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Computed Tomography for Detecting Patent Foramen Ovale: A Meta-Analysis

Jingjing Lou, MM,[1] Yaya Bao, MD,[2] Tian Lv, MM,[1] Yue Yang, MD[1]

[1]Department of Neurology, Zhuji People's Hospital of ZhejiangProvince, Zhuji, China;
[2]Department of Neurology, Shaoxing University Medical College, Shaoxing, China

ABSTRACT

Objective: Patent foramen ovale (PFO) has been regarded as a potential source of cryptogenic stroke, which was conventionally detected by transesophageal echocardiography. Cardiac computed tomography (CCT) is a promising, noninvasive test for detection of PFO. We sought to conduct a meta-analysis to evaluate the diagnostic performance of CCT in detecting PFO.

Methods: PubMed, ISI Web of Knowledge, Embase, Cochrane Library, and Wanfang from inception to June 2020 were searched for relevant studies comparing CCT and transesophageal echocardiography as the reference standard in detecting PFO. A bivariate model was used to pool sensitivity and specificity and to construct summary receiver operating characteristic (SROC) curves.

Results: A total of seven studies with 483 patients were included in this meta-analysis. For the diagnosis of PFO, CCT had a mean sensitivity and specificity of 0.70 [95% CI:0.58, 0.79] and 0.97 [95% CI: 0.95, 0.99]. The SROC analysis showed an area under the curve of 0.97.

Conclusion: CCT shows good diagnostic accuracy in detecting PFO with relatively high sensitivity and specificity. CCT could be considered a noninvasive alternative to transesophageal echocardiography for detecting PFO.

INTRODUCTION

The patent foramen ovale (PFO) connects the left and right atria, and this channel may be the main anatomical channel for embolus formation and contributing to stroke [Ning 2013]. Clinically, transesophageal echocardiogram (TEE) is the gold standard for diagnosing PFO, providing superior image resolution to improve the imaging effect of the heart structure, easily distinguish the location and size of the shunt, and detect the source of embolization [Mojadidi 2014]. However, TEE, a semi-invasive operation, cannot be used as a clinically routine examination for PFO screening. In recent years, many scholars have found that cardiovascular computed tomography (CCT) can be used to assist in the diagnosis of PFO [Saremi 2008; Williamson 2008; Hur 2009; Kim 2009; Revel 2008; Resen 2020; Boussel 2011]. It uses the visual difference of the contrast concentration between the left and right atria, which can detect the left atrial contrast injection or leakage to the right atrium, prove the presence of PFO, and detect the flap and channel of the atrial septum. However, the diagnostic value of CCT for PFO systematically has not been evaluated. Therefore, we comprehensively reviewed the current study reports and performed qualitative and quantitative meta-analysis to assess the diagnostic value of CCT to detect PFO.

MATERIALS AND METHODS

This study was conducted in accordance with the declaration of Helsinki and with approval from the Ethics Committee of Zhuji People's Hospital of Zhejiang Province.

Inclusion criteria: (1) Taking MDCT and TEE as the reference standards; (2) Including a multilayer CT scanner (64 layers); (3) The number of true positives, false positives, false negatives and true negatives is clearly stated, or can be inferred from the article; (4) Diagnostic criteria for CT diagnosis of PFO: free valve visible in the atrium, abnormal shunt (contrast flow into the contralateral atrium) and obvious abnormal shunt channel (contrast flow into the shunt channel) [Saremi 2008; Williamson 2008; Hur 2009; Kim 2009; Revel 2008; Resen 2020; Boussel 2011]; (5) The TEE diagnostic standard for PFO is to inject the stirred saline (foaming test) and perform the Valsalva action to detect PFO.

Exclusion criteria: (1) Repeated literature; (2) Non-original research (including case reports, reviews, and other literature); (3) Research unrelated to the subject content.

Literature search: Data retrieval in both Chinese and English languages, according to the retrieval method recommended by Cochrane collaboration network. The English databases included PubMed, Medline, ISI Web of Knowledge, and Cochrane Library. Retrieval strategy: The combined search of Patent foramen ovale or Oval Foramen, Patent or Patent Oval Foramen and CT and "transesophageal echocardiography (TEE)" or "trans-oesophageal echocardiography (TOE)." The Chinese database included Wanfang Medical Database, China Biomedical Literature Service System. And the search strategy: the combined search of "patent foramen ovale", "computed tomography", "transesophageal cardiac ultrasound", or "transesophageal ultrasound". All

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Correspondence: Yue Yang, Department of Neurology, Zhuji People's Hospital of Zhejiang Province, No. 9, Jianmin Road Taozhu Street, 311800 Zhuji, Zhejiang, China, Telephone +86 189 6955 9555 (e-mail: yueyang1693@163.com).

searches were conducted independently by two authors. The results were compared, and any questions or differences were resolved by consensus. The retrieval time limit is from self-construction to June 2020.

Data extraction and analysis: The following data were extracted from each study: sample size; data on demographic characteristics; technical methods related to CT and TEE, and detailed reference standards; and number of true positives, false positives, false negatives and true negatives. Data were extracted by two authors, using specific data tables and checked to meet the requirements.

Literature quality assessment: We evaluated the quality of the literature with the QUADAS-2 tool. This standard provides a standardized approach for grading the quality of studies in a meta-analysis of diagnostic accuracy. QUADAS-2 classified the risk of bias as low, unclear or high, and studied generalizability. Two commentators both independently scored the seven tools and resolved their differences through negotiation. That is, a face-to-face discussion about each disagreement.

Statistical analysis: The quality of included literature was evaluated using the QUADAS-2 tool with Review Manager 5.3 software. We selected the MIDAS module for the STATA software (version 16.0, Stata Corporation, College Station, TX). Sensitivity and specificity set indices with the corresponding 95% confidence interval (CI) were calculated, and the I^2 was calculated to assess the heterogeneity. The area under the SROC curve was calculated. Publication bias was tested using Deeks' funnel plot to explore the accuracy of CCT for the diagnosis of PFO.

RESULTS

Literature screening: The main search results involved 136 references. During the review, 32 duplicate documents were excluded, and 94 were titles and abstracts were read, including 69 case reports, five reviews, and 20 other documents. After reading the full text, eight documents were excluded, and seven documents were included [Saremi 2008; Williamson 2008; Hur 2009; Kim 2009; Revel 2008; Resen 2020; Boussel 2011]. (Figure 1)

Basic characteristics of the included studies: The main characteristics of the eligible studies are described in Table 1, including three retrospective studies [Saremi 2008; Williamson 2008; Kim 2009] and three prospective studies [Hur 2009; Revel 2008; Boussel 2011]. (Table 1) All were single-center studies. Three studies included stroke patients [Hur 2009; Resen 2020; Boussel 2011].

Literature quality evaluation – method quality survey: The results of the quality assessment of the diagnostic accuracy study of the QUADAS-2 tool can be found in Figures 2 and 3, which suggested most were low-risk literature. (Figure 2) (Figure 3)

Meta-analysis and calculation: The STATA software was used to calculate, and a fitted bivariate effect model was used. The sensitivity of MDCT to diagnose PFO was 0.70 [95% CI: 0.58, 0.79], and specificity was 0.97 [95% CI: 0.95, 0.99]. (Figure 4) Positive likelihood ratio was 26.5 [95% CI: 13.8-50.9]. Negative likelihood ratio was 0.31 [95% CI: 0.22, 0.45]. The combined diagnostic ratio (DOR) was 85 [95% CI: 38, 191]. The AUC area was 0.97, close to l. (Figure 5) Subsequently, we performed a Deek funnel plot test for all studies (P = 0.54), suggesting no publication bias. (Figure 6)

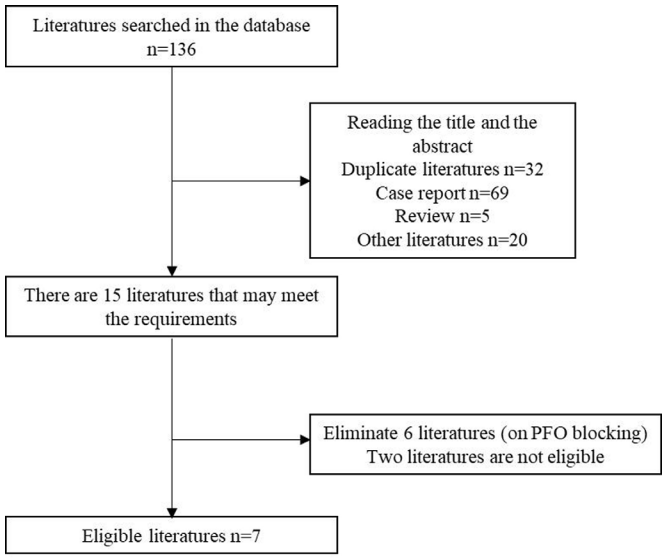

Figure 1. Flow chart of literature search and selection

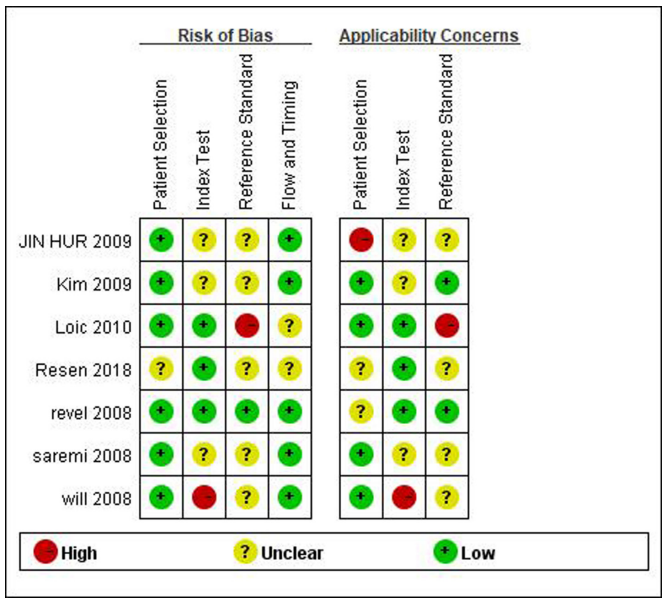

Figure 2. Evaluation of study quality and applicability

DISCUSSION

The atrial septum is a fusion of two separate valves of the flap valve system, which can provide continuous fluid circulation to the fetus in utero. About 70% of people have the

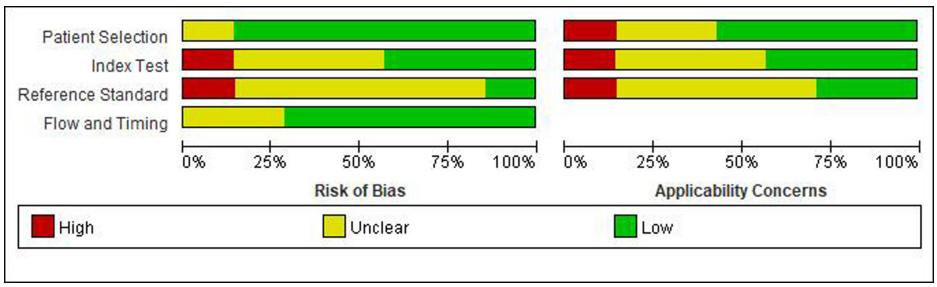

Figure 3. Evaluation of study quality and applicability. (The vertical axis in the figure is the quality assessment entry, and the horizontal axis is the percentage of assessment item "high," "unclear," and "low.")

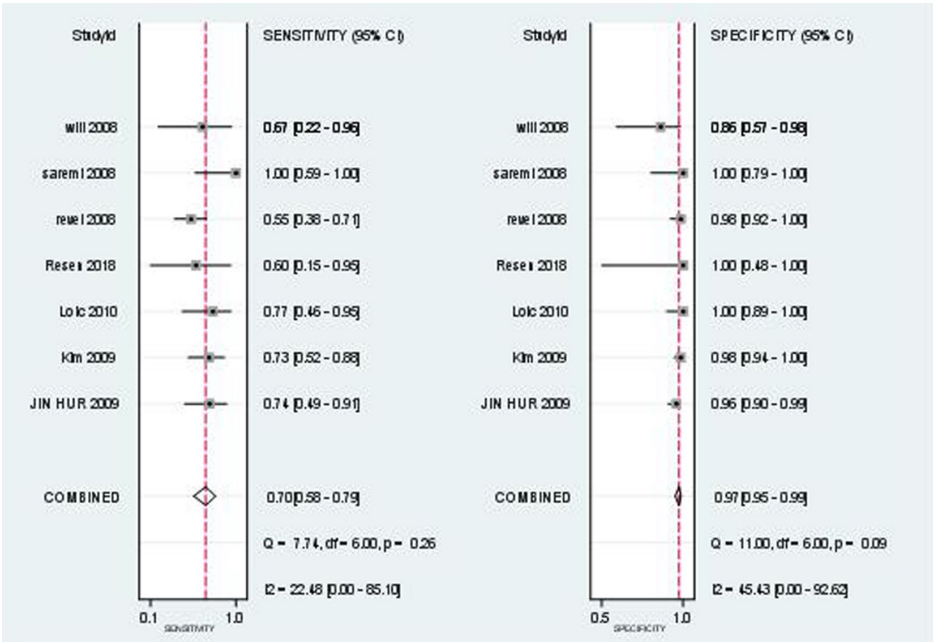

Figure 4. Sensitivity and specificity of CT for PFO diagnosis: PFO sensitivity 0.70 [95% CI: 0.58,0.79], specificity 0.97 [95% CI: 0.95,0.99], sensitivity heterogeneity I2 = 22.48, specificity heterogeneity I2 =45.43.

atrial septum fuse to form a complete barrier shortly after birth. If the flap valve system fails to fuse after birth, it may lead to PFO to connect the left and right atria, and this channel may be the main anatomical channel for embolus formation and contributing to stroke [Ning 2013]. The incidence of PFO in healthy adults is about 20%-25%, and most PFO patients are clinically asymptomatic. About 20%-40% of strokes have no cause to be identified, commonly referred to as cryptogenic strokes. Studies have shown that most of CS were caused by embolization, originating from the heart, aortic arch, or proximal cerebral artery. Among them, about 40%-50% of the patients with CS had PFO. Currently, PFO is considered as an independent risk factor for stroke, and it is also closely related to hypoxemia and migraine [Hara 2005; Fonseca 2015].

There are multiple imaging modalities for evaluating PFO that can be used to determine the presence of an abnormal shunt, including transthoracic echocardiography (TTE), TCD, TEE, CCT, and so on. Although each method has its advantages and limitations, TEE remains the primary means of PFO diagnosis, due to its ability to accurately display atrial septal anatomy. This technology provides superior image resolution to improve the imaging effect of the cardiac structure, easily distinguish the location and size of the shunt, and detect the source of the embolization [Hara 2005]. However, because TEE is a semi-invasive operation with rare complications, such as esophageal bleeding or perforation, it cannot be used as a clinical routine screening method for PFO. In addition, some diseases are contraindicated for TEE, including esophageal or gastric varices, esophageal or pharyngeal cancer, severe esophageal stenosis. TTE currently is the preferred method for PFO screening, due to its simple operation and high popularity. However, its sensitivity is low, and TTE is much weaker than TEE in displaying atrial structure, foramen ovale diameter, flap valve offset, and the ability to detect a smaller shunt. In the past 10 years, CCT widely has been

used to diagnose in the atrial interval, cardiac valvular disease, and atrial thrombosis [Yamashita 2017].

This study is the first meta-analysis comparing the accuracy of CCT and TEE in PFO screening. Currently, most scholars believe that TEE may be the final gold standard for PFO screening, and we summarize all the existing quantitative evidence on the diagnostic value of CT in PFO screening with TEE as a reference. Sensitivity was 0.70 [95% CI: 0.58, 0.79], and specificity was 0.97 [95% CI: 0.95, 0.99]. According to the meta-analysis published by Mojadidi et al. in 2014, the sensitivity of TEE for PFO was only 44% compared with TTE [Mojadidi 2014]. And, CCT showed more sensitivity compared with this study. DOR is the ratio of positive LR to negative LR. The higher the DOR, the higher the accuracy of the CCT for diagnosis [Glas 2003]. However, LR clinically is more significant. The positive likelihood ratio of 26.5 indicates that patients with PFO had a 26-times higher chance of being CCT positive than that in patients without PFO. Conversely, the negative likelihood ratio of 0.31 indicates that patients are 31% likely to have a PFO if CCT is negative [Lee 2021].

There are some limitations in this meta-analysis. First, the included studies had certain methodological quality flaws. For example, some retrospective studies did not use a blinding design as an index test and reference standard. Although this potential offset did not have a great impact on the meta-analysis, it could lead to an overestimation of the diagnostic performance of the CCT. Second, in our meta-analysis, TEE was used as the gold standard for detecting PFO, which also produced false negative results. Saremi et al. found an abnormal shunt in CT TEE did not show. Therefore, combination of CT and TEE can be used to improve the accuracy of PFO screening in the future. Moreover, the number of patients of studies included in this meta-analysis is small, and some studies have only included 10 cases, which may lead to bias. Therefore, clinical studies with large samples are still needed. We believe CCT can be used as the preferred technique to detect PFO in patients unable to undergo TTE.

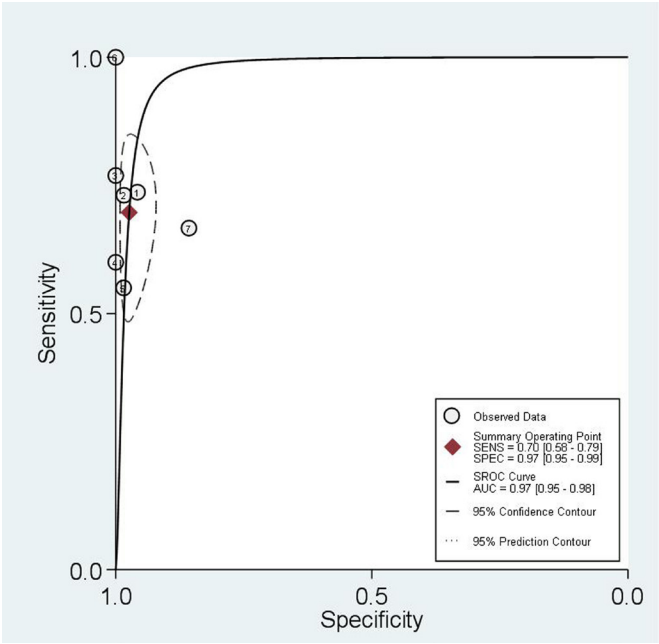

Figure 5. SROC curve: showing the 95% confidence interval and the 95% prediction interval

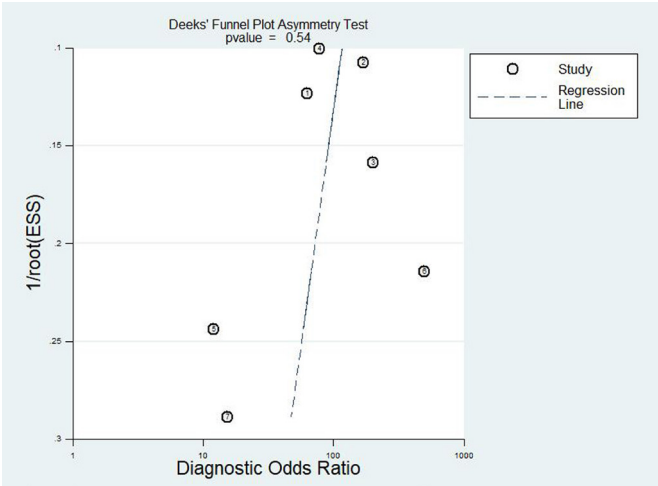

Figure 6. Deek funnel diagram. *P* = 0.54

Table 1. Main characteristics of the included studies

Study	Region	Year of publication	No. of patients	Average age	Male	Experiment design
Kim	Korea	2009	152	61.7	64.4%	Retrospective
Revel	France	2008	105	52	54.4%	Prospective
Saremi	USA	2008	23	62	69.5%	Retrospective
Williamson	USA	2008	20	56.8	80%	Retrospective
Hur	Korea	2009	137	61	69.3%	Prospective
Resen	Denmark	2018	10	56	83%	Not provided
Boussel	France	2010	46	Not provided	Not provided	Prospective

CONCLUSION

This study shows that with TEE as the reference standard, CCT has a high accuracy in PFO diagnosis, and it is expected to be the non-invasive preferred technical means for PFO detection in the future. However, the clinical value of CCT in PFO diagnosis and treatment needs to be verified by large clinical studies with more samples.

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