

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Diagnostic workup for fever of unknown origin: a multicenter collaborative retrospective study
AUTHORS	Naito, Toshio; Mizooka, Masafumi; Mitsumoto, Fujiko; Kanazawa, Kenji; Torikai, Keito; Ohno, Shiro; Morita, Hiroyuki; Ukimura, Akira; Mishima, Nobuhiko; Otsuka, Fumio; Ohyama, Yoshio; Nara, Noriko; Murakami, Kazunari; Mashiba, Kouichi; Akazawa, Kenichiro; Yamamoto, Koji; Senda, Shoichi; Yamanouchi, Masashi; Tazuma, Susumu; Hayashi, Jun

VERSION 1 - REVIEW

REVIEWER	Thierry ZENONE Department of internal medicine Centre hospitalier, Valence, FRANCE
REVIEW RETURNED	28-Sep-2013

GENERAL COMMENTS	The most common causative disease in the elderly was polymyalgia rheumatica. It was polymyalgia rheumatica or giant cell arteritis ? Temporal artery biopsy was not performed in FUO in patients > 55 years ? Precisions should be given by the authors.
-------------------------	--

REVIEWER	Chantal P. Bleeker-Rovers Radboud university medical center The Netherlands
REVIEW RETURNED	07-Oct-2013

GENERAL COMMENTS	<p>This article is a nice addition to the growing literature on the causes of FUO focusing on the situation in Japan.</p> <p>Introduction:</p> <ul style="list-style-type: none"> - Second paragraph: please add that “few studies have assessed the clinical usefulness of ... positron emission tomography (PET) in Japan”. Several studies have addressed this subject over the last ten years in other countries. - Although I understand the authors’ interest in identification of tests that are useful in FUO, this is not something that can be deduced in a reliable way from a retrospective study where it is up to the treating doctor to decide whether a certain test is performed or not. It would be better to leave the aim of the study at defining which causes of FUO are found in the Japanese situation. The article does not provide any useful data on the performance of these tests further arguing in favor of omitting this part. <p>Methods:</p>
-------------------------	--

	<ul style="list-style-type: none">- The fact that only 17 of 99 hospitals chose to participate with an over representation of university hospitals (both in number of hospitals as in number of included patients) may have caused bias and makes it more difficult to decide if the conclusions apply to all Japanese hospitals.- The authors state that they have performed a nationwide study, but they do not provide information on the localization of the participating hospitals.- Choosing for the FUI definition using a quantitative criterion (3 outpatient visits or 3 days of hospitalization) instead of the qualitative criterion that requires a list of investigations to be performed makes it more difficult to generalize the results from this study. What can be done in 3 days of hospitalization usually differs widely between hospitals and depends very much on the logistic organization of hospitals.- What is meant by “general biological examination”?- How long was the minimum follow-up to decide whether no diagnosis was reached? <p>Results:</p> <ul style="list-style-type: none">- A death rate of more than 10% among patients without a diagnosis is much higher than in previous studies. This needs further explanation: what were the causes of death of these patients? How long after the FUI episode did they die? Were their deaths possibly related to the FUI episode? Mortality in the patients without a diagnosis was 10.7% compared to 6.5% in patients with a diagnosis, most of them dying from malignancy. This is very remarkable.- It is stated that PMR was a common diagnosis especially among the elderly. In previous studies it has been shown that fever is more commonly seen in giant cell arteritis occurring together with PMR. This diagnosis can often only be made after FDG-PET/CT and/or temporal artery biopsy. How sure are the authors that these patients did not have giant cell arteritis (since FDG-PET was performed in less than 30% of all patients and no information is provided on temporal artery biopsies)?- In my opinion it is not very useful to mention how often certain tests were performed without saying anything on the performance of these tests. This also refers to Figure 5. <p>Discussion:</p> <ul style="list-style-type: none">- In the results section no information is provided on performance of procalcitonin while in the discussion section the use of procalcitonin is discussed extensively.- The remark that “in patients with negative results for ESR and CRP, false-negative results have been reported” is incorrect. This study showed that when ESR and CRP were normal, FDG-PET was always negative and in none of these patients, a diagnosis was reached, so the results were true-negative. This should be corrected.- The remark “The extent to which PET contributes to the evaluation of patients with fever of unknown origin is unclear” is also incorrect. Many studies have been performed on this subject all showing a percentage of helpfulness that exceeds that of CT, MRI or other diagnostic possibilities in this patient population. This should be adjusted. <p>Table 1:</p> <ul style="list-style-type: none">- It would be more informative to mention all causes of FUI and their frequency divided in groups of infection, NIID, malignancy and
--	---

	<p>miscellaneous. - Please explain how psychogenic fever was diagnosed. Was this fraudulent fever caused by manipulation with a thermometer or factitious fever (i.e., fever artificially induced by the patient for example by injecting contaminated water intravenously)? These terms are more commonly used than “psychogenic fever”.</p> <p>General remark: 20 authors for a retrospective study including 121 patients appears to be rather many.</p>
--	--

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

The most common causative disease in the elderly was polymyalgia rheumatica. It was polymyalgia rheumatica or giant cell arteritis ? Temporal artery biopsy was not performed in FUO in patients > 55 years ? Precisions should be given by the authors.

Among the 9 PMR patients, coexisting giant cell arteritis was ruled out by PET in 4 patients and temporal artery biopsy in 1 patient. In the remaining 4 patients, the symptoms and success of treatment with low-dose steroids suggested PMR alone. The low rate of surgical consultation and temporal artery biopsy in FUO evaluation is a problem in Japan.

Based on your comments, we have added the following to the Results section: "Among the 9 PMR patients, coexisting giant cell arteritis was ruled out by PET in 4 patients and temporal artery biopsy in 1 patient. In the remaining 4 patients, symptoms and the success of treatment with low-dose steroids suggested PMR alone."

Reviewer 2

This article is a nice addition to the growing literature on the causes of FUO focusing on the situation in Japan.

Introduction:

- Second paragraph: please add that “few studies have assessed the clinical usefulness of ... positron emission tomography (PET) in Japan”. Several studies have addressed this subject over the last ten years in other countries.

The text has been revised in accordance with your comments.

- Although I understand the authors' interest in identification of tests that are useful in FUO, this is not something that can be deducted in a reliable way from a retrospective study where it is up to the treating doctor to decide whether a certain test is performed or not. It would be better to leave the aim of the study at defining which causes of FUO are found in the Japanese situation. The article does not provide any useful data on the performance of these tests further arguing in favor of omitting this part. Based on your comments, we have changed "In addition, identification of tests that are useful in diagnosis can shorten the time needed to diagnose causative diseases of fever of unknown origin and hopefully reduce unnecessary testing in future clinical practice" to "In addition, we investigated the rate of performing various tests in the current diagnostic workup of FUO."

Methods:

- The fact that only 17 of 99 hospitals chose to participate with an over representation of university hospitals (both in number of hospitals as in number of included patients) may have caused bias and makes it more difficult to decide if the conclusions apply to all Japanese hospitals.

As you noted, we cannot exclude the possibility of bias due to the small number of participating

hospitals. We have therefore added the following at the end of the Discussion section: "Only 17 hospitals participated in this study, so the results may not be generalizable to the overall situation in Japan. We hope that more hospitals will participate in future studies."

- The authors state that they have performed a nationwide study, but they do not provide information on the localization of the participating hospitals.

Japan is generally divided into Eastern Japan and Western Japan. The participating hospitals in our study had a wide geographic distribution in Japan, with institutions in both regions. We have added the following text: "The hospitals participating in our study had a wide geographic distribution throughout Japan, including 7 hospitals in Eastern Japan and 10 hospitals in Western Japan."

- Choosing for the FEO definition using a quantitative criterion (3 outpatient visits or 3 days of hospitalization) instead of the qualitative criterion that requires a list of investigations to be performed makes it more difficult to generalize the results from this study. What can be done in 3 days of hospitalization usually differs widely between hospitals and depends very much on the logistic organization of hospitals.

We respectfully acknowledge your comments, but when we compared previous reports, we decided to use these criteria, which seem to be widely used in FEO studies.

- What is meant by "general biological examination"?

We have changed this to "biochemical examination."

- How long was the minimum follow-up to decide whether no diagnosis was reached?

Unfortunately, since this was a retrospective study, the minimum follow-up is unknown.

Results:

- A death rate of more than 10% among patients without a diagnosis is much higher than in previous studies. This needs further explanation: what were the causes of death of these patients? How long after the FEO episode did they die? Were their deaths possibly related to the FEO episode? Mortality in the patients without a diagnosis was 10.7% compared to 6.5% in patients with a diagnosis, most of them dying from malignancy. This is very remarkable.

As you commented, analysis of the patients in whom the cause of FEO remained unknown is important. The following text has been added:

"Among the 3 patients who died with undiagnosed FEO, one was a 72-year-old man who developed DIC 2 months after fever onset and died. Another was an 82-year-old man who similarly developed DIC of unknown cause 1 month after fever onset and died. The other was a 63-year-old woman in whom the cause of FEO remained unknown despite PET and random skin biopsies. This patient developed respiratory failure about 6 months after fever onset and died."

- It is stated that PMR was a common diagnosis especially among the elderly. In previous studies it has been shown that fever is more commonly seen in giant cell arteritis occurring together with PMR. This diagnosis can often only be made after FDG-PET/CT and/or temporal artery biopsy. How sure are the authors that these patients did not have giant cell arteritis (since FDG-PET was performed in less than 30% of all patients and no information is provided on temporal artery biopsies)?

The healthcare insurance system in Japan usually will not authorize FDG-PET/CT for patients with FEO. As a result, FDG-PET/CT is generally not used to diagnose PMR. Among the 9 patients diagnosed with PMR, 4 had undergone PET and temporal artery biopsy was performed for only 1 patient. The low rate of surgical consultation and temporal artery biopsy in FEO evaluation is a problem in Japan. In patients who did not undergo PET or temporal artery biopsy, the attending physicians ruled out giant cell arteritis based on clinical findings and good response to low-dose steroids. However, as you point out, the possibility of this coexisting condition cannot be completely excluded. We have therefore added the following to the Results section: "Among the 9 PMR patients,

coexisting giant cell arteritis was ruled out by PET in 4 patients and temporal artery biopsy in 1 patient. In the remaining 4 patients, symptoms and the success of treatment with low-dose steroids suggested PMR alone."

- In my opinion it is not very useful to mention how often certain tests were performed without saying anything on the performance of these tests. This also refers to Figure 5.

No conclusions can be made about which tests are useful in diagnosing FUO based on our study results. However, ascertaining the rates of performing various tests in the current diagnostic workup of FUO in Japan may be useful for future studies of FUO.

Discussion:

- In the results section no information is provided on performance of procalcitonin while in the discussion section the use of procalcitonin is discussed extensively.

Based on these comments, we have added the following to the Results section: "However, only 1 of 17 patients (5.9%) with a serum procalcitonin level ≥ 0.25 ng/ml showed bacterial infection, and 3 patients (11.5%) with a value < 0.25 ng/ml also had bacterial infection." The Discussion section has also been partially revised.

- The remark that "in patients with negative results for ESR and CRP, false-negative results have been reported" is incorrect. This study showed that when ESR and CRP were normal, FDG-PET was always negative and in none of these patients, a diagnosis was reached, so the results were true-negative. This should be corrected.

- The remark "The extent to which PET contributes to the evaluation of patients with fever of unknown origin is unclear" is also incorrect. Many studies have been performed on this subject all showing a percentage of helpfulness that exceeds that of CT, MRI or other diagnostic possibilities in this patient population. This should be adjusted.

Based on both of these comments, we have revised the Discussion section about PET, as shown below. Reference numbers 19 and 20, which support the usefulness of PET, have also been added. "PET appears promising as a useful test to evaluate FUO. Many studies have been performed using this modality in patients with FUO, all showing a percentage helpfulness that exceeds that of CT, MRI or other diagnostic possibilities (17-20). However, the fact that PET is not covered by National Health Insurance in Japan for patients with FUO is problematic. A previous Japanese study about PET included FUO patients evaluated by radiology departments (21). In the present study, it was interesting to see the frequency of PET use in general medical settings, mainly for evaluating FUO."

Table 1:

- It would be more informative to mention all causes of FUO and their frequency divided in groups of infection, NIID, malignancy and miscellaneous.

Based on your recommendations, Table 1 divides causes into groups and lists the diagnoses in greater detail. However, because the causative diseases are diverse and complex, only those causes identified in ≥ 2 patients are listed.

- Please explain how psychogenic fever was diagnosed. Was this fraudulent fever caused by manipulation with a thermometer or factitious fever (i.e., fever artificially induced by the patient for example by injecting contaminated water intravenously)? These terms are more commonly used than "psychogenic fever".

Each diagnosis was made by the physicians at each hospital. However, these cases were confirmed, and should be listed as and have been revised to "fraudulent fever", as per your comments.

General remark: 20 authors for a retrospective study including 121 patients appears to be rather many.

This was a nationwide study at multiple institutions, so a relatively large number of authors were involved.

VERSION 2 – REVIEW

REVIEWER	C.P. Bleeker-Rovers Radboud University Medical Centre Nijmegen, The Netherlands
REVIEW RETURNED	10-Nov-2013

GENERAL COMMENTS	Most of my previous comments have been addressed. I still have some doubts about the usefulness of just mentioning which tests were performed without being able to draw clear conclusions.
-------------------------	---