at the point of diagnosis of fever of unknown origin, and there is no control group.
238 Patient recruitment may favour patients with renal impairment, poor fitness for invasive biopsies,
239 and exclude patients taking metformin, recent surgery or unable to lie still. The room for bias is high
240 and these important patient characteristics are poorly documented in the included studies.

241 It is also striking that reported diagnostic yield does not address contribution beyond conventional
242 imaging as all the patients did not undergo conventional imaging, and reporting of those that did
243 was inconsistent. 5 studies included in this meta-analysis reported results of previous imaging. A
244 sub-group analysis of these data suggest the diagnostic yield of FDG-PET/CT beyond CT is 32%
245 (95%CI 22-44%) with significant heterogeneity (I^2 66%).

246 Case definitions of FUO adhered to outdated definitions that were established based on minimal
247 evidence. It is accepted that subsets of patients do not mount any fever, and for this reason it has
248 been suggested that IUO be included in future research. The definition also encompasses an
249 extensive list of diagnoses and possibilities, is geographically diverse and limited by resources.

250 FDG-PET/CT is perceived to be an objective intervention. However there is minimal data on inter-
251 reporter agreement, and none of the studies involved independent reporting by more than one
252 radiologist. Importantly the protocols frequently included nephrotoxic contrast, and high dose
253 attenuation CTs. Not only may this bias the outcome, but it demonstrates potential risks associated
254 with the scans. There is evidence that a special diet to reduce cardiac non-specific cardiac uptake
255 may improve outcomes, however the only study that included this protocol did not report cardiac
256 diagnoses.

257 There is no diagnostic reference standard for FUO, and many patients remain undiagnosed.
258 Furthermore there is a level of ambiguity in final diagnoses made by clinicians, and the impression of
259 whether the FDG-PET/CT contributed to the diagnosis. In most studies this was based on the result
260 of the FDG-PET/CT being compatible with the final diagnosis, however it did not demonstrate a
261 diagnostic yield over conventional imaging. Outcome measures need to be relevant to hard patient
262 outcomes and to current health systems processes. While sensitivity is not an appropriate outcome
263 measure, diagnostic yield may also overestimate the contribution and does not indicate the clinical
264 impact of the scan. Other possible outcomes include evaluating time to treatment, discharge or
265 mortality.

266 It is evident that studies included patients that had not had conventional cross-sectional imaging.
267 Furthermore, a referral for FDG-PET/CT was frequently made in spite of pathology identified on
268 cross-sectional imaging that could undergo alternative, more specific and objective investigation
269 such as a biopsy. With this in mind, the question of diagnostic yield of FDG-PET/CT beyond
270 abnormalities detected by cross-sectional imaging is clinically important.

271 The individual patient meta-analysis is limited by the low quality of included studies. It does provide
272 suggestion of diagnoses that did and did not benefit from FDG-PET/CT, see Figures 4-6. It is rational
273 that viral infections, urinary tract infections, bacteraemias and small vessel vasculitides are not easily
274 detected on FDG-PET/CT. There are limitations in interpretation of FDG avidity in the brain, heart

275 and urinary tract. The brain and the heart have high glucose uptake and the urinary tract
276 concentrates FDG during excreted.

277 This study provides a rigorous, updated and balanced insight into current evidence for the role of
278 FDG-PET/CT in FUO. It demonstrates a lack of evidence supporting the value and positioning of FDG-
279 PET/CT in investigative algorithms. The Delphi survey enabled the working group to interpret results
280 in line with current practice, and explore directions for research. It highlighted the need for a
281 paradigm shift in research, involving prospective studies recruiting at the point of diagnosis of FUO,
282 with updated case definitions and hard outcome measures. While these studies will be a significant
283 undertaking with multi-centre collaboration, their completion is vital for balancing both radiation
284 exposure and costs against the possible benefits of utilising FDG-PET/CT.

285

286

287 **Figure and Table Legends**

288

289 Figure 1: Flow diagram of study selection.

290

291 Figure 2: Summary of the Quality Assessment of Included Studies Using the NIH Tool

292

293 Figure 3: Diagnostic Yield of FDG-PET/CT in Fever of Unknown Origin (n=18), Proportion 0=0% to
294 1=100% +/- 95% CI. The size of the grey box provides a measure of the sample size. $I^2 > 50\%$ implies
295 moderate heterogeneity.

296

297 Figure 4: Infections (n=241; 32% of final diagnosis): Diagnostic yield from PET/CT

298

299 Figure 5: Inflammatory/ Autoimmune (n=171; 20% of final diagnosis): Diagnostic yield from PET/CT

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301 Figure 6: Malignancy (n=112; 13% of final diagnoses): Diagnostic yield from PET/CT

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303 Table 1: 2x2 table categorising possible study outcomes.

304

305 Table 2: Search Strategy and Study Selection

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1 **Key words**

2 Imaging, Nuclear Medicine, Fever of Unknown Origin, Diagnostics

3

4

5 **Abbreviations**

6

7 CI Confidence Intervals

8 FDG-PET/CT 2-[18F]-fluoro-2-deoxy-D-glucose - Positron Emission Tomography/Computed
9 Tomography

10 FUO Fever of Unknown Origin

11 IQR Interquartile Range

12 IUO Inflammation of Unknown Origin

13 KPI Key Performance Indicator

14 Introduction

15 Fever as an isolated clinical presentation has challenged clinicians for decades^{1,2}. In 1961 Petersdorf
16 and Beeson provided a case definition for 'fever (or pyrexia) of unknown origin': 1) a body
17 temperature above 38.3°C; 2) on several occasions; with 3) a duration of illness of at least three
18 weeks; and 4) no diagnosis within one week of hospital admission²⁻⁴. Fifty years on, definitions of
19 FUO and the spectrum of aetiologies have evolved, however the diagnostic challenges remain⁴. FUO
20 represents an estimated 2.9% of hospital admissions, with morbidity associated with prolonged
21 hospital stay, repeated cycles of invasive investigations and presumptive treatment, mortality rates
22 between 12-35%, and cost implications⁵.

23 2-[18F]-fluoro-2-deoxy-D-glucose (FDG)-Positron-Emission-Tomography/Computed-Tomography
24 (PET/CT) emerged at the end of the 20th century as an amalgamation between functional and
25 conventional anatomical imaging⁶. Its role in oncological staging has been well-defined, however in
26 other specialities there is less clarity⁷. Specifically, in the investigation of FUO the role of FDG-PET/CT
27 in clinical practice and diagnostic algorithms is inconsistent and unestablished. Existing guidelines
28 suggest that FDG-PET/CT *may* be used where conventional investigations have not revealed a
29 source⁸.

30 FDG-PET/CT is not associated with nephrotoxicity, and standard protocols expose patients to less
31 radiation than a conventional CT. An average FDG-PET/CT scan exposes a patient to 15mSv radiation,
32 approximately 5-6 years background radiation, rather than 20-25mSv in a contrast-enhanced chest-
33 abdomen-pelvis CT. Other advantages include imaging areas (e.g. head and neck, extremities) which
34 are beyond the range of most CT scans used in this context, and detection of vascular and truncal
35 musculoskeletal inflammation for which cross-sectional contrast CT imaging is insensitive⁹. The main
36 caveats are cost and accessibility, FDG-PET/CT costing £800, compared to £250 for a contrast-
37 enhanced chest-abdomen-pelvis CT. However this could easily be remunerated by earlier definitive

38 treatment associated with additional diagnostic sensitivity. A marginally reduced length of inpatient
39 stay could mitigate the cost, with an average £400 for one night hospital admission¹⁰.

40 Current literature evaluating the role of FDG-PET/CT in FUO is based on observational data involving
41 small samples, outdated case definitions, and poor generalisability. Outcomes reported by existing
42 meta-analyses focus on sensitivity of FDG-PET/CT in FUO^{11, 12}. Sensitivity refers to the proportion of
43 cases with a diagnosis to explain the FUO for which FDG-PET/CT contributed to the diagnosis, or
44 $A/(A+B)$ (Table 1). This is statistically inappropriate as there is no reference standard for the
45 investigation of FUO to enable estimates of diagnostic accuracy¹³. In comparison, 'diagnostic yield'
46 provides a more suitable outcome measure, calculated as the proportion of all FDG-PET/CT scans
47 (both normal and abnormal) that contribute to the diagnosis of FUO, $A/(A+B+C+D)$ (Table 1)¹⁴.
48 Strikingly, there has been limited analysis of diagnostic yield of FDG-PET/CT beyond that of
49 conventional CT. Further, previous meta-analyses have not studied individual patient data.

50

51 **Table 1**

52

53 We performed an up-to-date meta-analysis of the diagnostic yield of FDG-PET/CT in all patients with
54 FUO. Secondary outcomes included the proportion with an abnormal FDG-PET/CT, final diagnosis,
55 false positive results and mortality. The results of the meta-analysis were used to inform two rounds
56 of a Delphi survey and a half-day meeting, to develop a consensus on the current knowledge on the
57 role of FDG-PET/CT in FUO and inform future research.

58

59 **Materials and Methods**

60

61 Systematic Review and Meta-analysis

62 The protocol was prospectively registered with PROSPERO, an online international database of
63 systematic reviews (Study-ID CRD42016032696). It adhered to PRISMA guidelines. QUADAS-2,
64 STROBE, Cochrane guidelines and MOOSE guidelines were also utilised¹⁵⁻¹⁸.

65 Inclusion and Exclusion criteria: All patients were included irrespective of age, comorbidities or
66 immunocompromise. Inclusion criteria for FDG-PET/CT protocols were not defined, provided they
67 involved a standard [18]-FDG radiotracer. Exclusion criteria were case reports, significant missing
68 data such that the primary outcome could not be calculated and non-English studies.

69 Search strategy and study detection: See Table 2.

70

71 **Table 2**

72

73 Methodological quality assessment: Two authors (TB&AR) independently performed the quality
74 assessment and used this to identify studies to be included in the meta-synthesis. Disagreements
75 were resolved by a third author (SS). Existing research is restricted to case series and, in the absence
76 of comparison with a reference standard, these cannot be interpreted as diagnostic accuracy
77 studies. For this reason a specific quality assessment tool was utilised, with nine criteria scored as
78 'High', 'Unclear' or 'Low' risk of bias, see Supplement¹⁹. Each study is given a quality rating 'Poor',
79 'Fair' and 'Good', and quality assessment are summarised in Figure 3. The studies included in the
80 inter-rater agreement on the quality assessment is evaluated by a calculated kappa statistic, with

81 95% confidence intervals (CIs) ranging from zero (completely chance-explained agreement) and one
82 (perfect agreement)²⁰.

83 Data extraction: A data extraction form was developed using Microsoft Excel, see Supplement, and
84 two authors (TB&AR) independently piloted the form and subsequently performed the data
85 extraction. Disagreements were resolved by a third author (SS). Authors of included studies were
86 contacted for missing data.

87 Analysis: A qualitative synthesis and summary was performed. Results for studies included in the
88 quantitative analysis were calculated as proportions, with meta-analysis performed using a random-
89 effects model in Stata.13 to produce a summary outcome proportion with 95% CIs, and I² statistic for
90 heterogeneity. Sensitivity analyses was performed to exclude poor quality studies. Sub-group
91 analyses were performed for immunocompetent adults.

92

93 Delphi Consensus

94 The Delphi technique is an accepted method for generating consensus in a wide variety of
95 disciplines²¹⁻²³. It involves multiple iteration questionnaire surveys with anonymous and unbiased
96 methods. This study included 2-rounds of sequential pre-tested questionnaires, and a half-day face-
97 face meeting. The working-group included 30 UK-based clinicians with expertise in Epidemiology,
98 Research Methods, and Clinical Practice in the specialities of Nuclear Medicine, Radiology, Infectious
99 Diseases, Rheumatology, Haematology and General Medicine. The questionnaires were developed,
100 refined and administered, each consisting of single and multiple answer questions, free-text
101 comments, and 5-point Likert agreement scales. An initial survey was performed in 2015 before the
102 face-to-face meeting and consisted of 12 questions. After the meeting, a refined survey with 22
103 questions was performed. The surveys and discussion surrounded the current evidence and available
104 guidelines, availability of FDG-PET/CT, working case-definitions of FUO, position of FDG-PET/CT in

105 diagnostic algorithms of FUO, and potential factors involved in improving the outcomes in the
106 application of FDG-PET/CT. There was also a focus on the future direction of research. Consensus in
107 surveys (Supplement) was accepted if agreement (participants responding 'Strongly agree' or
108 'Agree') was over 60%.

109

110 **Results**

111

112 Systematic review and Meta-analysis

113 Study Selection: 22 studies were identified for the qualitative synthesis, and the quality assessment
114 selected 18 studies with a total of 905 patients for meta-analysis, see Figure 1. Interrater agreement
115 between reviewers was 91% with Kappa 0.85 (95% CI 0.75-0.96). Reasons for exclusions are
116 displayed in Supplementary Data²⁴⁻²⁷.

117

118 **Figure 1**

119

120 Quality Assessment and Study Design: The qualitative assessment demonstrated a high risk of bias
121 across all the included studies, see Figure 2. All the studies were observational case series with no
122 comparison group. They were largely (89%) retrospective, involving recruitment from the Nuclear
123 Medicine Department databases of patients referred for the indication of a FUO. The studies were
124 largely confined to tertiary care centres, and were geographically widely distributed across 15
125 different countries in Europe and Asia. The median sample size was 48 (Interquartile range, IQR 24-
126 74), with a median sample size per year 22 (IQR 8-29). The year of commencement of the studies
127 ranged from 2003-2010 (median 2007, IQR 2005-2007), with the year of publication ranging from
128 2008-2015 (median 2012, IQR 2010-2013). The median study duration was 35 (IQR 23-49) months.
129 There is insufficient data to report the proportion of children. Three studies included children and
130 none were exclusively performed in children. 50% of the over-all population was female. 10 (56%)
131 studies excluded immunocompromised patients.

132

133 **Figure 2**

134

135 Case definitions: The included studies largely reported standardised case definitions of FUO as a
136 fever for 3 weeks with at least one documented fever over 38°C (17, 94%). There was minimal
137 documentation on the duration of symptoms prior to admission or the length of inpatient stay.
138 Patients were referred to the nuclear medicine department for FDG-PET/CT at the discretion of the
139 responsible clinician. One study mandated discussion at a multidisciplinary meeting prior to referral.

140 Intervention: 17 (94%) studies reported details of their FDG-PET/CT protocols. The protocols
141 demonstrate the studies utilised the same radiotracer injected at a standard interval of 60-90 mins
142 prior to scan. 7 (39%) used IV and/or oral contrast. It was notable that at least 4 (28%) studies
143 utilised high-dose CT. One study incorporated a 24 hour carbohydrate restricted diet prior to the
144 scan to reduce non-specific cardiac uptake. No studies reported independent assessors interpreting
145 the scans, however 7 (39%) reported the involvement of discussion between two assessors, usually a
146 nuclear medicine physician and a radiologist.

147 Primary outcome: A meta-analysis of 18 studies suggest an overall diagnostic contribution of 56%
148 (95% CI 50-61%), I^2 61% of FDG-PET/CT in all patients with FUO, illustrated in the forest plot in Figure
149 3. Sub-group analysis for diagnostic contribution **was performed** in 1) adults, 2) immunocompetent
150 patients ('classical FUO'), 3) immunocompetent adults and 4) immunocompetent adults **undergoing**
151 **PET/CT without contrast enhancement. These analyses** reduced the heterogeneity in the model,
152 however the point estimate of diagnostic yield remained largely unchanged, Forest Plots included in
153 Supplementary Data.

154 Previous cross-sectional imaging and added contribution of FDG-PET/CT: There were sparse data on
155 the documentation or results of previous imaging. Previous investigations were reported in 12 (67%)
156 studies, with a median 51% (IQR 27-81%) receiving a CT prior to referral for FDG-PET/CT. Out of

157 these, 5 studies reported the results of previous imaging. A sub-group analysis of these data suggest
158 the diagnostic yield of FDG-PET/CT over CT is 32% (95% CI 22-44%), I^2 66%.

159

160 **Figure 3**

161

162 Secondary outcomes

163 Meta-analysis of the proportion with an abnormal FDG-PET/CT produced an overall result of 69%
164 (95% CI 63-75%), I^2 72. The higher proportion of abnormal scans was accounted for by a proportion
165 of 'false positives', abnormal scans with no contribution to the final diagnosis, with an overall result
166 of 9% (95% CI 5-14%), I^2 72. The overall estimate was low which is reassuring but there was striking
167 variation across individual studies, between 0 to 33% reported false positive scans.

168 73% (95% CI 68-78%) had a final diagnosis, mainly corresponding with three categories: infectious
169 diseases representing 32% (95% CI 27-37%), inflammatory causes 20% (95% CI 17-24%) and
170 malignancy 12% (95% CI 8-17%), data included in Supplementary Text. Individual patient data
171 extraction from 16/18 studies, totalling 749 patients facilitated stratification of diagnoses that did
172 and did not benefit from FDG-PET/CT, illustrated in Figures 4-6.

173 The presence of raised inflammatory markers were reported in 7 (39%) studies, and there were
174 insufficient data to suggest any association with contribution of FDG-PET/CT to diagnosis.

175 Methods for the establishment of the final diagnosis were not uniformly reported, however existing
176 data suggests a variety of methods including bone marrow, lymph node, tissue biopsy, serology,
177 microbiology cultures, immunology and autopsy.

178 There were limited data on the period of follow-up and final outcomes of patients. 12 (67%) studies
179 reported the length of follow-up, with median 6 (IQR 6-12) months.

180

181 **Figures 4-6**

182

183 Delphi Consensus

184 31/40 (78%) participants responded to the initial Delphi survey. 22/40 (55%) attended the face-to-
185 face meeting. 30/40 (75%) responded to the second Delphi. The initial Delphi survey consisted of
186 three parts aiming to assess 1) availability of FDG-PET/CT for FUO, 2) clinical practice in requesting of
187 FDG-PET/CT for FUO, and 3) decision-making in a hypothetical case of FUO, see Supplementary Data
188 for the full questionnaire. While 100% reported access to FDG-PET/CT, there was wide-variability in
189 reported time from referral to FDG-PET/CT ranging from 2 days to 2 weeks (UK Key Performance
190 Indicator, KPI 5 days), and time to reporting of scans ranging from 1 day to 1 week (UK KPI 2days).
191 There was widespread agreement (87% responders) that FDG-PET/CT does have a role in the
192 investigation of unknown origin (suggested to be 56%), however there was little consensus on sub-
193 groups or factors that might improve the diagnostic yield. There was also agreement in the value of
194 re-assessing patients for developing symptoms and signs, involving other specialities during the
195 investigation process, and involvement of nuclear medicine physicians in case discussions. The initial
196 survey demonstrated consensus of opinions that false positives needed to be taken into account in
197 the decision to refer, that FDG-PET/CT has a high negative predictive value and that false negatives
198 may arise due to empirical steroids.

199 The face-to-face meeting involved a presentation of the results of the systematic review, meta-
200 analysis and initial Delphi survey, with sufficient time for questions and discussion. There were
201 focussed debate surrounding the case-definition of FUO, investigations required and priority
202 outcomes. The meeting identified the variability in access and knowledge of FDG-PET/CT, the
203 heterogeneity and updated working definitions of FUO and dearth of evidence but encouraging

204 results in clinical practice. It highlighted the need for clinicians to be aware of the deficits of FDG-
205 PET/CT: not always imaging the brain, low sensitivity for cardiac and renal tract pathology and
206 reduced gastrointestinal uptake with certain medication. In contrast to previous opinions, there is no
207 evidence for poor glycaemic control as a contraindication to FDG-PET/CT. Further, the fact that low-
208 contrast imaging is incorporated into standard protocols does reduce the resolution as compared to
209 conventional contrast-CT. It was agreed that certain circumstances affect decision-making, e.g. renal
210 impairment, suitability for invasive tests and recent surgery. The meeting concluded with dialogue
211 on prospects and feasibility of future research. Current practice incorporates FDG-PET/CT late in
212 diagnostic algorithms, however there was acknowledgement that it may have a role as a 'front-
213 loaded' investigation in a subset of patients. This has potential to speed diagnosis, reduced radiation
214 exposure and shorten hospital stay, maybe reduce mortality.

215 The second Delphi aimed to develop agreement on a case definition of FDG-PET/CT, basic
216 investigations required and resolve disagreement to questions. The participants agreed that a febrile
217 illness for 2 weeks and without immediate diagnostic clues worked for their practice was a clinically
218 acceptable definition. They agreed the definition should incorporate 'Inflammation of Unknown
219 Origin', IUO, unexplained symptoms for 2 weeks with raised inflammatory markers. Specific
220 investigations prior to PET imaging were deemed important, including a cross-sectional CT, TTE and
221 specific serology (see supplementary data). However there was also agreement that a front-loaded
222 FDG-PET/CT prior to conventional imaging may have a role. There was indecision about whether
223 antibiotics should be delayed prior to FDG-PET/CT. Priorities in the outcome of a formal analysis of
224 the benefit of front-loaded PET/CT, in the order of importance (most to least important) were 1)
225 Time to diagnosis, 2) Time to treatment, 3) Mortality, 4) Side-effects of investigations/ treatment
226 and 5) Time to discharge.

227

228 **Conclusion**

229 PET is a functional imaging tool that provides added information about site and intensity of active
230 metabolism, and so unsurprisingly has found its way into the diagnostic pathway of the febrile
231 patient. However it is expensive, lacks specificity and needs adequate evidence for its diagnostic
232 role. This meta-analysis suggests that a diagnostic yield was achieved in 56% (95% CI 50-61%)
233 performed. The results are consistent with previous results of 54% 'overall helpfulness' (synonymous
234 with diagnostic yield) in a meta-analysis of 10 studies²⁸. Two meta-analyses reviewing sensitivity
235 reported 85% (95% CI 81-88%; 15 studies) and 98% (95% CI 94-99%; 9 studies).

236 The results are based on results of case series, involving convenience sampling of FUO patients
237 referred to Nuclear Medicine departments at the discretion of the responsible physician. Specifically,
238 recruitment is not at the point of diagnosis of fever of unknown origin, and there is no control group.
239 Patient recruitment may favour patients with renal impairment, poor fitness for invasive biopsies,
240 and exclude patients taking metformin, recent surgery or unable to lie still. The room for bias is high
241 and these important patient characteristics are poorly documented in the included studies.

242 It is also striking that reported diagnostic yield does not address contribution beyond conventional
243 imaging as all the patients did not undergo conventional imaging, and reporting of those that did
244 was inconsistent. 5 studies included in this meta-analysis reported results of previous imaging. A
245 sub-group analysis of these data suggest the diagnostic yield of FDG-PET/CT beyond CT is 32%
246 (95%CI 22-44%) with significant heterogeneity (I^2 66%).

247 Case definitions of FUO adhered to outdated definitions that were established based on minimal
248 evidence. It is accepted that subsets of patients do not mount any fever, and for this reason it has
249 been suggested that IUO be included in future research. The definition also encompasses an
250 extensive list of diagnoses and possibilities, is geographically diverse and limited by resources.

251 FDG-PET/CT is perceived to be an objective intervention. However there is minimal data on inter-
252 reporter agreement, and none of the studies involved independent reporting by more than one
253 radiologist. Importantly the protocols frequently included nephrotoxic contrast, and high dose
254 attenuation CTs. Not only may this bias the outcome, but it demonstrates potential risks associated
255 with the scans. There is evidence that a special diet to reduce cardiac non-specific cardiac uptake
256 may improve outcomes, however the only study that included this protocol did not report cardiac
257 diagnoses.

258 There is no diagnostic reference standard for FUO, and many patients remain undiagnosed.
259 Furthermore there is a level of ambiguity in final diagnoses made by clinicians, and the impression of
260 whether the FDG-PET/CT contributed to the diagnosis. In most studies this was based on the result
261 of the FDG-PET/CT being compatible with the final diagnosis, however it did not demonstrate a
262 diagnostic yield over conventional imaging. Outcome measures need to be relevant to hard patient
263 outcomes and to current health systems processes. While sensitivity is not an appropriate outcome
264 measure, diagnostic yield may also overestimate the contribution and does not indicate the clinical
265 impact of the scan. Other possible outcomes include evaluating time to treatment, discharge or
266 mortality.

267 It is evident that studies included patients that had not had conventional cross-sectional imaging.
268 Furthermore, a referral for FDG-PET/CT was frequently made in spite of pathology identified on
269 cross-sectional imaging that could undergo alternative, more specific and objective investigation
270 such as a biopsy. With this in mind, the question of diagnostic yield of FDG-PET/CT beyond
271 abnormalities detected by cross-sectional imaging is clinically important.

272 The individual patient meta-analysis is limited by the low quality of included studies. It does provide
273 suggestion of diagnoses that did and did not benefit from FDG-PET/CT, see Figures 4-6. It is rational
274 that viral infections, urinary tract infections, bacteraemias and small vessel vasculitides are not easily
275 detected on FDG-PET/CT. There are limitations in interpretation of FDG avidity in the brain, heart

276 and urinary tract. The brain and the heart have high glucose uptake and the urinary tract
277 concentrates FDG during excreted.

278 This study provides a rigorous, updated and balanced insight into current evidence for the role of
279 FDG-PET/CT in FUO. It demonstrates a lack of evidence supporting the value and positioning of FDG-
280 PET/CT in investigative algorithms. The Delphi survey enabled the working group to interpret results
281 in line with current practice, and explore directions for research. It highlighted the need for a
282 paradigm shift in research, involving prospective studies recruiting at the point of diagnosis of FUO,
283 with updated case definitions and hard outcome measures. While these studies will be a significant
284 undertaking with multi-centre collaboration, their completion is vital for balancing both radiation
285 exposure and costs against the possible benefits of utilising FDG-PET/CT.

286 Lastly, there is no doubt that the application of FDG-PET/CT is a rapidly evolving field. This review did
287 not cover emerging evidence from new modalities and tracers, such as FDG-leucocyte or Gallium-
288 labelled imaging ²⁹.

289

290

291 **Figure and Table Legends**

292

293 Figure 1: Flow diagram of study selection.

294

295 Figure 2: Summary of the Quality Assessment of Included Studies Using the NIH Tool

296

297 Figure 3: Diagnostic Yield of FDG-PET/CT in Fever of Unknown Origin (n=18), Proportion 0=0% to
298 1=100% +/- 95% CI. The size of the grey box provides a measure of the sample size. $I^2 > 50\%$ implies
299 moderate heterogeneity.

300

301 Figure 4: Infections (n=241; 32% of final diagnosis): Diagnostic yield from PET/CT

302

303 Figure 5: Inflammatory/ Autoimmune (n=171; 20% of final diagnosis): Diagnostic yield from PET/CT

304

305 Figure 6: Malignancy (n=112; 12% of final diagnoses): Diagnostic yield from PET/CT

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307 Table 1: 2x2 table categorising possible study outcomes.

308

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311

312 **References**

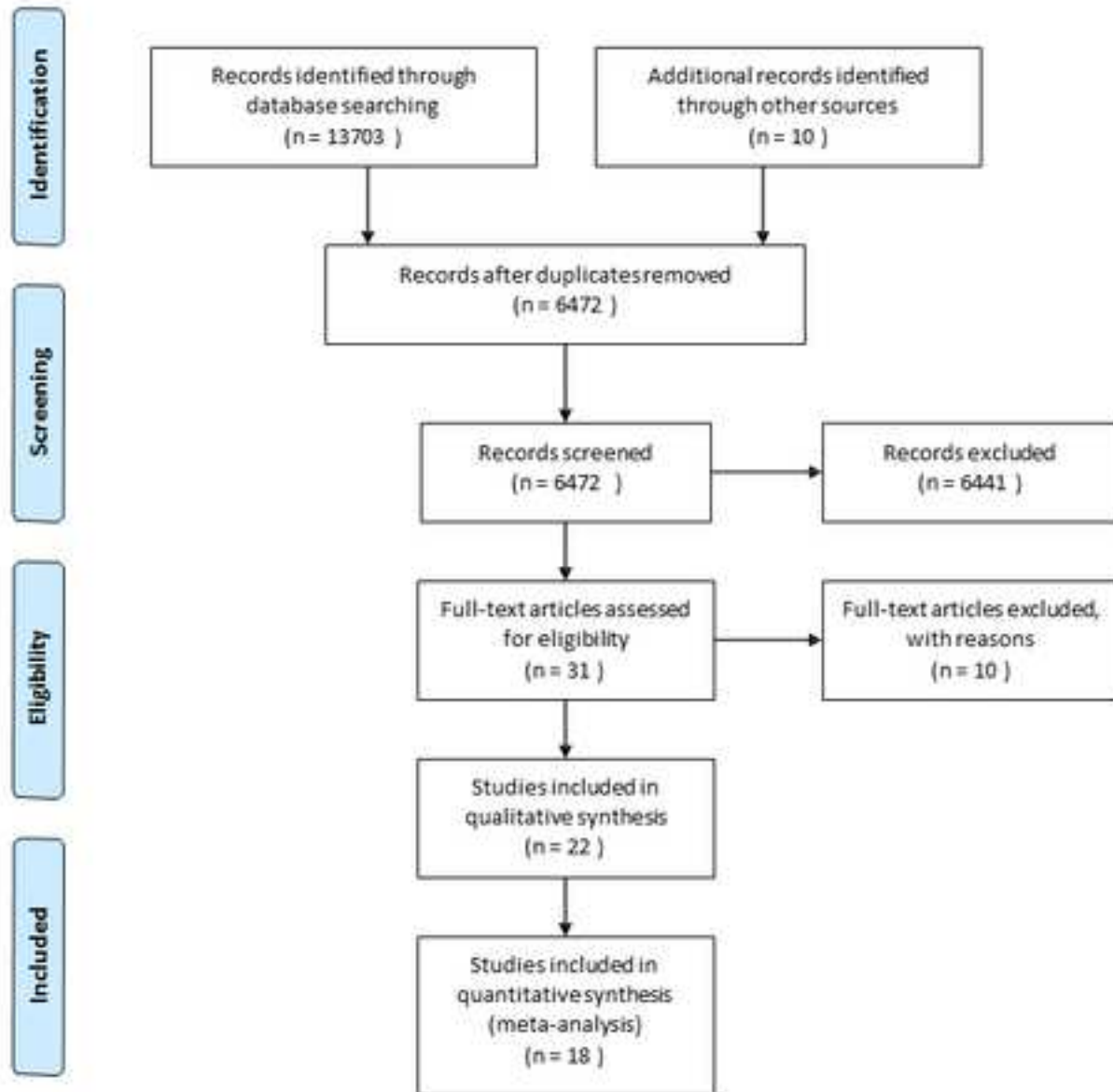
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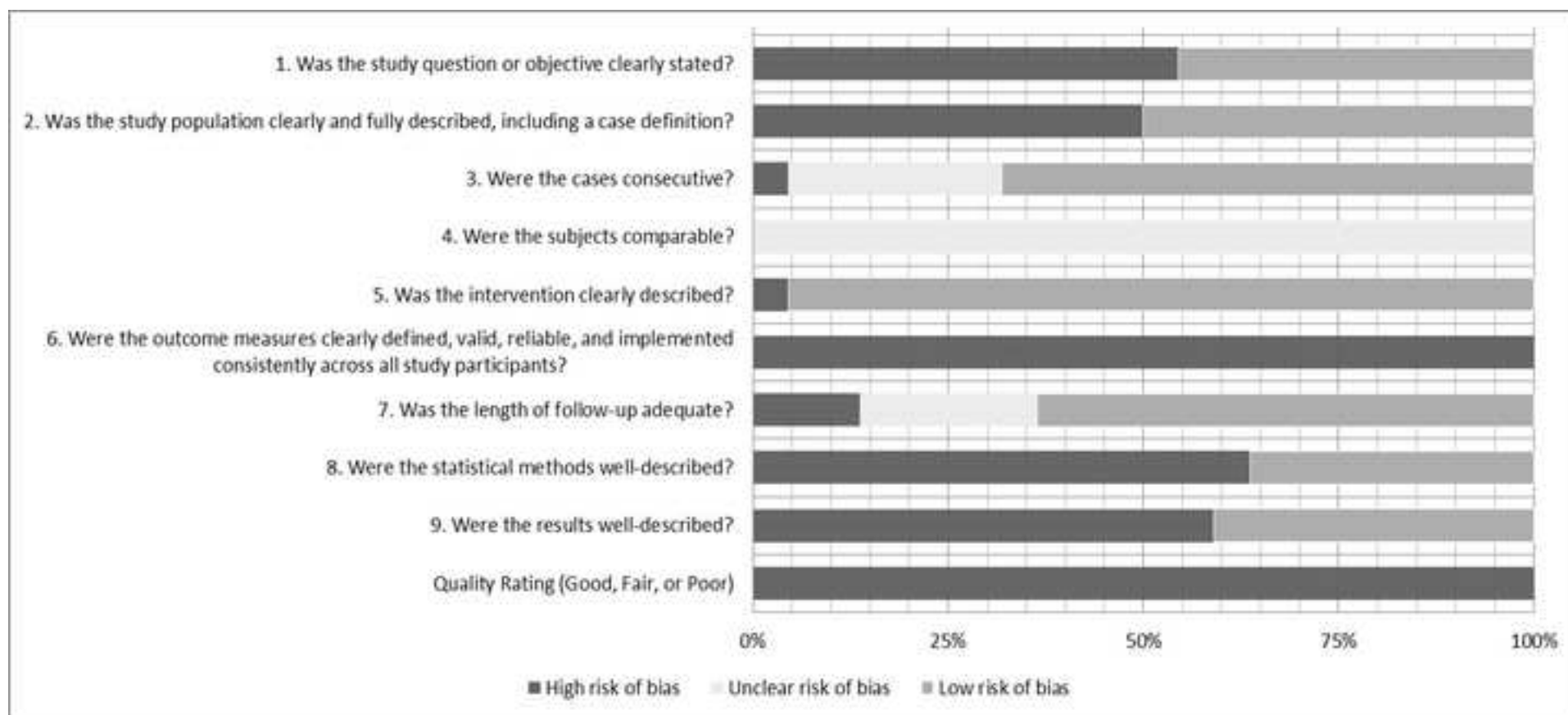


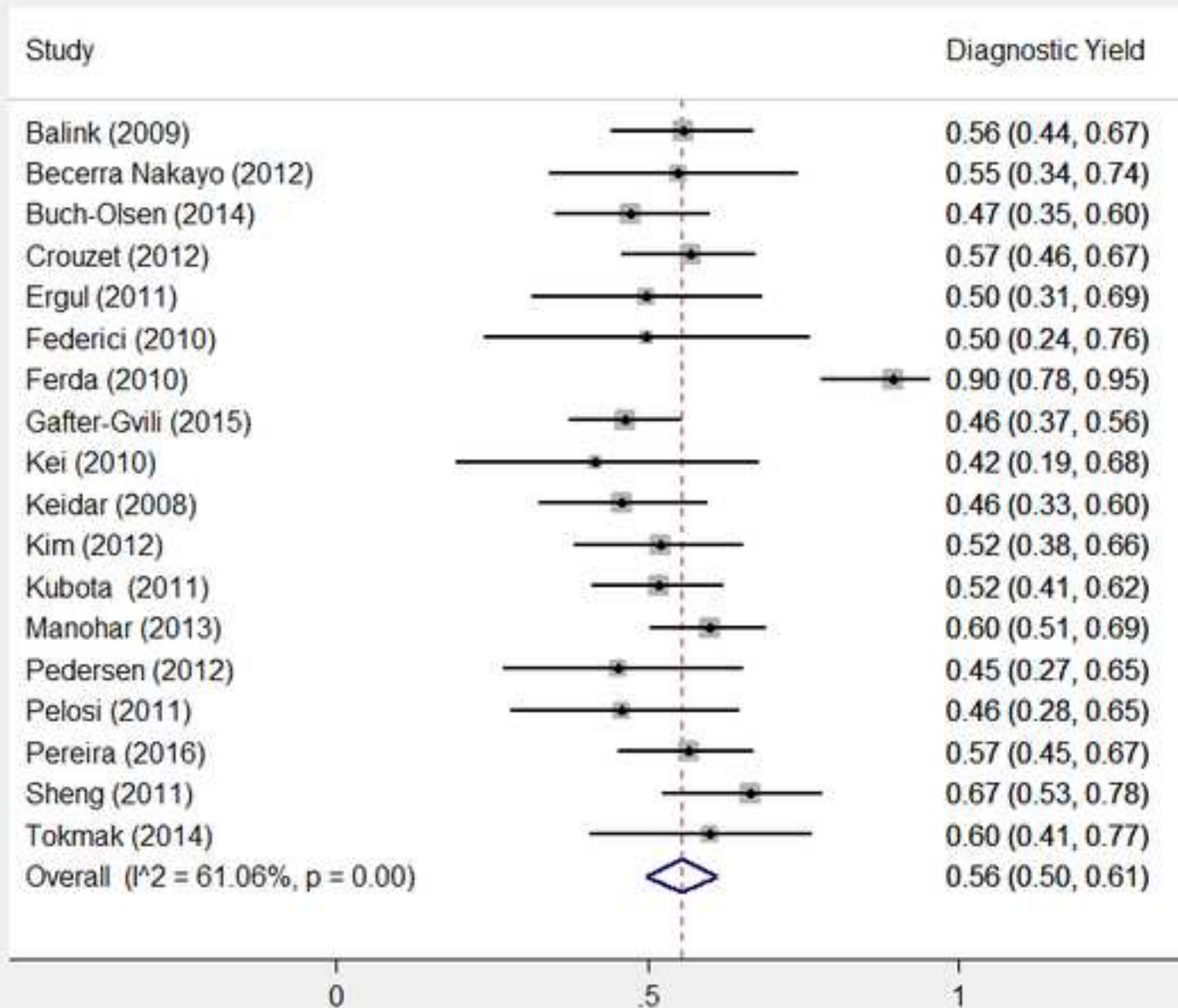
PRISMA 2009 Flow Diagram

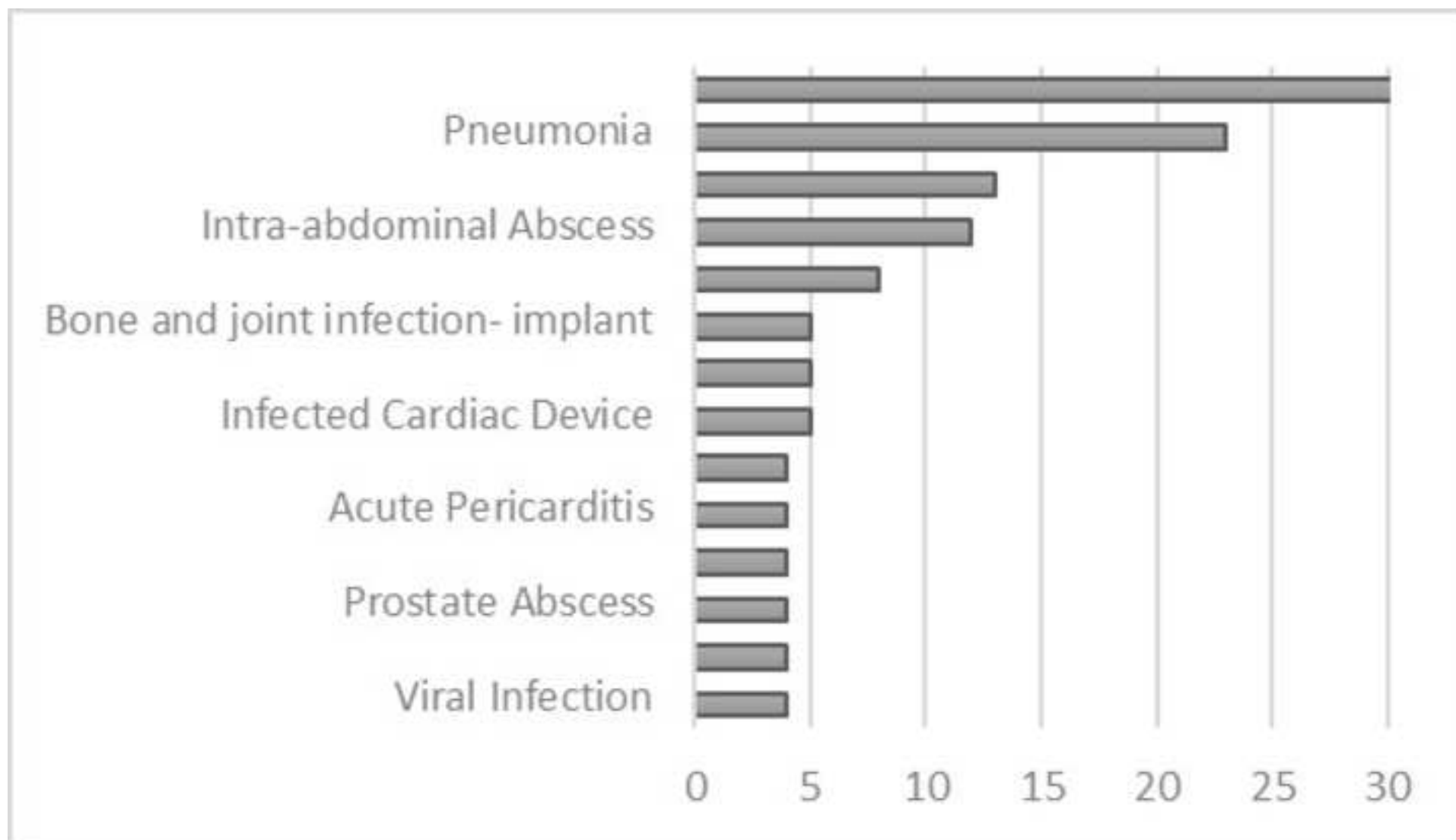


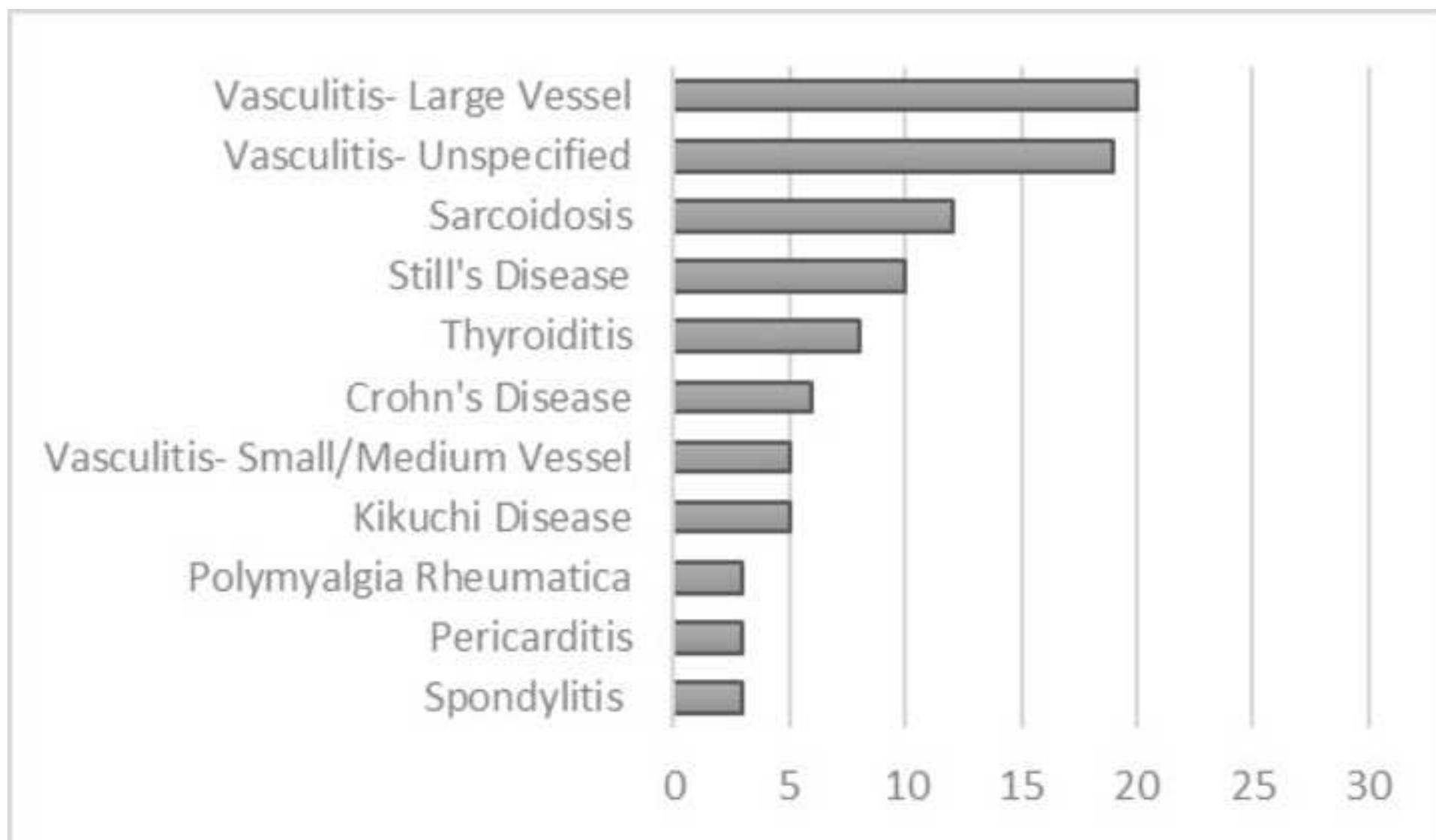
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For more information, visit www.prisma-statement.org.









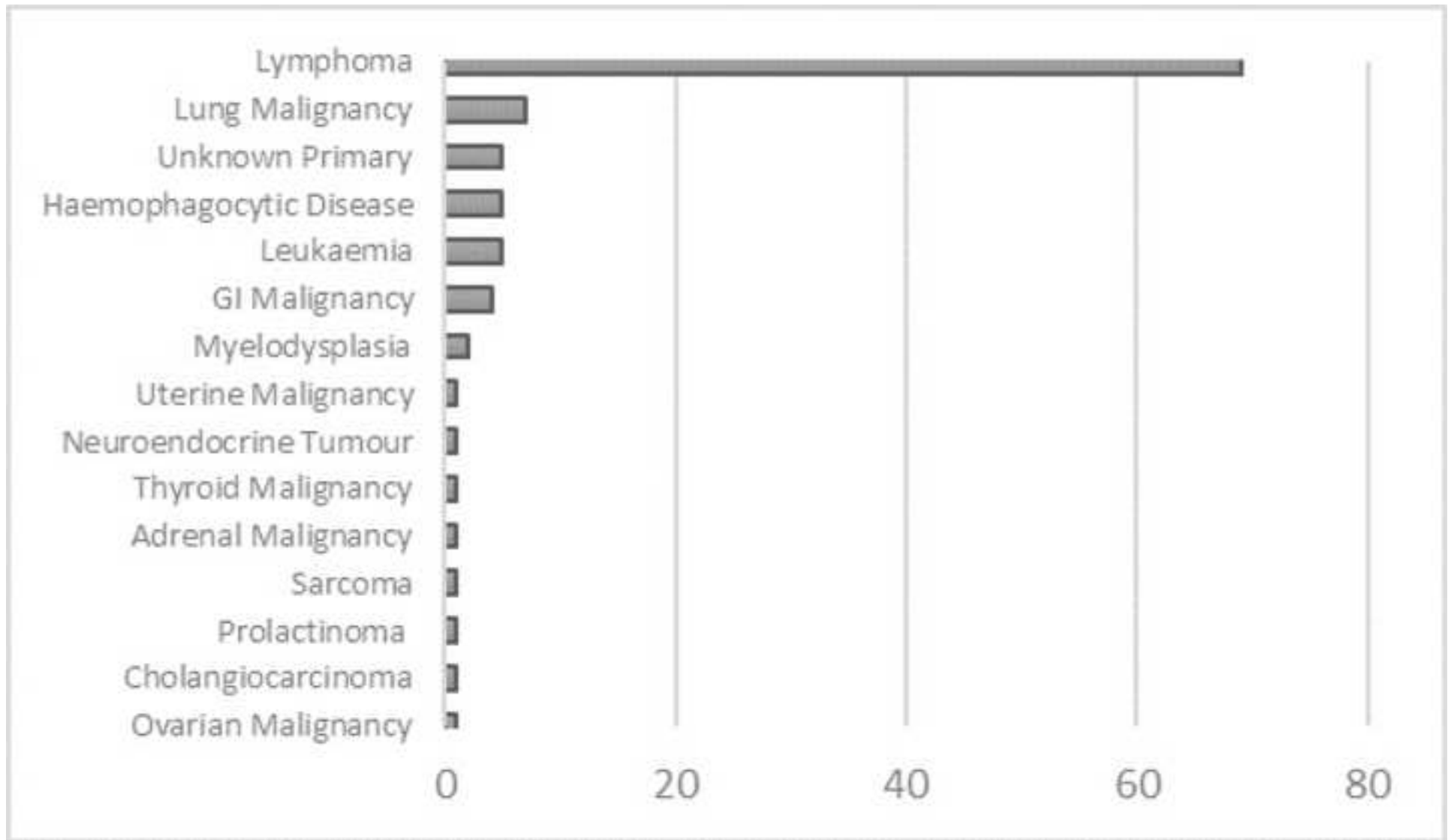


Table 1: 2x2 table categorising possible study outcomes.

| | |
|--|--|
| [A] <u>True Positives</u> : Patients with an abnormal FDG-PET/CT that contributed to diagnosing the cause of the FUO. | [B] <u>False Negatives</u> : Patients with a normal FDG-PET/CT that received a diagnosis by other means. |
| [C] <u>False Positive</u> : Patients with an abnormal FDG-PET/CT that did not contribute to diagnosing the FDG-PET/CT. | [D] <u>True Negative</u> : Patients with a normal FDG-PET/CT that remained undiagnosed after investigation or follow-up. |

Table 2: Search Strategy and Study Selection

Search Strategy:

Electronic searches were performed 1/12/15 in Medline, Embase, Web of Science and Cochrane Central Register of Controlled Trials.

All subheadings were included.

Hand-searching references was performed for included studies and identification of unpublished work was attempted by contacting experts and reviewing conference abstracts.

MESH terms: Ovid Medline: ('Tomography Positron-Emission' OR 'Fluorodeoxyglucose F18') AND ('Fever' exploded).

EMBASE: ('Positron Emission Tomography' OR 'Fluorodeoxyglucose F18') AND ('Fever' exploded).

Keyword searches for ('Positron Emission*' OR 'PET*' OR 'fluorodeoxyglucose*' OR 'fludeoxyglucose*' OR

'18fluorodeoxyglucose*' OR 'fdg*' OR 'ffdg*' OR '18fdg*' OR '18ffdg*' OR '(18)ffdg*' OR '(18)fdg*' OR

'2fluoro2deoxyglucose*' OR '2 fluoro 2 deoxyglucose*' OR '2 fluoro 2 deoxy d glucose*') in combination with ('Fever'

OR 'Pyrexia' OR 'Febrile' OR 'PUO' OR 'FUO').

Study selection: One author (TB) performed the de-duplication of records in EndNote XL, screened titles and excluded irrelevant publications. TB reviewed abstracts and/or full texts to identify eligibility for inclusion in the qualitative synthesis.

Supplements

1) Quality Assessment Tool

http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/case_series

Quality Assessment Tool for Case Series Studies

| Criteria | Yes | No | Other (CD, NR, NA)* |
|--|-----|----|---------------------|
| 1. Was the study question or objective clearly stated? | | | |
| 2. Was the study population clearly and fully described, including a case definition? | | | |
| 3. Were the cases consecutive? | | | |
| 4. Were the subjects comparable? | | | |
| 5. Was the intervention clearly described? | | | |
| 6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? | | | |
| 7. Was the length of follow-up adequate? | | | |
| 8. Were the statistical methods well-described? | | | |
| 9. Were the results well-described? | | | |

| Quality Rating (Good, Fair, or Poor) |
|--|
| Rater #1 initials: |
| Rater #2 initials: |
| Additional Comments (If POOR, please state why): |

*CD, cannot determine; NA, not applicable; NR, not reported

2) Data extraction form

Study ID

First author

Year of Publication

Country

Sample size

Start Year

Duration (in months)

Age range and Median age

Percentage of Female patients included

Study design and inclusions:

Case definition for FUO

Duration of symptoms prior to FDG-PET/CT

Inpatient stay prior to FDG-PET/CT

Study excluded immunocompromised patients

Study design (Retrospective; Consecutive; In/outpatients)

Patients excluded due to missing data and explanation

Prior diagnostic investigations documented

Outcomes:

Primary outcome: FDG-PET/CT Diagnostic Yield

Secondary Outcomes:

Abnormal FDG-PET/CT

False Positives

Final Diagnosis

-Infection

-Inflammation

-Malignancy

Mortality

Prior CT

Diagnostic yield over CT

%abnormal inflammatory markers in the group with diagnostic yield

Basis of diagnosis

Outcome

Follow-up

3) Delphi survey

See attached documents

4) Studies included in the qualitative synthesis

| | Author/ Year | Country | Sample size | Study design | Inclusion in Meta-analysis |
|-----|---------------------|-------------|-------------|--|---|
| 1. | Balink 2009 | Netherlands | 68 | Retrospective case series | Yes |
| 2. | Becerra Nakayo 2012 | Spain | 20 | Retrospective case series; Only immunocompetent | Yes |
| 3. | Bharucha 2013 | UK | 33 | Retrospective case series; Only immunocompetent | No- Reported different outcome. |
| 4. | Buch-Olsen 2014 | Netherlands | 57 | Retrospective case series | Yes |
| 5. | Castaigne 2009 | Belgium | 10 | Retrospective case series | No- Only HIV patients and only reviewed abnormal scans. |
| 6. | Crouzet 2012 | France | 79 | Retrospective case series; Only immunocompetent | Yes |
| 7. | Ergul 2011 | Turkey | 24 | Retrospective case series; Only immunocompetent | Yes |
| 8. | Federici 2010 | France | 10 | Retrospective case series; Only immunocompetent | Yes |
| 9. | Ferda 2010 | Czech Rep. | 48 | Retrospective case series | Yes |
| 10. | Gafter-Gvili 2015 | Israel | 112 | Retrospective case series | Yes |
| 11. | Jasper 2010 | Germany | 30 | Retrospective case series | No- Combined results for FDG-PET and FDG-PET/CT |
| 12. | Kei 2010 | Singapore | 12 | Retrospective case series | Yes |
| 13. | Keidar 2008 | Israel | 48 | Prospective case series; Only immunocompetent | Yes |

| | | | | | |
|-----|---------------|-------------|-----|--|---|
| 14. | Kim 2012 | South Korea | 48 | Retrospective case series; Only immunocompetent | Yes |
| 15. | Kubota 2011 | Japan | 81 | Retrospective case series | Yes |
| 16. | Manohar 2013 | India | 103 | Retrospective case series | Yes |
| 17. | Martin 2013 | Belgium | 20 | Retrospective case series | No- Only HIV patients and only reviewed abnormal scans. |
| 18. | Pedersen 2012 | Denmark | 22 | Retrospective case series; Only immunocompetent | Yes |
| 19. | Pelosi 2011 | Italy | 24 | Retrospective case series; Only immunocompetent | Yes |
| 20. | Pereira 2016 | Switzerland | 76 | Retrospective case series | Yes |
| 21. | Sheng 2011 | China | 48 | Prospective case series; Only immunocompetent | Yes |
| 22. | Tokmak 2014 | Turkey | 25 | Retrospective case series; Only immunocompetent | Yes |

5) Subgroup analysis of the primary outcome, Diagnostic Yield

Figure A: Subgroup Analysis for Diagnostic Yield of FDG-PET/CT only in adults with FUO, (n=15),

Proportion 0=0% to 1=100% +/- 95% CI. The size of the grey box provides a measure of the sample size. $I^2 > 50%$ implies moderate heterogeneity.

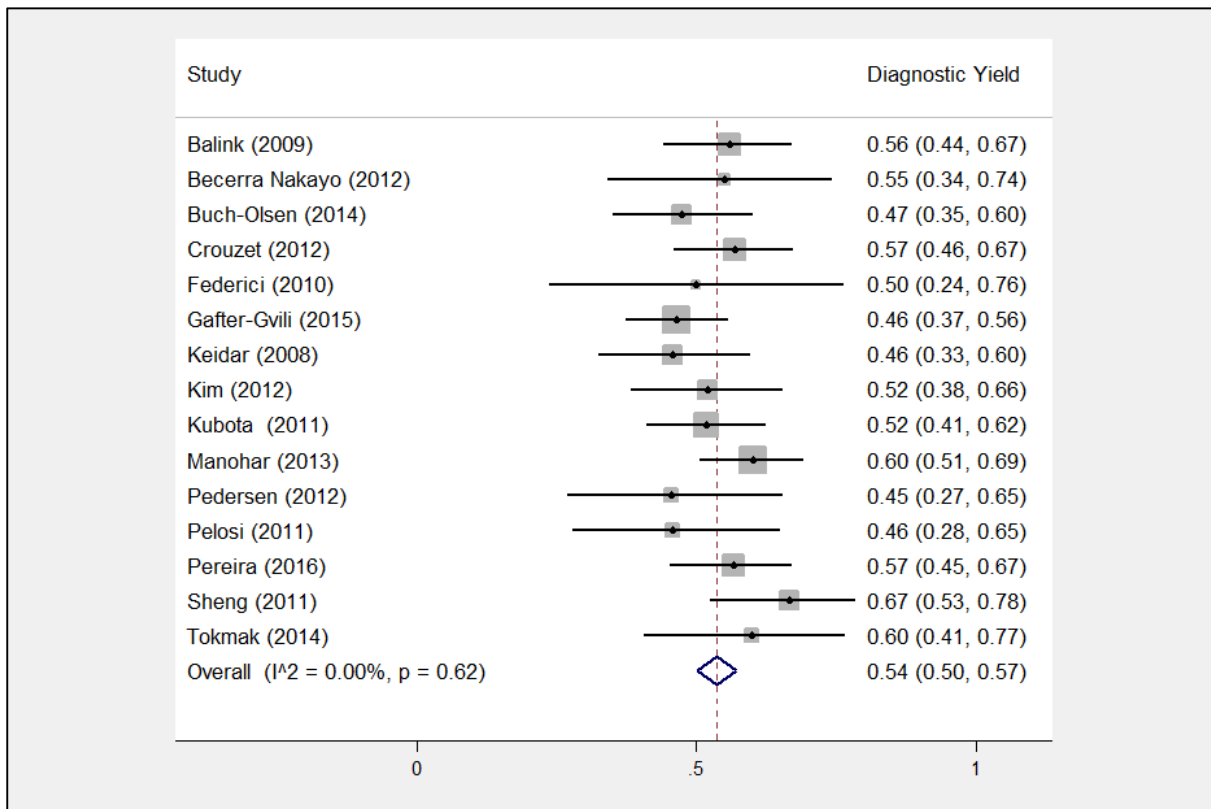


Figure B: Subgroup Analysis for Diagnostic Yield of FDG-PET/CT only in immunocompetent patients with FUO, (n=10), Proportion 0=0% to 1=100% +/- 95% CI. The size of the grey box provides a measure of the sample size. $I^2 > 50%$ implies moderate heterogeneity.

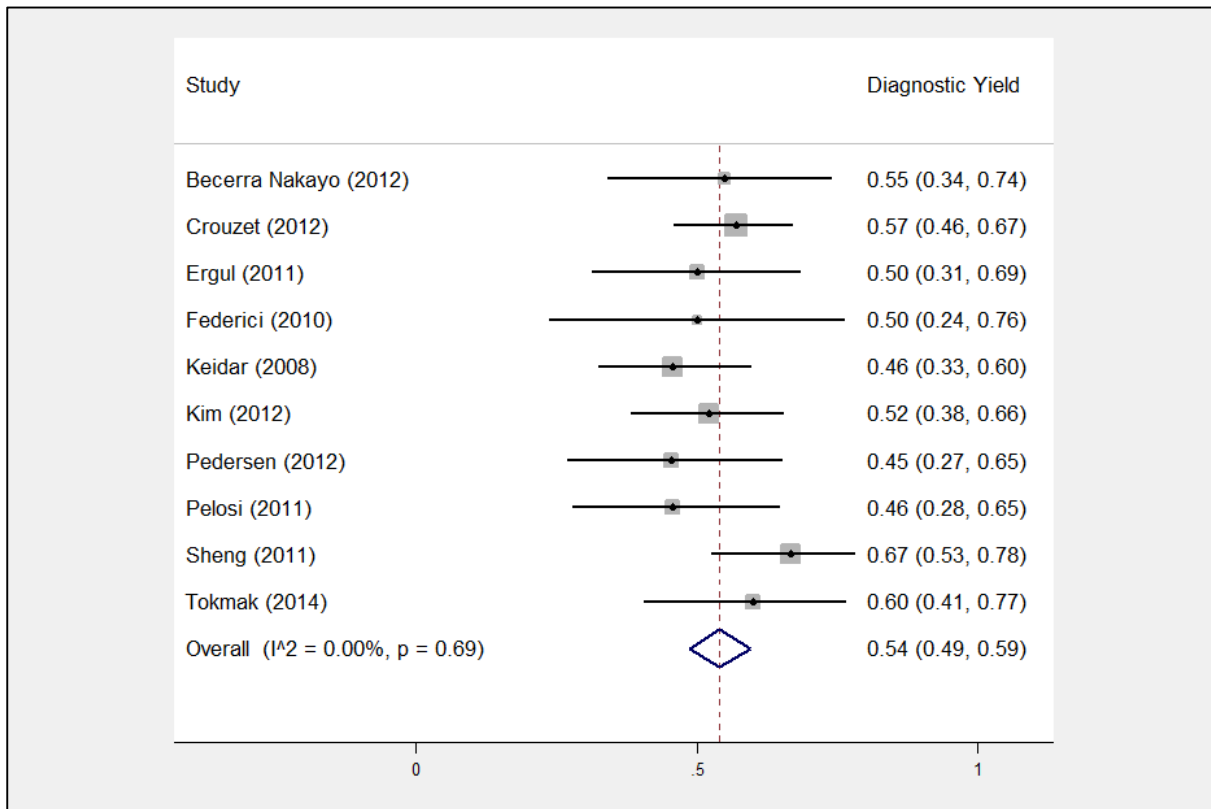


Figure C: Subgroup Analysis for Diagnostic Yield of FDG-PET/CT only in immunocompetent adults patients with FUO, (n=9), Proportion 0=0% to 1=100% +/- 95% CI. The size of the grey box provides a measure of the sample size. $I^2 > 50\%$ implies moderate heterogeneity.

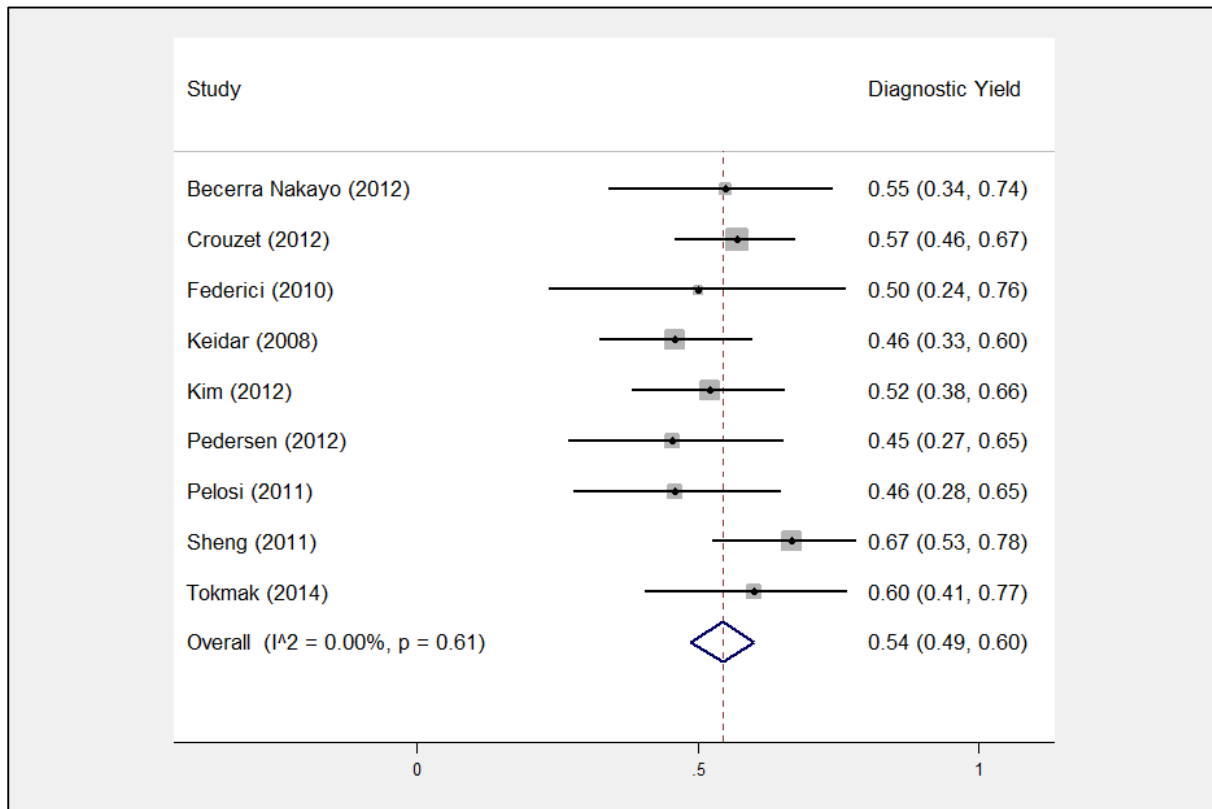
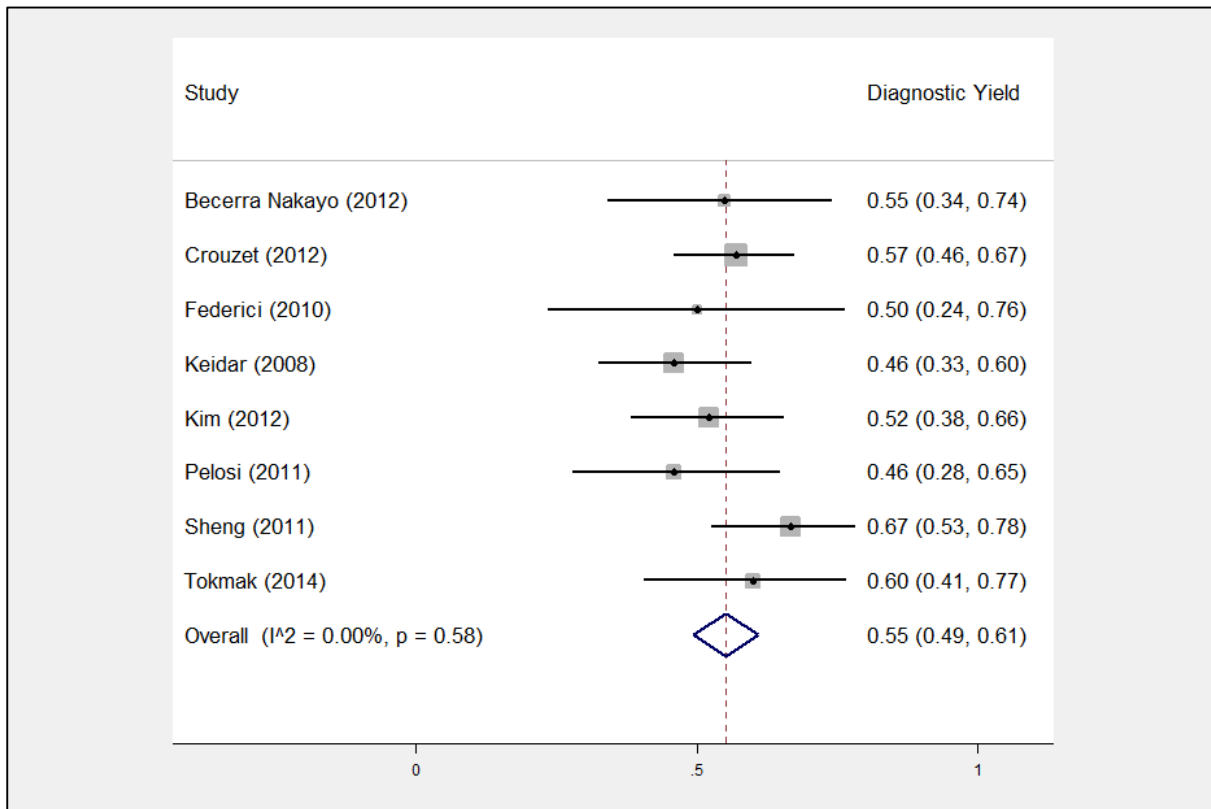


Figure D: Subgroup Analysis for Diagnostic Yield of FDG-PET/CT only in immunocompetent adults with FUO without contrast, (n=8), Proportion 0=0% to 1=100% +/- 95% CI. The size of the grey box provides a measure of the sample size. $I^2 > 50%$ implies moderate heterogeneity.



5) Forest plots for secondary outcomes:

Figure E: Abnormal FDG-PET/CT in Fever of Unknown Origin (n=18), Proportion 0=0% to 1=100% +/- 95% CI. The size of the grey box provides a measure of the sample size. $I^2 > 50\%$ implies moderate heterogeneity.

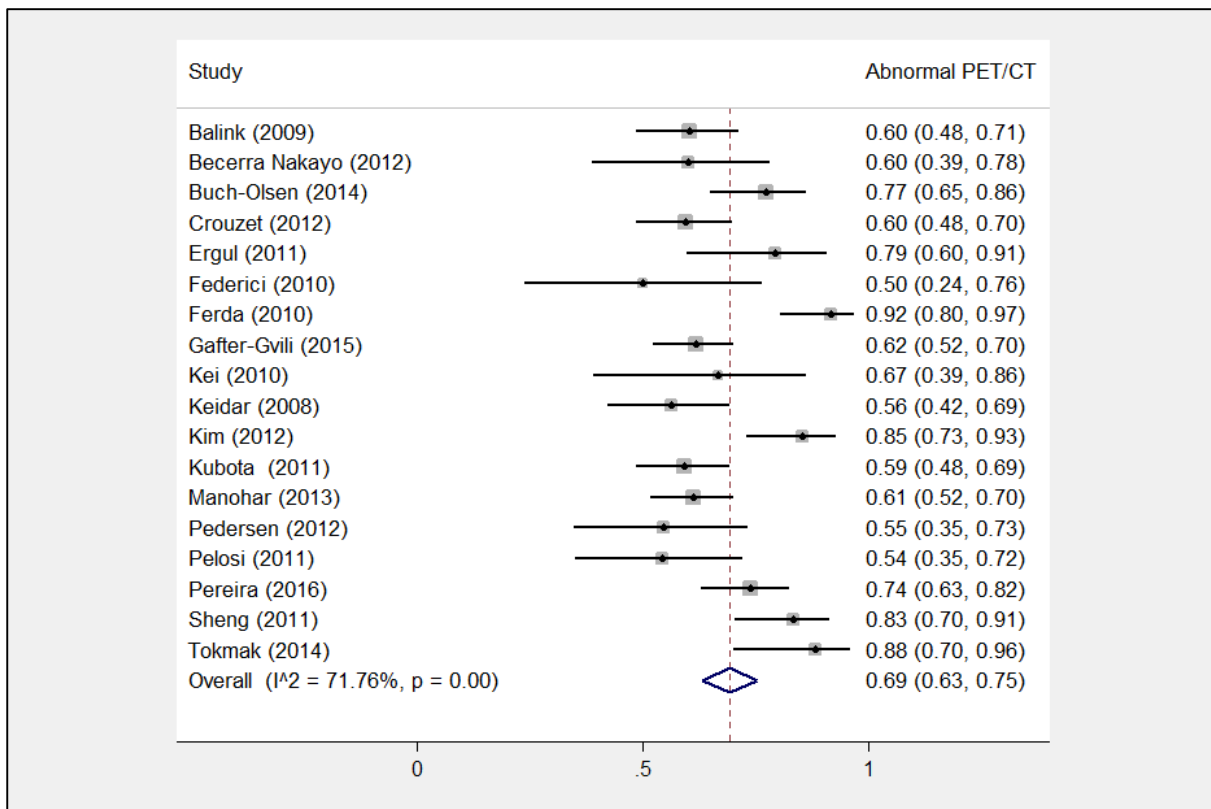


Figure F: False Positives of FDG-PET/CT in Fever of Unknown Origin (n=18), Proportion 0=0% to 1=100% +/- 95% CI. The size of the grey box provides a measure of the sample size. I²>50% implies moderate heterogeneity.

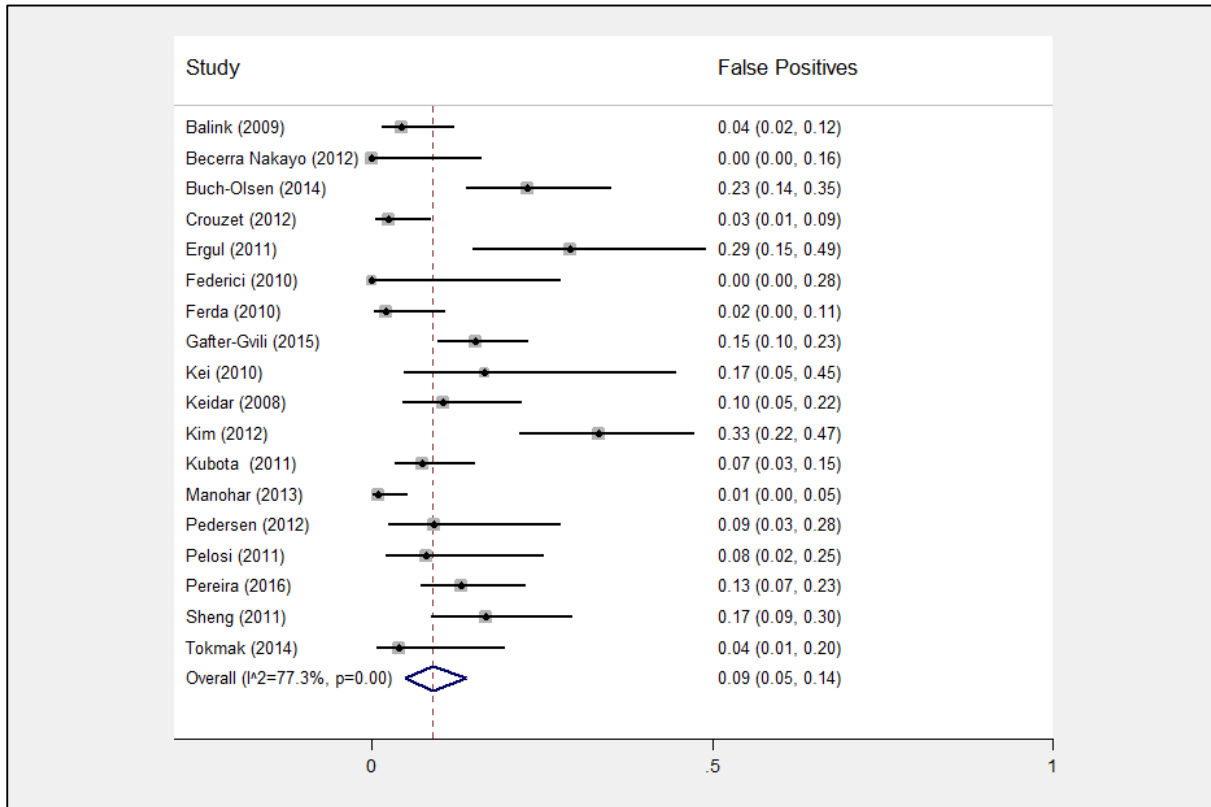


Figure G: Final Diagnosis of Fever of Unknown Origin identified (n=18), Proportion 0=0% to 1=100%

+/- 95% CI. The size of the grey box provides a measure of the sample size. $I^2 > 50\%$ implies moderate heterogeneity.

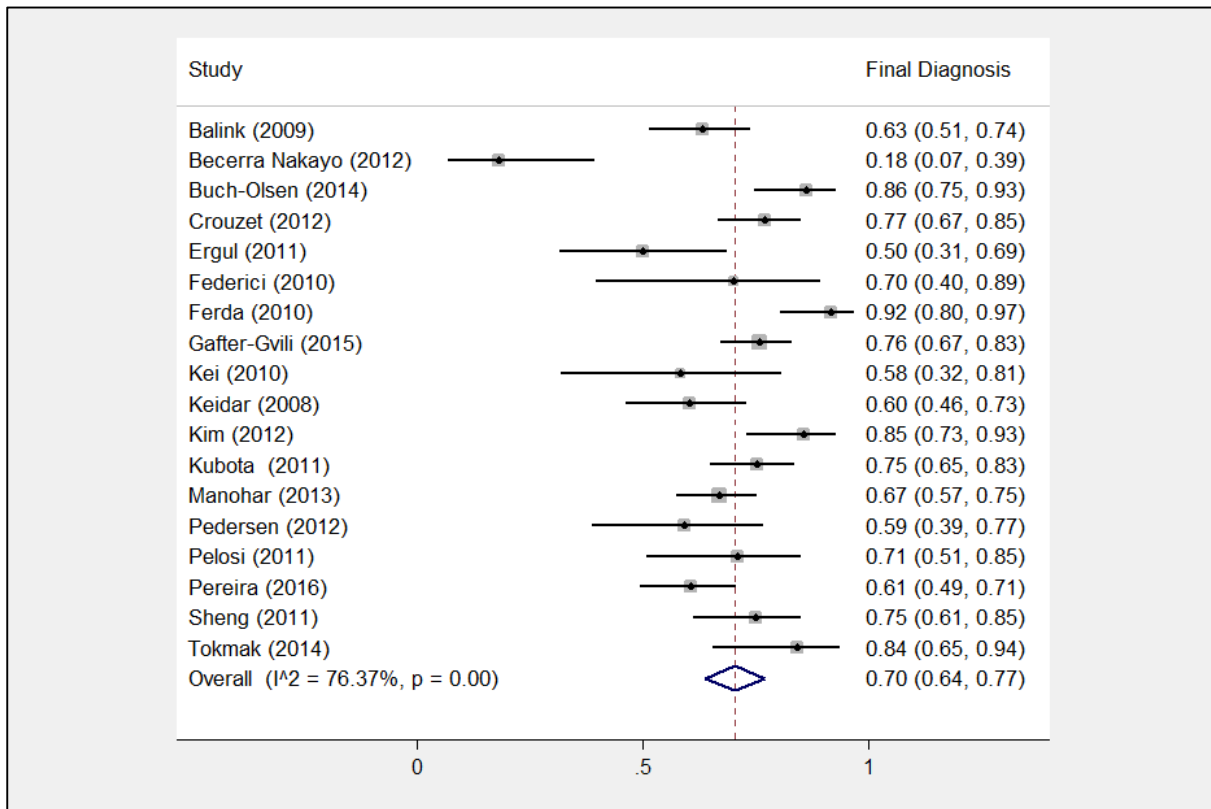


Figure H: Infectious Final Diagnoses in Fever of Unknown Origin (n=18), Proportion 0=0% to 1=100% +/- 95% CI. The size of the grey box provides a measure of the sample size. $I^2 > 50\%$ implies moderate heterogeneity.

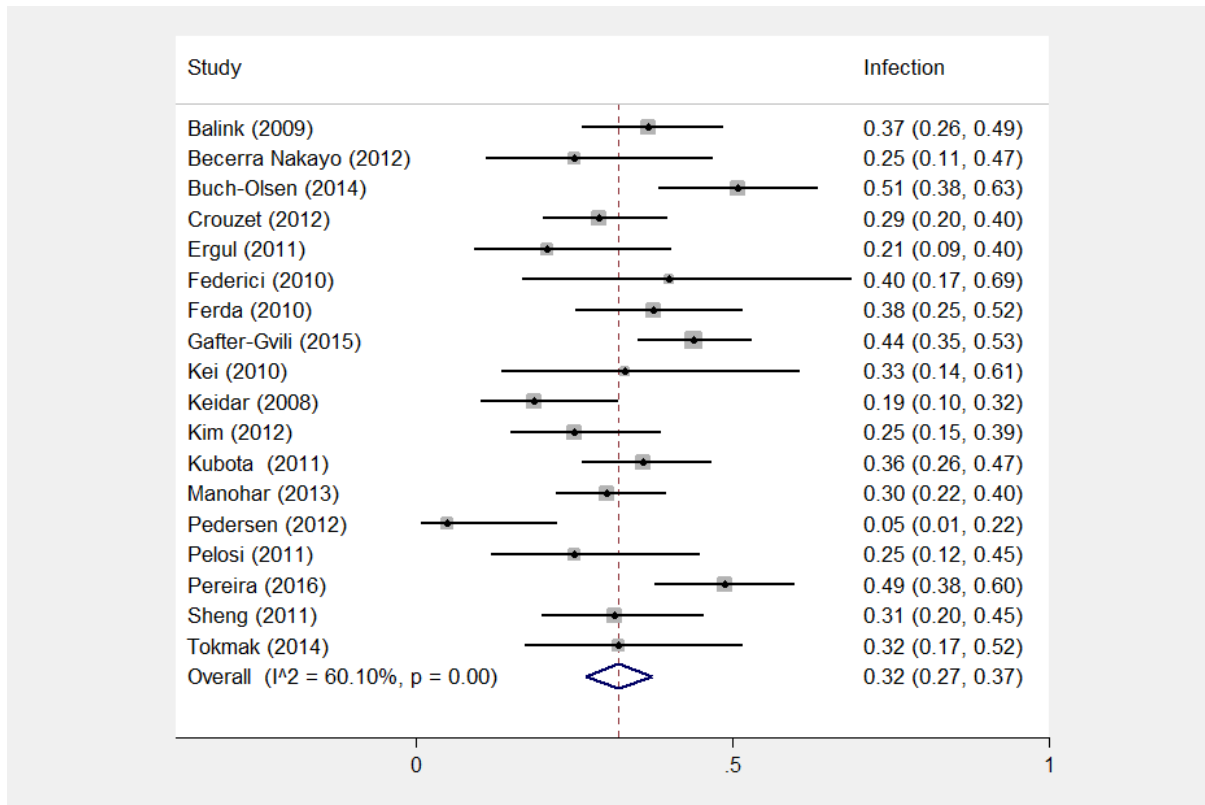


Figure I: Inflammatory Final Diagnoses in Fever of Unknown Origin (n=18), Proportion 0=0% to 1=100% +/- 95% CI. The size of the grey box provides a measure of the sample size. I²>50% implies moderate heterogeneity.

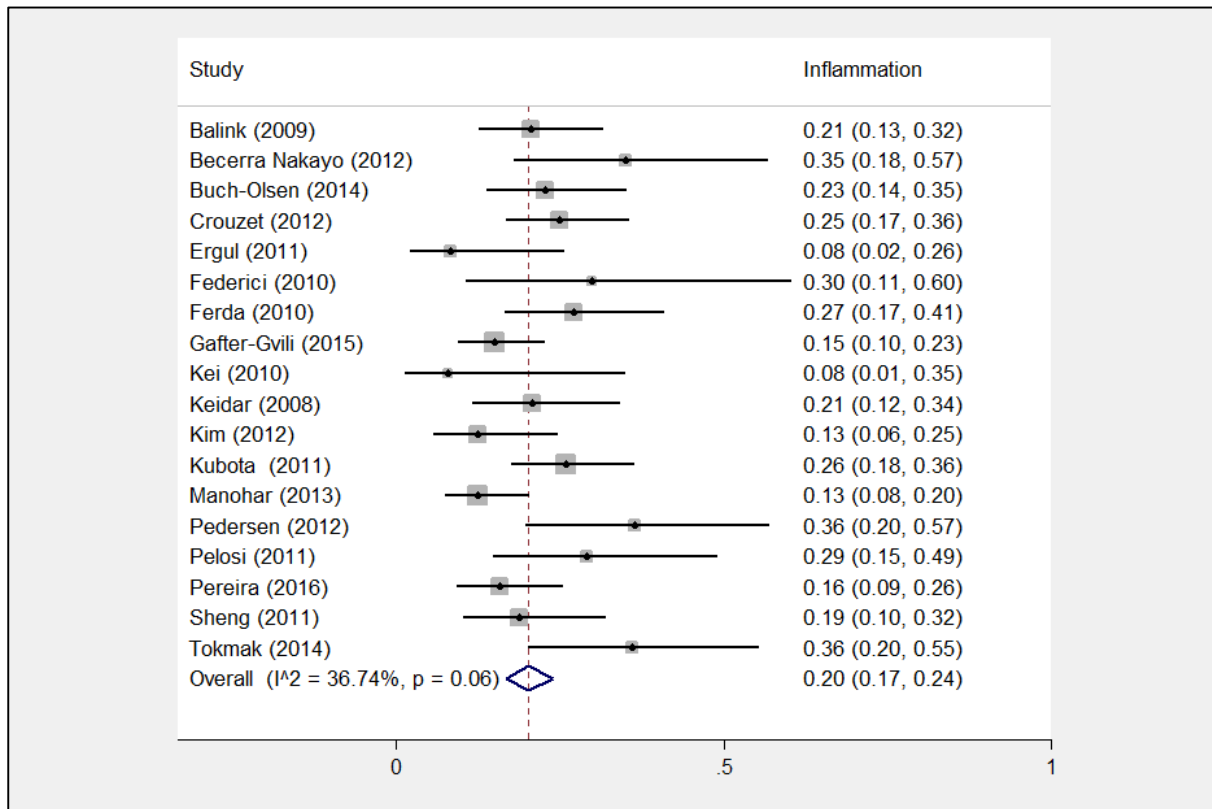
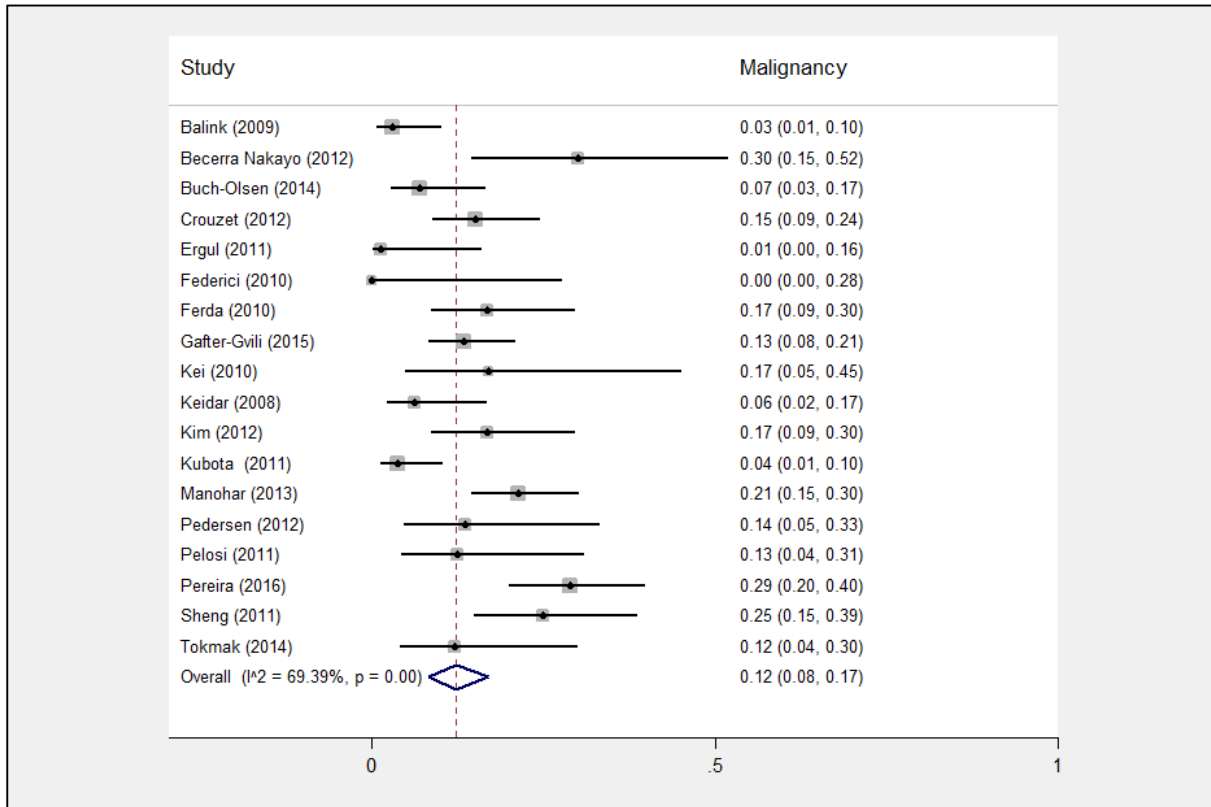


Figure J: Malignancy as Final Diagnoses in Fever of Unknown Origin (n=18), Proportion 0=0% to 1=100% +/- 95% CI. The size of the grey box provides a measure of the sample size. I²>50% implies moderate heterogeneity.



Highlights

- A systematic review identified 18 eligible studies, 905 patients, of FDG-PET/CT in FUO
- Pooled diagnostic yield was 56% (95%CI 50-61%), I²=61%
- Sub-group analysis of diagnostic yield over conventional CT was 32% (95%CI 22-44%) I²=66%
- Iterative Delphi Surveys generated interspeciality consensus on the topic.
- There is insufficient evidence to support the value of FDG-PET/CT in investigative algorithms