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Molecular Imaging for the diagnosis of infective endocarditis: A systematic literature review and meta-analysis☆

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ABSTRACT

Background: Infective endocarditis (IE) is a serious, potentially life-threatening condition. Currently, the modified Duke criteria is used to assist with the diagnosis of IE, but it can still remain difficult. Growing data supports the potential use of molecular imaging to assist in the diagnosis of IE. Our objective was to understand the potential utility of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography-computed tomography (PET-CT), ^{67}Ga citrate and radiolabeled white blood cell (WBC) scintigraphy in the diagnosis of IE.

Methods and results: A systematic review of the literature and meta-analysis on the use of all 3 modalities in IE was conducted. The literature search identified 2753 articles. A total of 14 studies met the inclusion criteria (10 for ^{18}F-FDG, 3 for WBC and 1 for both modalities). No ^{67}Ga citrate study met the inclusion criteria. Pooled sensitivity of ^{18}F-FDG studies with adequate cardiac preparation for the diagnosis of IE was 81% (95% CI, 73%–86%) and pooled specificity was 85% (95% CI, 78%–91%). There was good overall accuracy with an area under the curve (AUC) of 0.897. Pooled sensitivity of WBC for the diagnosis of IE was 86% (95% CI, 77%–92%) and pooled specificity was 97% (95% CI, 92%–99%). The overall accuracy of WBC was excellent with an AUC of 0.957.

Conclusions: Both ^{18}F-FDG and WBC have good sensitivity, specificity and accuracy for the diagnosis of IE. Both modalities are useful in the investigation of IE, and should be considered in cases where the diagnosis is uncertain.

1. Introduction

Infective endocarditis (IE) is a serious, potentially life-threatening condition. Despite efforts towards its prevention, there has been no decline in incidence [1]. Early diagnosis and therapy are important in limiting morbidity and mortality, but remain challenging [2]. The current diagnostic approach often revolves around the modified Duke criteria, a composite of clinical criteria, blood cultures and echocardiographic findings [3], but clinicians often encounter cases of uncertainty.

While echocardiography (trans-thoracic or trans-oesophageal) remains the first line imaging modality of choice in IE, it can be limited in the early stages of IE, in the early post-operative period, or in patients with prosthetic valve and intracardiac devices. These limitations have led to an increased interest in the use of other imaging modalities that might complement echocardiography. Positron emission tomography computed tomography (PET-CT) using fluor-18-fluorodeoxyglucose (^{18}F-FDG) and single-photon emission computed tomography (SPECT) using labeled white blood cell (WBC) or ^{67}Ga citrate have long been used in a variety of infectious and inflammatory conditions [4,5]. Several reports have shown promising results with these tests to assist in the diagnosis of IE. This has led the European Society of Cardiology to include these functional and molecular imaging modalities as new diagnostic criteria in their latest IE guidelines [6].

To understand the value of these modalities in IE, a systematic literature review and meta-analysis on the use of ^{18}F-FDG PET-CT, ^{67}Ga citrate and labeled WBC scintigraphy was undertaken.

2. Methods

The search strategy for the systematic review was developed jointly by the review team and an experienced medical information expert. The initial database searches were performed on November 25 and 26, 2015, and were updated on October 7, 2016. We searched Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, and Embase using the OVID platform and the CENTRAL database on Wiley. The updated search included the newly added MEDLINE® Epub Ahead of Print database. PubMed was searched only for the most recent and unindexed citations. As well, we used existing results from our initial database search in the investigation of cardiac implantable electronic device infection [7].

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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A combination of keywords and controlled vocabulary were used in the search strategies, with appropriate adjustment in vocabulary and syntax across databases. Opinion pieces and animal studies were excluded from the results when possible. A focused grey literature search was also conducted, covering Google Scholar and major health technology assessment organizations. Complete details regarding the strategies are outlined in Appendix C.

To be included, studies had to be peer-reviewed and had to investigate the diagnostic accuracy of ^{18}F-FDG PET-CT, ^{67}Ga citrate scintigraphy or WBC scintigraphy (labeled with either ^{99m}Tc or ^{111}In) in IE in the adult population. IE could be of native valves, prosthetic valves or related to intracardiac devices. Abstracts, case reports, case series, animal studies and studies in the pediatric population were excluded. Studies that failed to provide enough information to calculate true positive, false positive, true negative and false negative values for the diagnosis of IE were excluded. To reflect the current standard in clinical practice for ^{67}Ga citrate or WBC imaging, only studies that used single-photon emission computed tomography (SPECT) alone or in combination with CT were included.

All abstracts were screened for adherence to the inclusion criteria by two independent reviewers. At the abstract level, acceptance by either reviewer was sufficient for a study to progress to full text review. Any disagreements at the full text review stage were resolved through consensus. In cases where consensus could not be achieved, a third reviewer was consulted. Once the full text review was completed, the bibliographies of included studies were reviewed by both reviewers for potentially missed articles.

One reviewer extracted the absolute numbers for true positive, false positive, true negative, and false negative examinations from the studies that met inclusion criteria. All extracted data were verified by the second reviewer. For each study, estimates of sensitivity and specificity, and their 95% confidence intervals were calculated. Weighted averages using the patient population size were also used to calculate pooled estimates of sensitivity and specificity. Heterogeneity between studies was assessed with the Cochran Q test and the Inconsistency Index I^2. Area under the curve (AUC) calculated on summary receiver operating characteristic (SROC) curves were used as a measure of diagnostic accuracy. We used the Moses constant of linear model, under the assumption of symmetry, to compute the shape of the curves, and we used the Spearman correlation between sensitivity and specificity to assess for threshold effect. To validate the assumption of symmetry in the receiver operating characteristic curve, we used the Moses-Shapiro-Littenberg model. All analyses were performed using Meta-DiSc version 1.4 (Clinical Biostatistics Unit, Ramon y Cajal Hospital, Madrid, Spain).

For the meta-analysis, we only included ^{18}F-FDG studies which indicated that they employed adequate patient preparation for suppression of physiological myocardial FDG uptake [8], defined as:

- Prolonged fasting (at least 12 h), and/or
- Heparin injection before ^{18}F-FDG injection, and/or
- High fat, carbohydrate restricted, protein permitted diet (minimum 2 meals or 24 h)

In cases where no information was provided about patient preparation, it was assumed no cardiac preparation had been used.

When enough information was available, we also performed sub-analyses for the accuracy of the tests in native valve IE versus prosthetic valve IE versus intracardiac device related IE.

We used the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool to assess all included studies for risk of bias and applicability concerns [9].

3. Results

The literature search identified 2753 studies, after the removal of duplicates. A total of 14 studies met all eligibility criteria (Fig. 1). Of these, 10 investigated the use of ^{18}F-FDG PET-CT (407 patients) [10–19], 3 investigated the use of WBC SPECT (207 patients) [20–22],

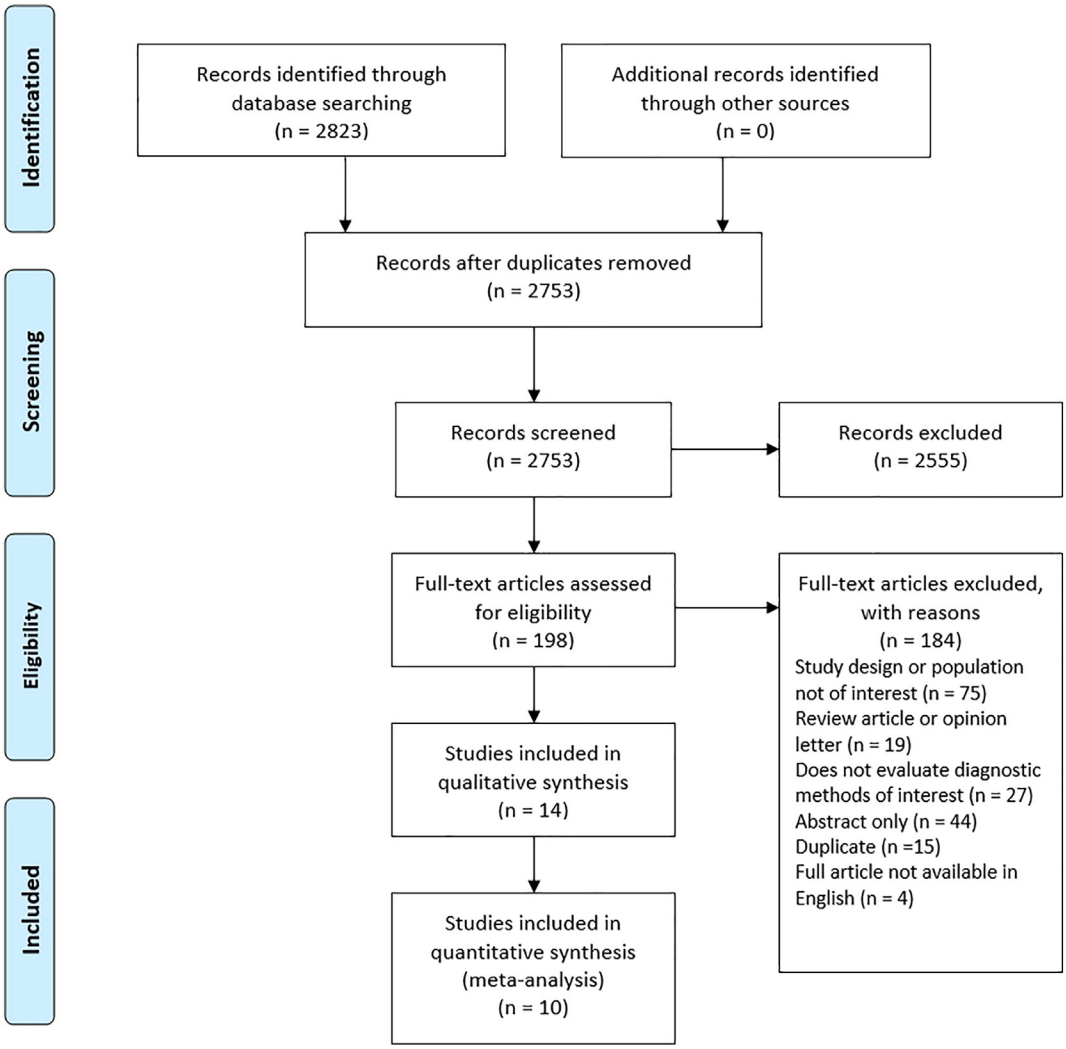

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram.

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