Executive Summary

Background and Purpose

Fever of unknown origin (FUO) is defined as temperature > 38.3℃ (101°F) on several occasions duration of fever of more than 3 weeks and failure to reach to diagnosis despite one week of inpatient investigations. In general, the causes of FUO have been grouped into four categories: infection or inflammation, non-infectious inflammatory disease, malignancies and miscellaneous. The age, geographic factors, physician's experience, diagnosis methods, and the developmental status of the country could influence the spectrum of FUO. Infection is the most common cause of FUO, but the high percentage of cases with collagen disease, neoplasm in recent studies suggests the need to be aware of these likely causes of FUO.

In FUO, there is no diagnostic gold standard, and the final diagnoses are determined in a number of ways, including a comprehensive history, physical examination, laboratory tests, anatomical imaging modalities, and a nuclear medicine imaging. Positron emission tomography (PET) is a nuclear medicine imaging technique that detects pairs of gamma rays emitted by a positron-emitting radionuclide, which is introduced into the body on a biologically active molecule. It may detect biochemical changes in a tissue that can identify the onset of a disease process, and then has been successfully used to evaluate different malignant tumors. Positron emission tomography–computed tomography (PET-CT) is able to perform fusion of functional PET and anatomical CT images. In the diagnosis of FUO, Whole-body screening PET is used to provide the detailed metabolic and functional information of the foci while PET-CT offers more definitive anatomic and morphologic information.

Several recent studies suggest that it will probably become the preferred diagnostic procedure, when a definite diagnosis cannot easily be achieved. However, the diagnostic accuracy of FDG PET/PET-CT in patients with FUO has varied across studies. Thus, this study aimed to perform a systematic review and meta-analysis to examine the overall diagnostic performance of FDG-PET/PET CT in identifying the causal source of FUO.

Methods

We searched potentially relevant studies using electronic databases such as Ovid-Medline, Ovid-EMBASE and Cochrane library, as well as two local databases (KoreaMed, Kmbase) providing information on Korean medical research, from their inception to May, 2012.

Two reviewers independently evaluated titles, abstract and citations to assess potential relevance for full review and selected articles on the basis of predetermined selection criteria. The selection criteria were as follows: the patients examined in the studies had to have met the criteria for the definition of classical FUO; all the reference standards used in the individual studies were accepted; the reported primary data must have been sufficient to discriminate between the true positive (TP), false positive (FP), false negative (FN), and true negative (TN) results of FUO and to allow us to determine the sensitivity and specificity. Two independent reviewers extracted prespecified data from each studies using a standardized form. Disagreements between reviewers were resolved by discussion or in consultation with a third reviewer. The quality of the selected studies was assessed using Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2). Qualitative and quantitative analyses of studies were performed to compute and compare estimates of the diagnostic accuracy of FDG PET and FDG PET-CT and investigate the variability of results between studies. .

Results

A total of 15 studies representing 592 patients were eligible for inclusion in this study, of which six were FDG-PET studies and 9 were FDG-PET/CT studies.

【FDG PET】

AUC of SROC based on the sensitivity and specificity of 6 literatures was 0.7955, and the pooled diagnostic odds ratio (DOR) was 9.38 (95% CI 1.44-60.91). Pooled sensitivity using the bivariate model was 0.859 (95% CI 0.729-0.932), and the pooled specificity was 0.664 (95% CI 0.416-0.845). The positive likelihood ratio (PLR) calculated based on pooled sensitivity and pooled specificity was 2.557 (95% CI 1.248-6.013) and negative likelihood ratio (NLR) was 0.212 (95% CI 0.080-0.651). The range of positive predictive values (PPVs) and negative predictive values (NPVs) according to 30-80% of the underlying etiologic lesion discovery rate were 52.3-91.1% and 54.1-91.7%, respectively.

For the diagnostic accuracy for each specific disease, the range of sensitivity in infection was 75-100% when excluding 1 literature (Kjaer et al., 2010) reported with 25%, and the sensitivity in inflammation was 67-100%, and the sensitivity in malignancies appeared as 100% from all the studies.

【FDG PET-CT】

AUC of SROC based on 9 literatures was 0.8071, and the pooled DOR was 10.93 (95% CI 4.67-25.57). pooled sensitivity was 0.838 (95% CI 0.715-0.914), and the pooled specificity was 0.714(95% CI 0.588-0.814), and the PLR calculated based on pooled sensitivity and pooled specificity was 2.930 (95% CI 1.735-4.914) and the NLR

calculated was 0.227 (95% CI 0.106-0.485). The range of PPVs and NPVs according to 30-80% prevalence of the underlying etiologic lesion were 55.7-92.1% and 52.4-91.1%, respectively.

For the diagnostic accuracy for each specific disease, the range of sensitivity in infection was 50-100%, and the sensitivity in inflammation was 57-100% when excluding 1 literature (Federici et al., 2010) reported to have 33%, and the sensitivity in malignancies appeared as 100% from most of the studies.

【FDG PET/PET-CT】

According to the integrated analysis of FDG PET and FDG PET-CT test, the pooled DOR of 15 studies was 10.31 (95% CI 4.23-25.11), and AUC was 0.7978. Pooled sensitivity was 0.844 (95% CI 0.760-0.902), and the pooled specificity was 0.681 (95% CI 0.553-0.787). The calculated PLR was 2.646 (95% CI 1.700-4.235) and calculated NLR was 0.229 (95% CI 0.125-0.434). The range of PPVs and NPVs according to 30-80% prevalence range were 53.1-91.4% and 52.2-91.1%, respectively.

As a result of analyzing bivariate including respective covariate (blindness upon analysis of target test interpretation, multi-center study) which appeared as the cause of potential heterogeneity between studies, pooled sensitivity appeared in a range of 83.7-94.3%, and pooled specificity 66.5-84.6%. There was no significant statistical difference between two subgroups (blind/non-blind or unclear; multi-center/single center) of each covariate.

Although integrated measured values for the diagnostic accuracy of each specific diseases were not assumed in respective analysis of FDG PET and PET-CT test, some specific diseases were analyzed with bivariate model from the integrated analysis of two tests. Its pooled

sensitivity was 0.790 (95% CI 0.673-0.873), and pooled specificity was 0.049 (95% CI 0.001-0.679) in infection. The pooled sensitivity was 0.736 (95% CI 0.633-0.819), and pooled specificity 0.248 (95% CI 0.052-0.668) in inflammatory diseases, and no estimations were given for malignancies and no-diagnosis.

Conclusions

This study was to evaluate the diagnostic accuracy of FDG PET/PET-CT for the detection of the causes of FUO. We analyzed fifteen studies by test modality that collectively evaluated 592 patients in whom conventional diagnostic methods failed to detect the origin of their fever. FDG PET/PET-CT test appeared to have a high sensitivity and a moderate specificity for the detection of the causes of FUO.

The results of this study suggest that FDG PET/PET-CT are helpful in the diagnosis of the source of origin for patients with FUO and may play an important role in the assessment of patients with FUO, and provide the useful information with the help of other tests, such as biopsy and culture facilitate timely definitive diagnosis. However, since a limited number of studies are available in this study and those included studies were heterogeneous with respect to the aspect of study design, the method of interpretation of test result. More rigorous and larger prospective studies are needed to determine the diagnostic accuracy of FDG PET/PET-CT for patients with FUO.