Systematic review and meta-analysis of diagnostic test accuracy (DTA) studies: the role of cerebral perfusion imaging in prognosis evaluation of mild cognitive impairment

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Background: The application value of cerebral perfusion imaging, such as fluorodeoxyglucose-positron-emission computed tomography (FDG-PET), single-photon emission computed tomography (SPECT), and structural magnetic resonance imaging (MRI), in the prognostic assessment of mild cognitive impairment (MCI) remains unclear. Thus, it was the focus of this meta-analysis, which aimed to provide a theoretical basis for early diagnosis of neurological diseases.

Methods: The Boolean logic retrieval method was used to retrieve related literature, with "cognitive disorder", "cerebral perfusion imaging", "cerebral imaging", "mild cognitive impairment", and "prognostic assessment" as search terms. The PubMed, Medline, CNKI (China National Knowledge Infrastructure), and other databases were searched from the date of establishment of the database to December 30, 2020 for literature on the prognostic assessment of MCI using FDG-PET, SPECT, and MRI imaging. Meta-analysis was performed using Review Manager software.

Results: A total of 16 references were identified, most of which had a low risk of bias (i.e. medium and high-quality). The meta-analysis results showed that the sensitivity and specificity of FDG-PET imaging was significantly higher than those of SPECT and MRI imaging, and the differences were statistically significant ($P<0.05$). The summary receiver operating characteristic (sROC) curves for the sensitivity and specificity of FDG-PET, SPECT, and MRI imaging did not present a "shoulder arm" distribution, and there was no threshold effect.

Discussion: Cerebral perfusion imaging has good prognostic value for patients with MCI, and FDG-PET imaging has better predictive ability of the prognosis for patients with MCI.

Keywords: Cerebral perfusion imaging; cognitive impairment; computed tomography; prognosis evaluation

Introduction

Mild cognitive impairment (MCI) refers to a mild decline in cognitive functions such as memory, orientation, thinking judgment, spatial configuration, and language. Although MCI has not yet affected the ability to perform daily living, it may develop into dementia without intervention (1). Studies have shown that MCI is a precursor to dementia, with more than 10% of people with MCI converting to dementia each year. Only 1 to 2 percent of normal older adults develop dementia each year, so MCI is at high risk of developing dementia. Once detected and diagnosed, it is important to actively treat the disease. There are many causes of MCI, including neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, frontotemporal degeneration, and cortical basal ganglia degeneration (2). Vascular factors (such as cerebral infarction, cerebral thrombosis, and cerebral hemorrhage), infections (such as autoimmune encephalitis, viral encephalitis, and limbic encephalitis), and nutrient/vitamin deficiency and metabolic dysfunction (such as hypothyroidism) (3). If the above factors can be effectively controlled, cognitive dysfunction may not progress and can be stabilized or even restored to normal. The main clinical manifestations of MCI is memory impairment, and it is the short-term memory that declines first; that is, daily activities and some commonly used items are often forgotten (4). Cerebral blood perfusion disorder is one of the high risk factors for the onset and progression of cognitive dysfunction. Cerebral blood perfusion imaging is helpful to discover hemodynamic changes in patients with cognitive dysfunction and dementia, so as to diagnose the disease.

Study found that timely intervention in patients with mild cognitive dysfunction can delay the progress of dementia, help patients keep positive and optimistic attitude, so as to effectively improve memory function in patients with MCI, currently on the intervention of the disease including nonspecific intervention, cognitive training, drug intervention and regulate lifestyle (sleep), control diet led, etc. (5). In order to reveal the cause of MCI or associated with disease, besides neuropsychological assessment of patients, also suggested that detection of hematology, including blood counts, blood sedimentation, blood electrolyte, thyroid hormone levels, etc., in addition, some patients still need to improve the head CT (computer tomography) scan, head magnetic resonance (MRI) scan imaging examination, etc. Brain perfusion imaging (BRAIN perfusion imaging) refers to the diagnosis of brain diseases using radioactive drugs that can pass the normal blood-brain barrier into the body and obtain clear images reflecting brain function and metabolism through imaging instruments. Cerebral perfusion imaging is mainly used to evaluate the state of cerebral blood flow and metabolism. Together with cerebral vascular anatomical structure examination represented by total cerebral angiography, it sketches the original appearance of cerebrovascular disease. It is mainly used to evaluate cerebral ischemic focus and collateral circulation clinically, and the gold standard for judging ischemia is cerebral oxygen metabolism rate (6). Cerebral perfusion imaging agent into the amount of brain cells is proportional to the local cerebral blood flow, using brain perfusion imaging, after image reconstruction can obtain the transverse, coronal and sagittal plane image, according to the brain, the cerebellum, basal ganglia and brain stem parts local blood flow imaging, according to a certain number of physical model can calculate the various parts of the local blood flow and average whole brain blood flow.

Relevant studies have shown that cerebral perfusion imaging can be used to evaluate the local hemodynamic changes of hematoma and its surrounding areas, thus assisting in the diagnosis and prognosis of cerebral hemorrhage. To some extent, for the diagnosis of brain diseases, besides total cerebral angiography, many patients need cerebral perfusion imaging, especially for ischemic cerebrovascular disease, so as to have a comprehensive and in-depth understanding of the disease. Therefore, this study adopted the meta-analysis method to study the application value of cerebral perfusion imaging in the treatment prognosis evaluation of patients with MCI.

We present the following article in accordance with the PRISMA-DTA reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-21-3916/rc).

Methods

Literature retrieve

The Boolean logic retrieval method was adopted to select relevant literatures, with "cognitive disorder", "cerebral perfusion imaging", "cerebral imaging", "mild cognitive impairment", "prognostic assessment" as search terms. PubMed, Medline, EMbase, China Biomedical Literature Database, CNKI database, Wanfang Database, VIP database, and Google Scholar were searched for literature on the prognostic evaluation of MCI using cerebral perfusion imaging. The retrieval time was from the establishment of the database to December 30, 2020. The

search terms were combined freely, and after several rounds of searching to determine the literature, the search engine was used to trace the identified references. The quality of the literature was evaluated using RevMan 5.2 software provided by Cochrane system.

Literature inclusion and exclusion criteria

The literature to be included was required to meet all of the following criteria: (I) the study subjects were patients diagnosed with MCI without pathological type limitation; (II) prognostic assessment was conducted through cerebral perfusion imaging, including fluorodeoxyglucose-positron-emission computed tomography (FDG-PET), single-photon emission computed tomography (SPECT), and structural magnetic resonance imaging (MRI); and (III) study types: diagnostic accuracy test.

References that met any of the following criteria were excluded: (I) the included subjects had severe infections; (II) repeated literature and studies with too few experimental samples; (III) invalid or missing data; and (IV) overlapping research subjects or data.

Two senior experts independently carried out the screening of the abstracts and the full texts, and three pre-experiments were conducted before screening. Disagreements were resolved through discussion or arbitration by a third expert.

Quality assessment

In this study, the Newcastle-Ottawa Scale (NOS) of the Cochrane Collaboration was used to evaluate the literature quality, and a star system was used for measurement, factoring in the subjects, case comparison, and inter-group comparison (the total score was 9). Studies with a score of ≥7 stars were considered high quality; that is, had a low risk of bias. Studies with ≤1 star were considered low quality; that is, had a high risk of bias. Studies with 2–6 stars were considered medium quality; that is, had a medium risk of bias.

Quality evaluation of the references was carried out independently by two experts, and three pre-experiments were carried out before the evaluation. Disagreements were resolved through discussion or arbitration by a third expert.

Data extraction

Two experts used a unified Excel table for independent extraction of data, and three pre-experiments were carried out before extraction. Disagreements were resolved through discussion or arbitration by a third expert. The following data were collated: (I) first author and publication year; (II) age of enrolled patients; (III) follow-up time and mental state scores of patients; (IV) the progression of the patient's cognitive dysfunction (whether it progressed to Alzheimer's disease).

Statistical analysis

Meta-analysis was performed using Review manager 5.3 software (provided by Cochrane International Collaboration Network for systematic review workers). The mean deviation (MD) or standard mean deviation (SMD) and 95% confidence interval (CI) were used for efficacy analysis statistics. The heterogeneity test (Q test) was first performed on the included studies. The risk of bias of the included references was assessed using Review Manager software. Each effect was expressed using the 95% CI. When P>0.1 and I^2<50%, the fixed-effect model (FEM) was used for meta-analysis; however, when P<0.1 and I^2>50%, the random-effects model (REM) was used.

Results

Literature retrieve and NOS results

As shown in *Figure 1*, a total of 527 references were initially retrieved. Of these, 136 were excluded after reading the titles and abstracts. A further 148 references were removed by reading the full texts, and finally 16 references [including five FDG-PET (7-11), four SPECT (12-15), seven MRI (16-22) were included for meta-analysis]. Literature was excluded based on the following: subjects with primary acute and chronic cardiopulmonary dysfunction and serious mental diseases (40 articles); animal experiments (33 articles); overlapping subjects (37 articles); related information could not be extracted (45 articles); cerebral perfusion imaging was not performed on patients (63 articles); and lack of original data (66 articles). *Tables 1-3* show the basic information of the included literature published from 2005 to 2020. *Figure 2* displays the NOS results. Notably, there were seven references with ≥7 stars or above, eight references with 2–6 stars, and one reference with >2 stars. All of the included articles were medium- and high-quality references.
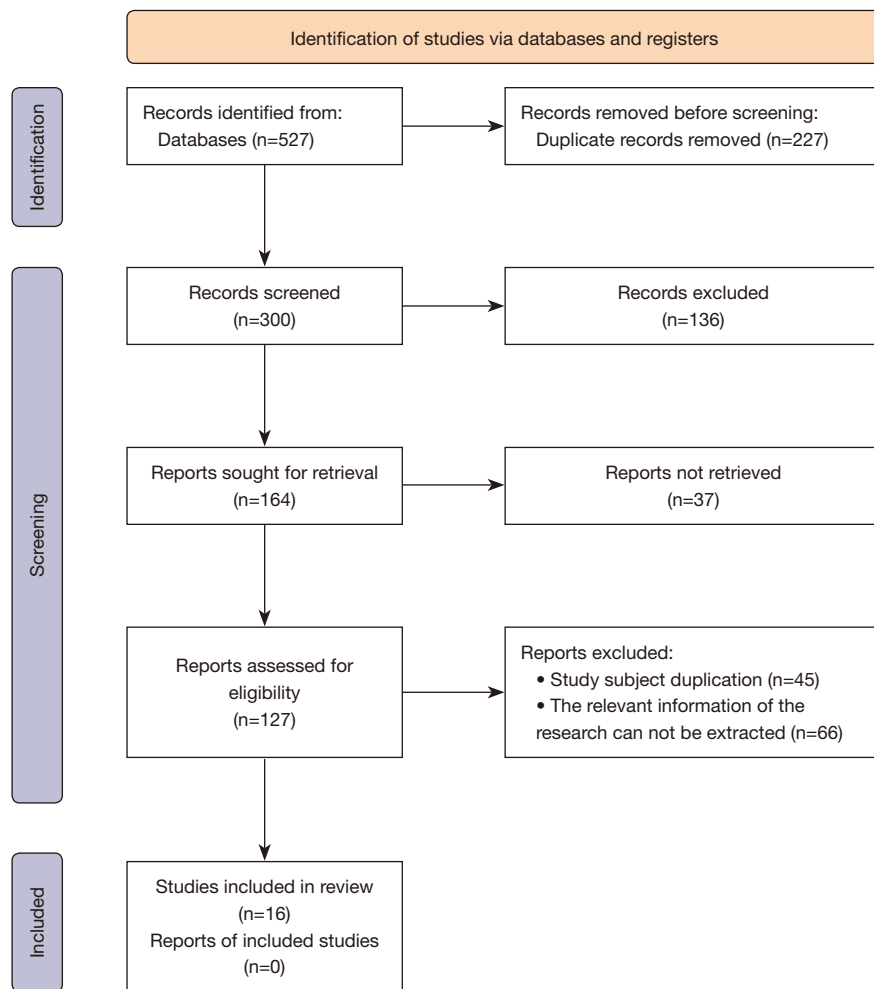
Figure 1 Literature screening flowchart.

Table 1 Basic information of the included literature (FDG-PET)

Author	Publication year	Disease course	Age (years)	Follow-up time (months)	Mental state score
Mosconi (7)	2004	Mild cognitive impairment to Alzheimer's disease	67.1±7.7	12	28.0±1.5
Chételat (8)	2003	MCI to Alzheimer's disease	69.9±6.7	18	27.2±1.3
Drzezga (9)	2005	MCI to dementia of the Alzheimer type (DAT)	70±8	15	26.9±1.9
Anchisi (10)	2005	Amnestic mild cognitive impairment to Alzheimer's disease	67.7±8.3	12	27.7±1.7
Arnáiz (11)	2001	MCI to Alzheimer's disease	62.7±8.5	36.5	26.9±2.3

FDG-PET, fluorodeoxyglucose-positron-emission computed tomography; MCI, mild cognitive impairment.

Table 2 Basic information of the included literature (SPECT)

| Author	Publication year	Disease course	Age (years)	Follow-up time (months)	Mental state score
Encinas (12)	2003	MCI to Alzheimer's disease	76.5±4.2	≥12	–
Borroni (13)	2006	MCI to Alzheimer's disease	69.4±7.1	24	27.5±1.9
Hirao (14)	2005	Amnestic mild cognitive impairment to Alzheimer's disease	69.0±8.6	36	26.5±1.6
Johnson (15)	1998	Suspected Alzheimer's disease → Alzheimer's disease	72.5	≥24	–

SPECT, single-photon emission computed tomography; MCI, mild cognitive impairment.

Table 3 Basic information of the included literature (MRI)

Author	Publication year	Disease course	Age (years)	Follow-up time (months)	Mental state score
Dickerson (16)	2001	MCI to Alzheimer's disease	68.6±8.6	12	27.0±2.2
Duchesne (17)	2010	Amnestic mild cognitive impairment to Alzheimer's disease	76.6±4.7	26	27.1±1.3
Convit (18)	2000	MCI to Alzheimer's disease	74.0±7.0	38	27.8±2.4
Devanand (19)	2007	MCI to Alzheimer's disease	66.8±9.8	60	27.5±2.2
Visser (20)	2002	Suspected Alzheimer's disease → Alzheimer's disease	64.9±9.5	22.8	27.7±1.8
Galton (21)	2005	Questionable dementia → Alzheimer's disease	63.7±9.9	24	27.4±2.4
Teipel (22)	2007	Mild cognitive impairment to Alzheimer's disease	69.7±8.5	27	27.0±1.8

MRI, magnetic resonance imaging; MCI, mild cognitive impairment.
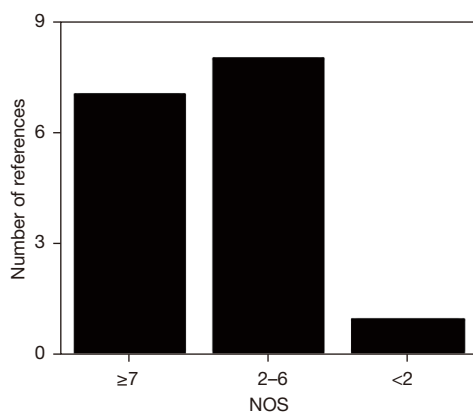
Figure 2 Newcastle-Ottawa Scale (NOS) results.

Risk bias evaluation results

Figures 3,4 show the multiple risk bias evaluations results of FDG-PET imaging, as drawn by Review Manager software. With each methodology feature considered, the evaluation results were input into the software to generate the bias-risk map. It was observed that the patient selection, test indicators, reference standards, and flow and timing in the FDG-PET references all had a low risk of bias, and that the low-risk bias for the blinding of subjects and researchers (implementation bias) was approximately 20%, respectively. Except for the reference of Chételat *et al.* [2003] (8), the risk bias of the other literature was
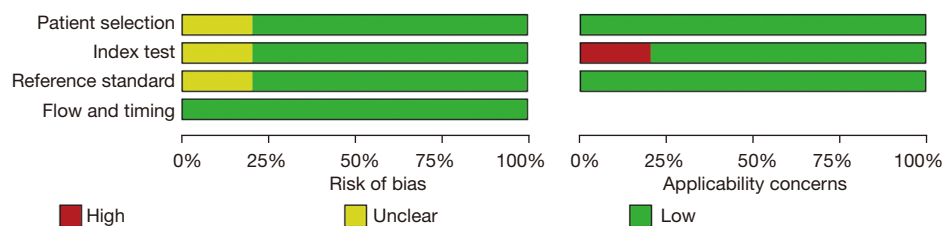
Figure 3 Bias risk evaluation results (FDG-PET). FDG-PET, fluorodeoxyglucose-positron-emission computed tomography.
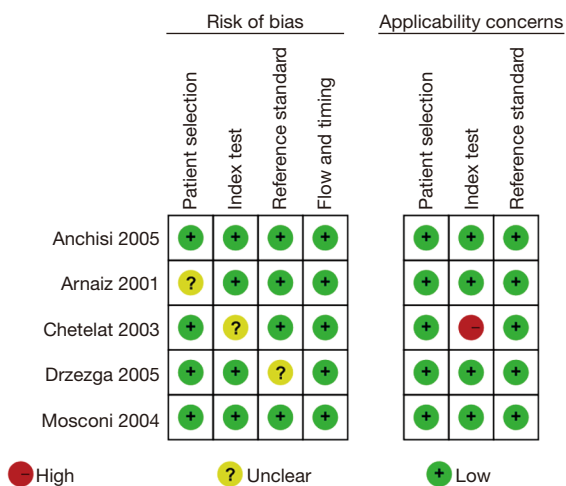
Figure 4 Multi-risk bias evaluation results (FDG-PET). FDG-PET, fluorodeoxyglucose-positron-emission computed tomography.
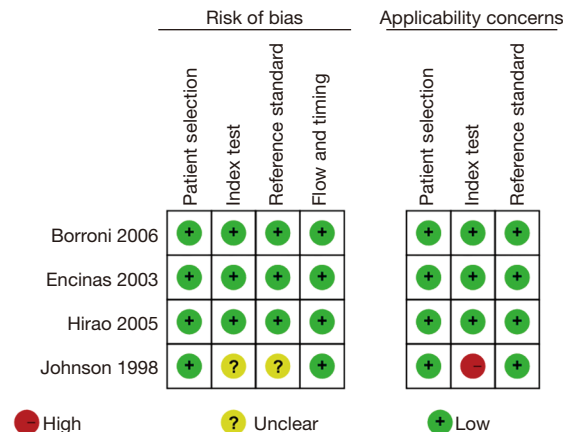

Figure 6 Multi-risk bias evaluation results (SPECT). SPECT, single-photon emission computed tomography.
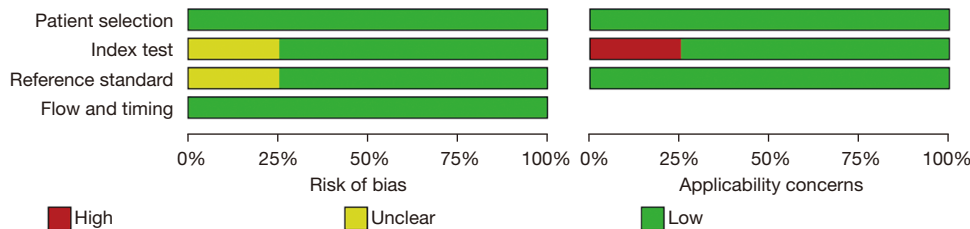

Figure 5 Bias risk evaluation results (SPECT). SPECT, single-photon emission computed tomography.

significantly low.

Figures 5,6 display the multiple risk bias evaluation results of patients using SPECT imaging, as drawn by Review Manager software. With each methodology feature considered, the evaluation results were input into the software to generate the bias-risk map. It was found that the patient selection, test indicators, reference standards, and flow and timing in the SPECT studies all had a low risk of bias, and that the low-risk bias for the blinding of subjects and researchers (implementation bias) was approximately 20%, respectively. Except for the reference of Johnson *et al*. [1998] (15), the risk bias of the other literature was significantly low.

Figures 7,8 show the multiple risk bias evaluation results of MRI imaging, as drawn by Review Manager software. With each methodology feature considered, the evaluation results were input into the software to generate the bias-risk map. It was found that the patient selection, test indicators, reference standards, and flow and timing in the MRI studies

all had a low risk of bias, and that the low-risk bias for the blinding of subjects and researchers (implementation bias) was approximately 15%, respectively. Except for the reference of Convit *et al*. [2000] (18), the risk bias of other literature was significantly low.

Sensitivity and specificity of the three imaging methods

Tables 4-6 display the sensitivity and specificity of FDG-PET, SPECT, and MRI imaging, respectively. It was found that the sensitivity, specificity, and positive likelihood ratio of FDG-PET imaging were significantly higher than those of SPECT and MRI imaging, and the differences were statistically significant (P<0.05).

sROC curve of cerebral perfusion imaging

Figures 9-11 were the summary receiver operating characteristic (sROC) curves of sensitivity and specificity
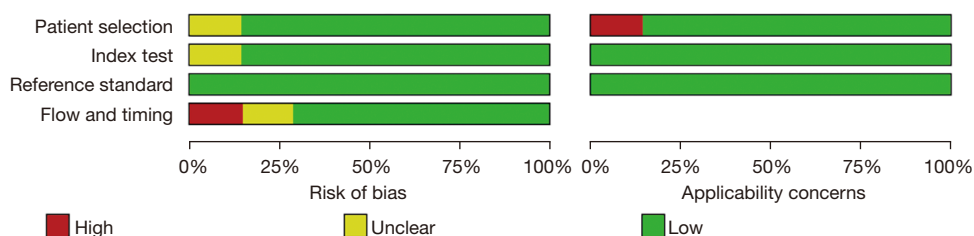
Figure 7 Bias risk evaluation results (MRI). MRI, magnetic resonance imaging.
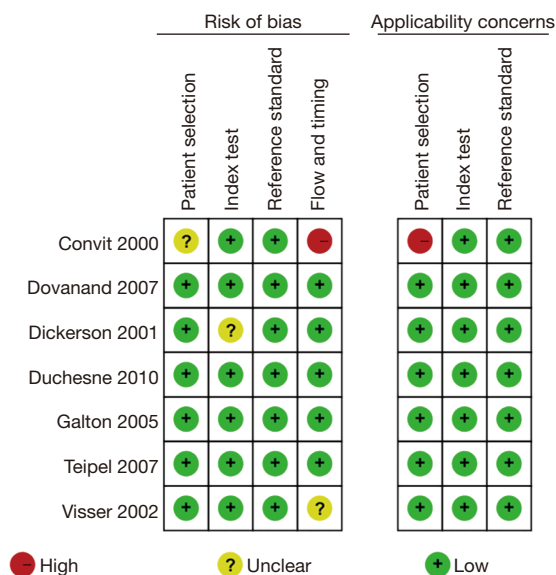

Figure 8 Multi-risk bias evaluation results (MRI). MRI, magnetic resonance imaging.

for FDG-PET, SPECT, and MRI imaging, respectively. It was observed that the sROC plane graph did not present a "shoulder-arm" distribution, and there was no threshold effect.

Discussion

Previous studies have shown that MCI is common in the elderly, and the risk of developing MCI increases with age (23). The cause of some MCI can be traced back, so it is necessary to go to the relevant outpatient clinic in time to understand the situation of cognitive impairment, judge whether it can be effectively treated, assess the risk of progression to dementia, and know the disease progress in detail (24,25). More importantly, the basic data of patients' cognitive function should be kept to determine whether it has changed in the future. Early assessment

is important because MCI is not a normal aging process and has a high risk of progression to dementia (26,27). Regarding MCI assessment, it is important to understand the following: (I) subjective memory problems are not the basis of the diagnosis of MCI; (II) positive screening does not necessarily mean MCI; (III) MCI is not Alzheimer's disease; (IV) the diagnosis of MCI still requires further evaluation; and (V) there are no reliable biomarkers for MCI (28).

In this meta-analysis, 16 articles were finally included. Of these, 14 adopted randomized controlled grouping, and only two used retrospective analysis, exhibiting bias. However, in general, this did not affect the results of this study. Meta-analysis was performed in this study to quantitatively combine each reference, which can not only avoid the sampling differences, but also expand the sample size and improve the credibility of the conclusion by assigning different weights to the references based on their results. The quality of meta-analysis mainly depends on the authenticity and integrity of the analyzed literature. Due to the objective factors, the number of included literature in this study was limited, so the sample size should be increased in subsequent studies to prevent bias in the analysis.

In this study, the application value of cerebral perfusion imaging in the prognosis assessment of MCI was investigated by meta-analysis of 16 references included in the Boolean logic retrieval method using FDG-PET, SPECT and MRI imaging respectively. The sensitivity and specificity positive likelihood ratio of FDG-PET imaging were significantly higher than those of SPECT and MRI imaging, the differences were statistically significant (P<0.05). This is similar to the results of Rane (29), indicating that cerebral perfusion imaging has better prognostic value for MCI, and FDG-PET imaging has better prognostic ability and effect for patients with MCI. In summary, SPECT, DG-PET, and MRI imaging have their own advantages and disadvantages in

Table 4 Meta-analysis of FDG-PET imaging

Index	Value	95% CI	P	I^2
Sensitivity (%)	87.2	81.3–92.1	0.013	65.9%
Specificity (%)	89.35	77.6–91.8	0.036	56.8%
Positive likelihood ratio	5.973	3.15–6.72	0.498	<0.1%
Negative likelihood ratio	0.132	0.05–0.49	<0.001	80.93%
Odds ratio	38.996	17.66–87.1	0.748	<0.1%

FDG-PET, fluorodeoxyglucose-positron-emission computed tomography.

Table 5 Meta-analysis of SPECT imaging

Index	Value	95% CI	P	I^2
Sensitivity (%)	80.5	78.3–90.12	0.006	63.1%
Specificity (%)	74.3	61.3–78.5	<0.001	71.9%
Positive likelihood ratio	2.637	1.38–4.81	<0.001	79.98%
Negative likelihood ratio	0.334	0.18–0.50	0.291	18.11%
Odds ratio	11.27	4.52–20.01	0.331	24.33%

SPECT, single-photon emission computed tomography.

Table 6 Meta-analysis of MRI

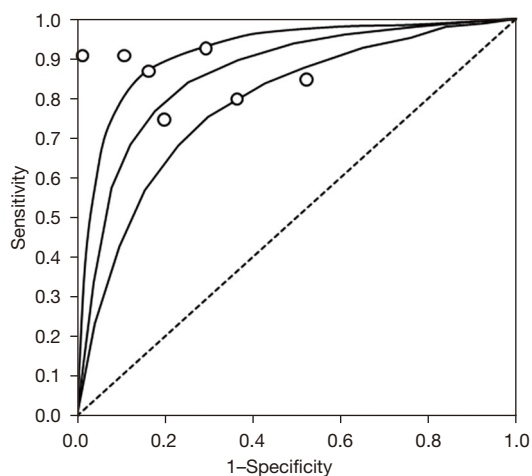| Index	Value	95% CI	P	I^2
Sensitivity (%)	71.9	64.8–80.12	0.594	<0.1%
Specificity (%)	79.44	77.6–91.8	0.089	40.1%
Positive likelihood ratio	3.298	2.59–6.72	0.301	14.8%
Negative likelihood ratio	0.365	0.30–0.48	0.844	<0.1%
Odds ratio	11.751	5.99–16.38	0.521	<0.1%

MRI, magnetic resonance imaging.

Figure 9 sROC curve of FDG-PET imaging. sROC, summary receiver operating characteristic; FDG-PET, fluorodeoxyglucose-positron-emission computed tomography.
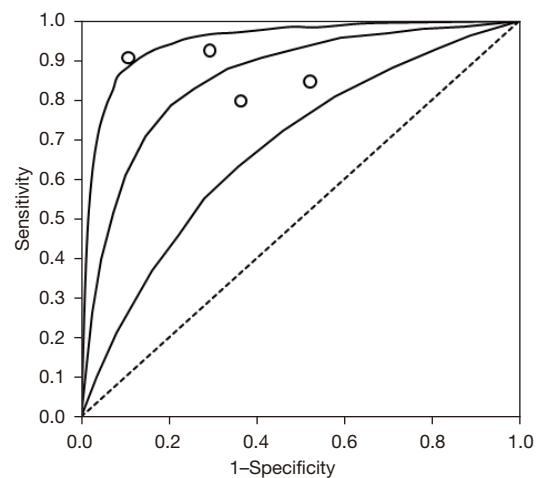
Figure 10 sROC of SPECT imaging. sROC, summary receiver operating characteristic; SPECT, single-photon emission computed tomography.
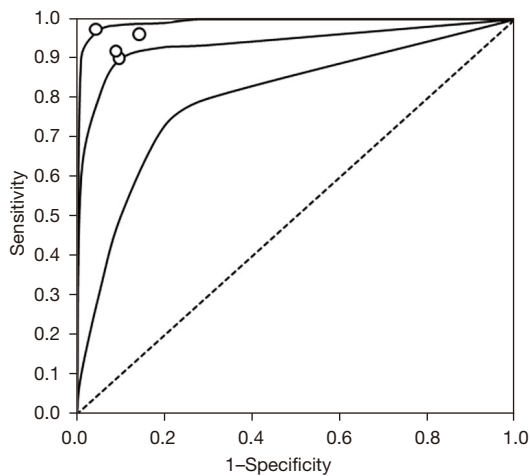
Figure 11 sROC of MRI. sROC, summary receiver operating characteristic; MRI, magnetic resonance imaging.

evaluating cerebral blood perfusion. Rational application of multiple perfusion imaging techniques can provide valuable information for the occurrence mechanism and therapeutic effect evaluation of cognitive dysfunction and other diseases, which is of wide application value.

Conclusions

This meta-analysis investigated the application value of cerebral perfusion imaging in the prognostic assessment of MCI. The literature was retrieved using the Boolean logic retrieval method, and 16 references concerning FDG-PET, SPECT, and MRI imaging were included. The results showed that cerebral perfusion imaging had good prognostic value in patients with MCI, and FDG-PET imaging had superior prognostic ability in patients with MCI.

However, some limitations in this study should be noted. The references included in the study are all case-control studies, and thus, there exists a survival bias. Also, numerous risk factors and indicators were not been included in the study, which greatly reduces the combined effect. In future research, follow-up analysis of patients with MCI should be performed, in order to evaluate the prognostic value of cerebral perfusion imaging for MCI, and to strengthen the findings of this meta-analysis. In conclusion, this study provides a theoretical basis and data support for the clinical diagnosis of MCI and other diseases.v

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