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Performance of PET imaging for the localization of epileptogenic zone in patients with epilepsy: a meta-analysis

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Abstract

Objectives The aim of this meta-analysis was to estimate the clinical use value of ^{11}C-FMZ and ^{18}F-FDG in PET for the localization of epileptogenic zone and to provide evidence for practitioners' clinical decision-making.

Methods We searched PubMed and Embase in a time frame from inception to May 31, 2020. Studies utilizing FMZ or FDG-PET or FDG-PET/MRI used in patients with epilepsy, with EEG or surgical outcomes as the gold standard and corresponding outcomes such as concordance rates of PET or PET/MRI scan compared with reference standard, absolute numbers of participants with true-positive (TP), false-positive (FP), true-negative (TN), and false-negative (FN) results in FDG or FMZ PET. Pooled concordance rates, overall sensitivity, and specificity of ^{11}C-FMZ-PET and ^{18}F-FDG-PET were calculated.

Results In total, 44 studies met the inclusion criteria. The pooled concordance rates of FDG-PET, FMZ-PET, and FDG-PET/MRI coregistration compared with reference standard were 0.67 (95% CI: 0.60–0.73), 0.75 (95% CI: 0.57–0.93), and 0.93 (95% CI: 0.89–0.97), respectively. The concordance rate of ^{18}F-FDG-PET in patients with temporal lobe epilepsy (TLE) was 0.79 (0.63; 0.92). The overall sensitivity and specificity of ^{18}F-FDG-PET were 0.66 (95% CI: 0.58–0.73) and 0.71 (95% CI: 0.63–0.78), respectively. ^{11}C-FMZ-PET displayed an overall sensitivity of 0.62 (95% CI: 0.49–0.73) and specificity of 0.73 (95% CI: 0.59–0.84).

Conclusions Both ^{11}C-FMZ PET and ^{18}F-FDG PET are the choice of modalities for the localization of epileptogenic zone, especially when coregistered with MRI.

Key Points

• *^{11}C-FMZ-PET may be more helpful than ^{18}F-FDG-PET in the localization of epilepsy foci.*

• *Coregistration of FDG-PET and MRI is recommended in the localization of epileptogenic zone.*

Keywords Humans · Fluorodeoxyglucose F18 · Carbon-11 · Positron emission tomography · Epilepsy

Abbreviations

^{11}C-FMZ	^{11}C-flumazenil
^{18}F-FDG	^{18}F-2-fluoro-2-deoxy-D-glucose
AEDs	Antiepileptic drugs
AMT	a-Methyl-L-tryptophan
AUCs	Area under the sROC curves
CIs	Confidence intervals
EEG	Electroencephalograph
FLE	Frontal lobe epilepsy
FN	False negative
FP	False positive
LR	Likelihood ratio
MRI	Magnetic resonance imaging
NMDA	*N*-Methyl-D-aspartate
OR	Odds ratio
PET	Positron emission tomography
PRISMA	The Preferred Reporting Items for Systematic Review and Meta-analysis
QUADAS	Quality assessment of diagnostic accuracy studies
SPECT	Single-photon emission computed tomography
sROC	Summarized receiver operating characteristic curves
TLE	Temporal lobe epilepsy
TN	True negative
TP	True positive

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Introduction

Epilepsy is one of the most common and serious chronic cerebral disorders, which affects over 70 million people worldwide [1, 2]. Almost 80% of patients with epilepsy reside in low- and middle-income countries or districts [3]. Among infants < 1 year old and people > 50 years old, the performances of epilepsy which appear a bimodal distribution with two peaks are more implicated than people in other age groups [4, 5]. Clinically, epileptic seizures vary widely in manifestation from abnormal sensations to motor symptoms.

Epilepsy is a multi-symptom disease with complex risk factors and in many cases has a strong inherited tendency, instead of a situation with a single cause and a single expression [3, 6]. For decades, the etiology, pathophysiology, and antiepileptic drugs (AEDs) are continually being explored and investigated [2, 7–9]. Currently, AEDs are effective in only about two-thirds of patients in developed countries, and despite being available of more than 25 medications worldwide, only a few of them are considered first-line [10]. Furthermore, epilepsy surgery is considered to be the most efficacious way to attain long-term seizure freedom, but it has been confined to individuals with drug-resistant epilepsy and still underused [11–14].

Nowadays, the insufficient understanding and absence of specific biomarkers of the epileptogenic process are the major constraints in the research and development of new AEDs that are able to prevent the underlying disease or improve prognosis [15]. The rapid advances in neuroimaging modalities have expanded our chances to investigate the disease of epilepsy by means of noninvasive research modalities. The field of neuroimaging has been remarkably developed in recent years. Neuroimaging techniques used in clinical settings for the assessment of patients with epilepsy include but not limited to non-contrast computerized tomography (CT), structural and functional MRI (fMRI), electroencephalograph combined with fMRI (EEG/fMRI), MR spectroscopy (MRS), positron emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetoencephalography (MEG) [16]. The utilities of these modalities depend on specific circumstances and clinical questions to be addressed [17]. Currently, chronic intracranial EEG monitoring remains the gold standard in defining epileptic foci, but it also has boundedness and its application is highly dependent on other localization information [18, 19].

PET is manifested to be an available noninvasive method to guide intracranial electrode placement, and it can also reduce the number of patients requiring invasive EEG [20]. PET also plays a very important role in the evaluation of epilepsy. The most commonly used PET tracer in epilepsy is [^{18}F]2-fluoro-2-deoxy-D-glucose (^{18}F-FDG), usually performed in the seizure-free interval and aimed at the identification of cerebral regions with decreased glucose metabolism; it is considered to partially reflect the reduction of synaptic activity [21]. However, the epileptic areas are commonly smaller than the hypometabolic regions [18, 22, 23]. Besides ^{18}F-FDG-PET, the GABA-A receptor ligand ^{11}C-flumazenil (^{11}C-FMZ) has displayed promising results in epileptic foci localization and lateralization [15, 24, 25]. Other potential PET tracers for detecting epileptic regions include [^{11}C]a-methyl-L-tryptophan (AMT) which detects tryptophan metabolism, most recently 5-hydroxytryptamine type 1A (5-HT-1A) receptor ligands, and other radioligands that bind to opioid, histamine, *N*-methyl-D-aspartate (NMDA), “peripheral benzodiazepine” or acetylcholine receptors. Although the clinical application of most of them in epilepsy has not been systematically established, they have very important research value.

However, to our knowledge, only a few studies limited to small sample size directly compared the clinical performance of ^{18}F-FDG-PET or ^{11}C-FMZ PET compared with EEG or surgical outcome in localization of epileptogenic areas. We firstly did a meta-analysis by collating the available evidence to generate a precise estimation of the clinical utility of ^{18}F-FDG-PET and ^{11}C-FMZ-PET for the localization of the epileptogenic foci in patients with epilepsy, and secondly to provide evidence or clues for practitioners’ clinical decision-making and practice.

Methods

Search strategy and selection criteria

This meta-analysis was performed on the basis of the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines [26]. The research question of this study was raised in terms of PICOS, populations (participants with diagnosed epilepsy), interventions (FMZ or FDG-PET or coregistration of FDG-PET and MRI), comparators (EEG or surgical outcomes), outcomes (absolute numbers of participants with true-positive (TP), false-positive (FP), true-negative (TN), and false-negative (FN) results), and study designs (retrospective and prospective studies). The search strategy was restrictively based on the pre-designed protocol. We did a systematic search on PubMed and Embase to assay studies from inception to May 31, 2020, with articles in English considered. The following search terms were used: (^{11}C-flumazenil OR ^{18}F-FDG) AND (epilepsy OR epilepsies OR seizure disorder OR seizure disorders OR cryptogenic epilepsy) AND ((positron emission tomography) OR PET). We supplemented the online search with manual screen of the reference lists of all primary studies as well as relevant review articles. We considered studies using FMZ or FDG-PET or coregistration of FDG-PET and MRI for the assessment of patients with epilepsy. Inclusion criteria were as follows: FMZ or FDG-PET or FDG-PET/MRI used in participants with diagnosed epilepsy; use of EEG or surgical outcomes as the gold standard to evaluate diagnostic performance; corresponding outcomes such as concordance rates

Table 1 Study characteristics

Study	Year of publication	Number of patients	Modalities	Age of patients (years)	Gender ratio (M/F)	Duration of epilepsy (years)	Type of epilepsy	Reference standard	Population	Machine
Savic' et al	1995	6	11C-FMZ-PET	(24–45)[a]	3/3	NR	NR	EEG and seizure semiology	Adults	PC 384-7B system (General Electric/PC 2084-15B system
Mastin' et al	1996	35	18F-FDG PET	29.8 (13–45)	10/25	NR	Intractable partial epilepsy	Surgery outcome	Adults and children	ECAT 951 two-ring scanner
Szelies' et al	1996	10	FDG/FMZ	20.1± 12.4[b]	5/5	19.8±12.1	TLE	EEG	Adults	Siemens/CTI ECAT EXACT HR
Debets' et al	1997	23	FDG/FMZ	33.7± 11.3	9/14	24.9±11.3	TLE	EEG	Adults and children	951 CTI/Siemens tomograph
Theodore' et al	1997	35	18F-FDG PET	NR	NR	NR	NR	Surgery outcome	NR	NeuroPET, Scanditronix 1, or Scanditronix 2 scanner
Ryvlin' et al	1998	100	18F-FDG PET, 11C-FMZ-PET	NR	NR	NR	NR	EEG	NR	Time of flight device (TTV03, LETI, CENG)
Juhasz' et al	1999	12	FDG/FMZ	32.9± 12.4	6/6	20.8±11.4	TLE	EEG	Adults and children	CTI/Siemens EXACT/HR
Szelies' et al	2000	14	FDG/FMZ	36.2± 10.2	8/6	23.1±11.2	TLE	EEG	Adults	ECAT Exact HR scanner (Siemens CTI)
Hammers' et al	2001	15	11C-FMZ-PET	31 (19–49)	4/11	24 (12–45)	Mesial temporal lobe epilepsy	VEEG	Adults	953B Siemens/CTI PET camera
DellaBadia' et al	2002	69	18F-FDG PET	35 (11–66)	32/37	25	NR	Surgery outcome	Adults and children	NR
Hammers' et al	2002	18	11C-FMZ-PET	37 (17–64)	7/11	13 (1–34)	Medically refractory TLE	VEEG	Adults and children	953B Siemens/CTI PET camera
Padma' et al	2004	20	FDG/FMZ	35.2 (20–51)	12/8	23.93	TLE	EEG	Adults	Siemens ECAT EXACT HR+scanner with 3-D mode (CTI PET Systems Inc)
Seo' et al	2009	27	18F-FDG PET 3.2(0.08–11)	16/11	NR	Medically intractable epilepsy	Surgery outcome	Children	NR	
Chassoux' et al	2010	23	18F-FDG PET, PET/MRI	7–38	12/11	NR	NR	SEEG and surgery outcome	Adults and children	ECAT 953/31B Siemens/3D camera allowing axial sampling of 2.46 mm (HR+ CTI Exact Siemens)
Kumar' et al	2010	20	18F-FDG PET	11±3.8	10/10	5.9±4.9	Intractable focal epilepsy	EEG	Children	CTI/Siemens EXACT/HR whole-body PET scanner
Seo' et al	2010	14	18F-FDG PET	12.6±3.9	6/8	NR		EEG	Children	NR

Table 1 (continued)

Study	Year of publication	Number of patients	Modalities	Age of patients (years)	Gender ratio (M/F)	Duration of epilepsy (years)	Type of epilepsy	Reference standard	Population	Machine
							Non-lesional intractable focal epilepsy			
Rubi' et al	2011	31	18F-FDG PET, PET/MRI	7.8 (0–17)	15/16	7.6±4.7	Refractory epilepsy	VEEG	Children	Siemens PET/CT Biograph equipment (Siemens)
Desai' et al	2013	53	18F-FDG PET	32 (1–60)	26/27	NR	Medically intractable epilepsy	EEG	Adults and children	General Electric Discovery ST machine (General Electric Company)
Dorfmuller' et al	2014	19	18F-FDG PET	3.2 (1.7–-5)	NR	NR	Focal epilepsy	SEEG	Children	Head-dedicated PET camera (ECAT EXACT HR+, Siemens Medical Solutions)
Kargiotis' et al	2014	13	18F-FDG PET	7 (1–32)	4/9	NR	TLE	Surgery outcome	Adults and children	Siemens Biograph® 16 or 24 PET/CT hybrid scanners
Perissinotti' et al	2014	54	18F-FDG PET	8.8±5.5	29/25	NR	Medically intractable epilepsy	VEEG	Children	PET/CT equipment (Biograph; Siemens)
Rathore' et al	2014	194	18F-FDG PET	32.5 (16–6-1)	92/102	17 (2–50)	Drug-resistant focal epilepsy	VEEG	Adults and children	GE Discovery DST and DVCT scanners
van'tKlooster' et al	2014	41	18F-FDG PET	26±11	22/19	15.4±9.7	Refractory focal epilepsy	ECoG	Adults and children	ECAT EXACT HR+ scanner (CTI/Siemens)
Fernandez' et al	2015	35	18F-FDG PET, PET/MRI	28 (6–57)	16/19	NR	Refractory focal epilepsy	EEG	Adults and children	(CTI/Exact/HR whole body tomography system; Siemens)
Gokdemir' et al	2015	121	18F-FDG PET	28.98± 11.53	45/76	NR	NR	EEG	Adults and children	PET/ CT scanner (LSO HI-REZ Siemens)
Komoto' et al	2015	10	FDG/FMZ	27.8±8.4	4/6	NR	Focal epilepsy	EEG	Adults and children	Discovery ST Elite PET/CT scanner (GE Medical Systems)
Lascano' et al	2015	190	18F-FDG PET	25.3± 15.3	99/91	NR	NR	EEG	NR	BiographHiRez Sensation 16 (Siemens Healthcare)
Menon' et al	2015	117	18F-FDG PET	5–42	68/49	NR	Drug-resistant epilepsy	VEEG	Adults and children	16-slice PET-CT scanner (GE DISCOVERY STE)
Sierra-Marcos' et al	2015	25	18F-FDG PET	32.4± 13.8	9/16	NR	Neocortical epilepsy	VEEG	NR	A PET/CT scanner (Biograph, Siemens)
Wang' et al	2015	16	18F-FDG PET	20.2±6.8	9/7	11.1±6.0	TLE	VEEG	Adults and children	Discovery ST PET/CT (General Electric Healthcare) scanner
Yankam' et al	2015	16	FDG/FMZ	23.5±8.6	4/12	26.5±9.0	TLE	EEG	Adults	Exact ECAT HR+ scanner (Siemens)
Zhang' et al	2016	85	18F-FDG PET	18.5±4.6	53/32	NR	Non-lesional epilepsy	VEEG	Adults and children	Discovery ST PET/CT (General Electric Healthcare) scanner
Coelho' et al	2017	39	18F-FDG PET	29.5 (3–62)	17/22	NR	TLE,FLE	VEEG and surgery outcome	Adults and children	Siemens CTI Molecular Imaging
Elkins' et al	2017	25	18F-FDG PET		12/13	NR		EEG		Siemens Biograph 40 PET/CT

Table 1 (continued)

Study	Year of publication	Number of patients	Modalities	Age of patients (years)	Gender ratio (M/F)	Duration of epilepsy (years)	Type of epilepsy	Reference standard	Population	Machine
				20 (2–48)			Medically refractory epilepsy		Adults and children	
Wang' et al	2017	166	18F-FDG PET	8.9±2.7	95/71	NR	NR	VEEG	Children	Tracerlab FXFN synthesizer from GE Medical Systems
Chan' et al	2018	62	18F-FDG PET	34 (20–6-8)	33/29	NR	Refractory epilepsy	VEEG	Adults	NR
Desarnaud' et al	2018	103	18F-FDG PET	24.8± 11.7	52/51	17.7±10.9	Drug-resistant partial epilepsy	VEEG	Adults and children	Head-dedicated PET camera (ECAT-953/31B; Siemens) or a 3D camera (HR+ CTI Exact; Siemens), PET/CT system (Biograph 6; Siemens)
Ding' et al	2018	67	18F-FDG PET, PET/MRI	3–54	28/39	8.7±8.6	ETLE	VEEG	Adults and children	PET/CT scanner (Biograph mCT, Siemens Medical Solutions)
Fei' et al	2018	18	18F-FDG PET	39 (19–5-2)	7/11	20.3(3–52)	Operculoinsular epilepsy (OIE)	VEEG	Adults	Philips Gemini TF PET/CT scanner (Philips) or on a GE Advance tomograph (General Electric)
Shang' et al	2018	20	18F-FDG PET	26.5± 9.48	13/7	14.1±9.3	TLE	EEG	Adults and children	integrated simultaneous Signa PET/MR imaging system (GE Healthcare)
Sharma' et al	2018	88	18F-FDG PET	39 (7–63)	38/49	NR	Drug-resistant focal epilepsy	Surgery outcome	Adults and children	NR
Avendano-Estrada' et al	2019	7	18F-FDG PET	29.6± 11.5	2/5	19.3±6.3	TLE	EEG	Adults	PET/CT Siemens Biograph 64 scanner
Duez' et al	2019	141	18F-FDG PET	32 (8–70)	82/59	NR	NR	Surgery outcome	Adults and children	NR
Akdemir' et al	2020	49	18F-FDG PET	36.2±7.7	17/32	17.7±7.7	TLE	Surgery outcome	Adults	Discovery ST PET-CT camera (GE Medical Systems)

TLE: temporal lobe epilepsy; *FLE*, frontal lobe epilepsy; *OIE*, operculoinsular epilepsy; *EEG*, electroencephalograph; *ECoG*, electrocorticograph; *SEEG*, stereo electroencephalograph; *VEEG*, video electroencephalograph; *NR*, not reported

[a] Data in parentheses is range of age

[b] Data is presented as mean ± standard deviation

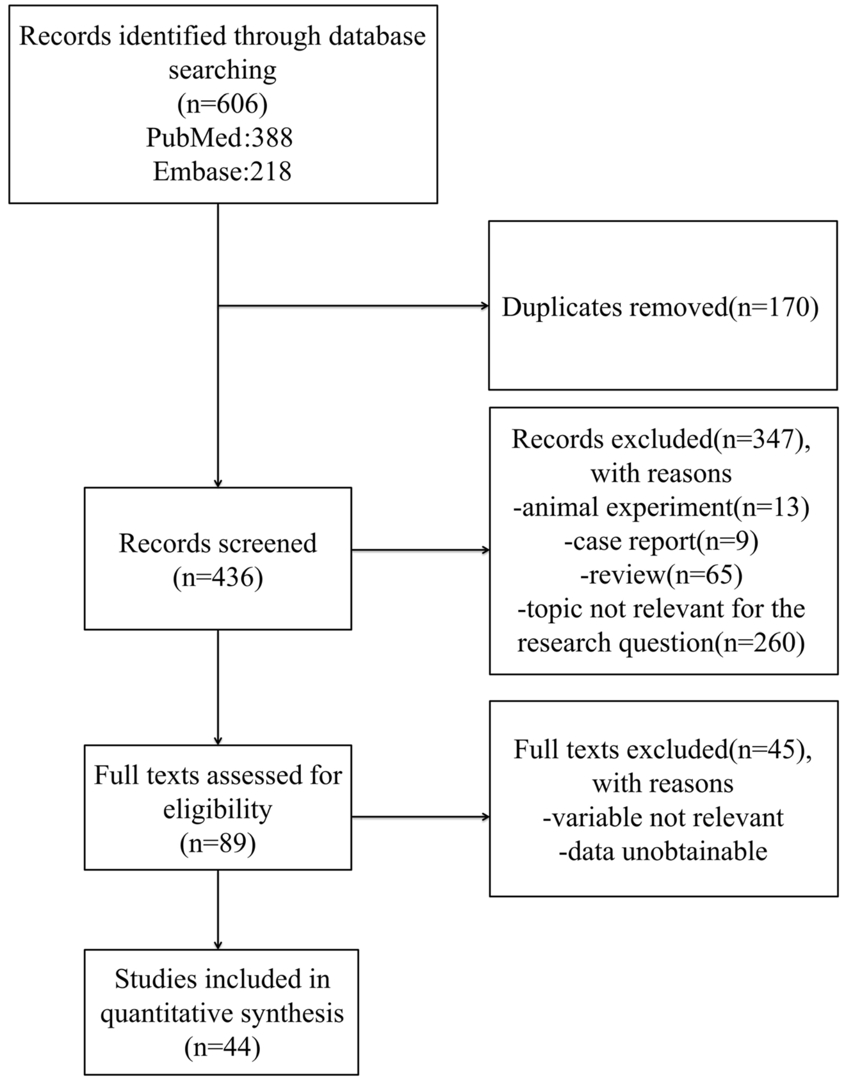


Fig. 1 Search results and flow chart of the meta-analysis

of PET or PET/MRI scan compared with the reference standard, absolute numbers of participants with TP, FP, TN, and FN results via FDG or FMZ PET. If studies recruited participants over the same period of time or from the same study center, only the research with the largest sample size or yielding the most pertinent outcomes was included to avoid duplications. Both retrospective and prospective studies were considered. Studies in abstract form, case reports, and successive cases seen in a unit were excluded.

Two independent investigators (Haiqun Xing and Meiqi Wu) conducted the process of literature search and study inclusion. When disagreement occurred, they discussed their arguments, and a third reviewer (Na Niu) was involved in case that no consensus was achieved.

Data extraction and quality assessments

Data were extracted from each selected publication by two investigators (Yanru Ma and Yimin Liu) independently. The following information were recorded: name of the first investigator, year of publication, number of participants, duration of epilepsy, age, gender ratio, type of epilepsy, reference standard, concordance rates of PET or PET/MRI compared with the reference standard, TP, FP, TN, and FN. To assess the methodological quality of the included studies and risk of bias and applicability concerns, we used the checklist of QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. This tool contains components in terms of patient selection, index test, and reference standard, as well as flow and timing.

Statistical analysis

All analysis was performed at the study level with the Stata15.0, R4.0.2 software and Review Manager 5.3 software. $p < 0.05$ was considered to be statistically significant. We calculated pooled concordance rates, sensitivity, specificity, positive likelihood ratio (LR) and negative

Table 2 Subgroup analysis for the pooled concordance rate of ^{18}F-FDG-PET, ^{11}C-FMZ-PET, and FDG-PET/MRI

	^{18}F-FDG-PET		^{11}C-FMZ-PET		FDG-PET/MRI	
Characteristic	Pooled concordance rate	*p* value	Pooled concordance rate	*p* value	Pooled concordance rate	*p* value
Age (years)						
< 30	0.70 (0.60; 0.79)	0.493	–	0.906	0.90 (0.80; 0.97)	0.264
≥ 30	0.62 (0.54; 0.70)		0.72 (0.18; 1.00)	–		
NR	0.67 (0.53; 0.80)		0.75 (0.66; 0.84)		0.95 (0.89; 0.99)	
Duration of epilepsy (years)						
< 20	0.74 (0.62; 0.84)	0.346	0.44	0.009	0.92 (0.82; 0.98)	0.847
≥ 20	0.60 (0.39; 0.80)	0.94	–			
NR	0.65 (0.56; 0.73)		0.75 (0.66; 0.84)	0.93 (0.85; 0.99)		
Type of epilepsy						
TLE	0.79 (0.63; 0.92)	0.155	–	–	–	–
Others	0.66 (0.59; 0.72)		0.74 (0.54; 0.91)		0.93 (0.88; 0.97)	
Population						
Children	0.84 (0.75; 0.92)	0.001	–	0.011	0.86	0.245
Adults	0.68 (0.45; 0.87)		0.92 (0.74; 1.00)	–		
Adults and children	0.60 (0.54; 0.66)		0.44		0.94 (0.89; 0.98)	
NR	0.68 (0.61; 0.76)		0.73	–		

LR, odds ratio (OR) with their respective 95% confidence intervals (CIs), and area under the summarized receiver operating characteristic (sROC) curves (AUCs). We used the Cochran Q and the I^2 statistics to evaluate the heterogeneity of results between studies included. I^2 values of 0–25%, 25–50%, 50–75%, and 75–100% indicate insignificant, low, moderate, and high heterogeneity, respectively. We created funnel plots to assess publication and related bias. Deeks' method was used to statistically check the asymmetry of the funnel plot and detect publication bias. Moreover, subgroup analysis was performed to explore the potential sources of heterogeneity of different studies and influence analysis was used for the detection of outliers (studies) which affected the pooled results statistically.

Results

Study selection and characteristics

A total of 606 articles were identified from the databases searched. One hundred seventy duplicates were removed and 347 studies were excluded through an initial screening. After a full-text assessment for eligibility of the remaining 89 articles, 44 studies were identified for inclusion in this meta-analysis. No additional studies were found through the screening of references of the included full-text articles (see Fig. 1). The selected 44 studies containing a total of 2246 patients with diagnosed epilepsy. These articles were published from 1995 to 2020. More details of the studies included are shown in Table 1.

Comparison between PET and reference standard

The pooled concordance rate of FDG-PET compared with the reference standard was 0.67 (95% CI: 0.60–0.73); as for FMZ-PET, the concordance rate was 0.75 (95% CI: 0.57–0.93). Concordance rate for FDG-PET/MRI coregistration was 0.93 (95% CI: 0.89–0.97) (see Figs. 2, 3, and 4). Subgroup analysis revealed that ^{18}F-FDG-PET showed the highest concordance rate in children 0.84 (0.75; 0.92); ^{11}C-FMZ had the highest concordance rate in the subgroup of adults 0.92 (0.74; 1.00). In patients with TLE, the pooled concordance rate of ^{18}F-FDG-PET was 0.79 (0.63; 0.92) (see Table 2).

Diagnostic performances of ^{11}C-FMZ and ^{18}F-FDG PET

Data from the 12 studies were used in the bivariate mixed-effects regression model to compute the pooled results on the basis of threshold analysis on FDG-PET ($p = 0.67$) and 7 studies with respect to FMZ-PET ($p = 0.94$) were analyzed. FDG-PET demonstrated an overall sensitivity of 0.66 (95% CI: 0.58–0.73) and specificity of 0.71 (95% CI: 0.63–0.78), with an AUC of 0.71 (95% CI: 0.67–0.75), positive LR of 2.3 (95% CI: 1.7–3.0), negative LR of 0.48 (95% CI: 0.38–0.61), and diagnostic OR

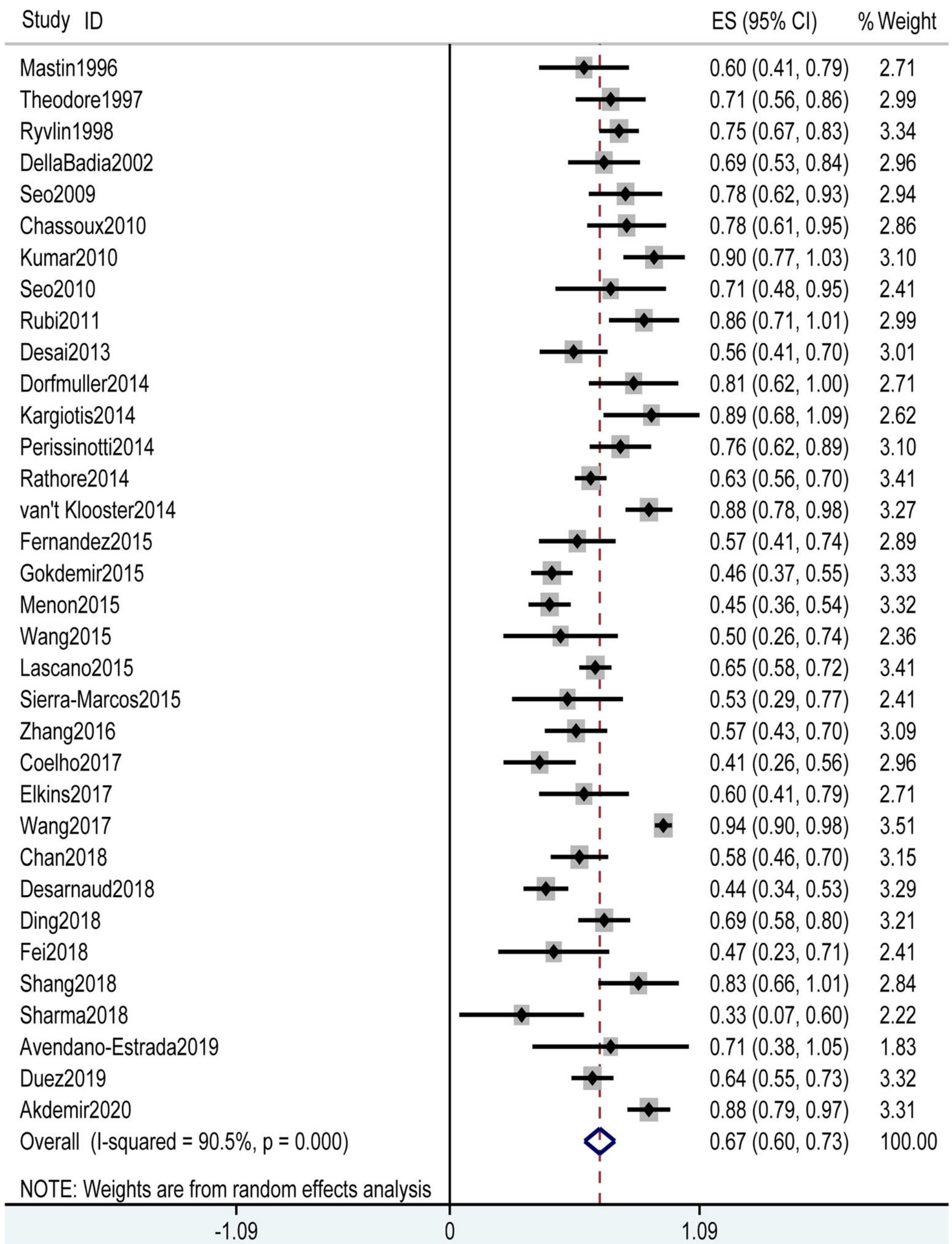


Fig. 2 Forest plot of pooled concordance rate for FDG-PET compared with the reference standard. The pooled concordance rate of FDG-PET was 0.67. Heterogeneity was high and statistically significant

of 5 (95% CI: 3–8) for the localization of epileptogenic zone in patients with epilepsy. FMZ-PET showed an overall sensitivity of 0.62 (95% CI: 0.49–0.73) and specificity of 0.73 (95% CI: 0.59–0.84), with an AUC of 0.71 (95% CI: 0.67–0.75), positive LR of 2.3 (95% CI: 1.3–4.0), negative LR of 0.52 (95% CI: 0.36–0.77), and diagnostic OR of 4 (95% CI: 2–11) (Fig. 5). The results of subgroup analysis manifested that there was no statistical significance in different subgroups of ^{18}F-FDG-PET performance. ^{11}C-FMZ-PET showed better diagnostic performance in the TLE subgroup and adults, respectively. Besides, pooled sensitivity and specificity for FDG-PET were 0.67 (0.55–0.79) and 0.76 (0.64–0.87) (Table 3).

Heterogeneity and quality of studies

A forest plot showed no heterogeneity for the sensitivity of ^{18}F-FDG PET (Cochran $Q = 1.82$, $p = 0.38$, $I^2 = 6.9\%$), and there was no heterogeneity for the specificity of ^{18}F-FDG PET (Cochran $Q = 11.65$, $p = 0.38$, $I^2 = 5.6\%$). As for the results of ^{11}C-FMZ PET, no significant heterogeneity of sensitivity (Cochran $Q = 9.13$, $p = 0.17$, $I^2 = 34.3\%$) and specificity (Cochran $Q = 9.85$, $p = 0.13$, $I^2 = 37.1\%$) were found (see Fig. 5).

Quality assessment by QUADAS-2 scale showed that 37 studies had low risk of bias for patient selection, 2 studies had high risk of bias, and 5 studies had unclear risk of bias. Thirty-

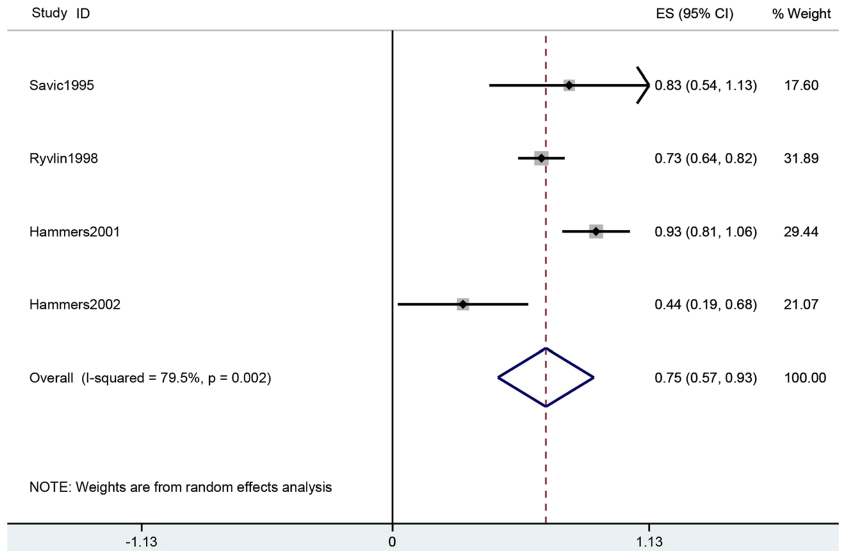


Fig. 3 Forest plot of pooled concordance rate for FMZ-PET compared with the reference standard. The pooled concordance rate of FMZ-PET was 0.75. Heterogeneity was high and statistically significant

one studies had low risk of bias for index test, 3 studies had high risk of bias, and 10 studies had unclear risk of bias. Thirty-seven studies had low risk of bias for reference standard and 7 studies had unclear risk of bias. Clinical applicability concerns of each study included were also evaluated (Supplementary Figures 1 and 2).

The results of subgroup analysis demonstrated statistical difference between subgroups of population in the concordance rate analysis for FDG PET ($p = 0.001$). As for FMZ PET, difference was present in subgroups of duration and population ($p = 0.009$, $p = 0.011$). Subgroup analysis of diagnostic performance of ^{11}C-FMZ-PET showed statistically significant difference in the TLE patients and adults (see Tables 2 and 3).

Influence analysis showed that no single study had significant impact on the overall outcomes in all pooled analysis.

Publication bias

Deeks' funnel plot asymmetry tests yielded a p value of 0.59 for ^{18}F-FDG PET and a p value of 0.24 for ^{11}C-FMZ PET, respectively (see Fig. 6).

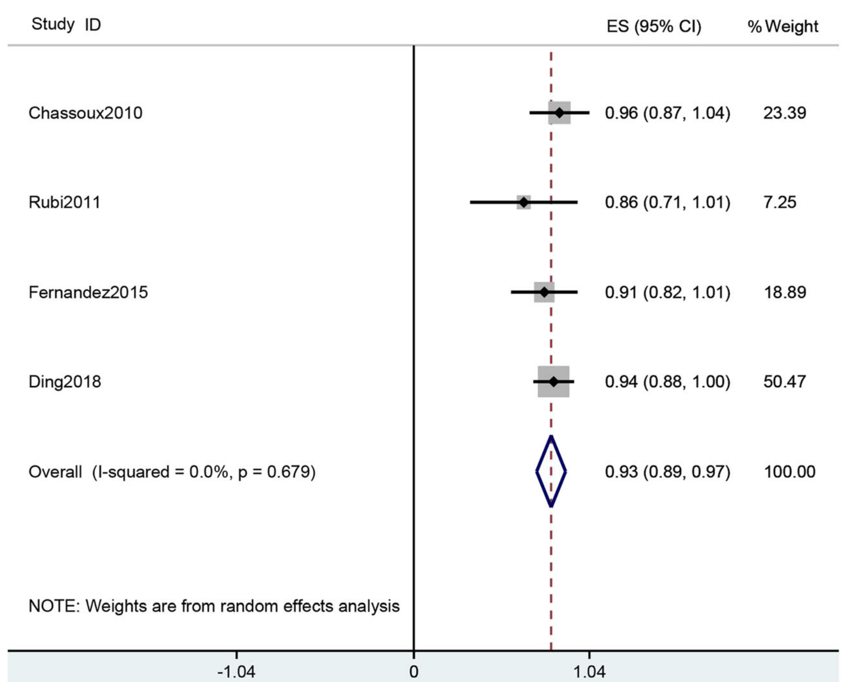


Fig. 4 Forest plot of pooled concordance rate for PET/MRI coregistration compared with the reference standard. The pooled concordance rate of PET/MRI coregistration was 0.93. Heterogeneity was statistically insignificant

Table 3 Subgroup analysis for the diagnostic performance of ^{18}F-FDG-PET and ^{11}C-FMZ-PET

	^{18}F-FDG-PET				^{11}C-FMZ-PET			
Characteristic	Number of studies	Sensitivity	Specificity	*p* value	Number of studies	Sensitivity	Specificity	*p* value
Age (years)								
< 30	5	0.65 (0.55–0.76)	0.66 (0.54–0.79)	0.57	3	0.58 (0.40–0.76)	0.68 (0.49–0.88)	0.74
≥ 30	7	0.66 (0.57–0.76)	0.74 (0.65–0.83)	4	0.65 (0.49–0.80)	0.77 (0.62–0.92)		
Duration of epilepsy (years)								
< 20	2	0.68 (0.47–0.89)	0.76 (0.57–0.95)	0.84	1	0.64	0.67	0.91
≥ 20	10	0.66 (0.58–0.73)	0.70 (0.62–0.79)	6	0.61 (0.47–0.75)	0.74 (0.61–0.87)		
Type of epilepsy								
TLE	6	0.67 (0.55–0.79)	0.76 (0.64–0.87)	0.63	6	0.68 (0.56–0.79)	0.73 (0.59–0.87)	0.04
Others	6	0.65 (0.56–0.74)	0.68 (0.58–0.78)	1	0.22	0.73		
Population								
Adults only	5	0.65 (0.55–0.75)	0.73 (0.61–0.85)	0.89	4	0.70 (0.57–0.83)	0.81 (0.69–0.92)	0.04
Others	7	0.67 (0.57–0.77)	0.70 (0.59–0.80)		3	0.46 (0.26–0.66)	0.61 (0.40–0.82)	

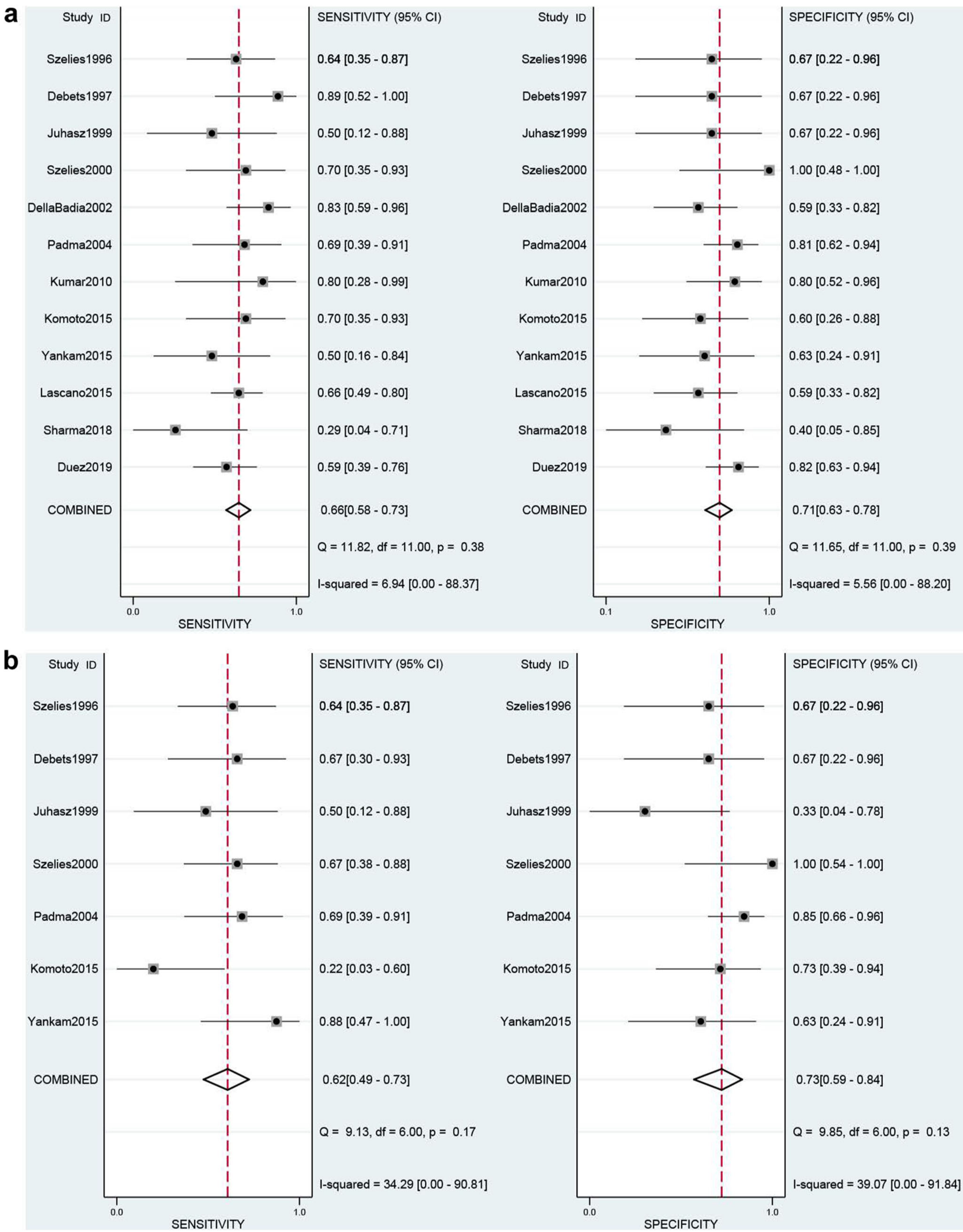
Discussion

PET is considered to be a neuroimaging technique that provided satisfactory insights into the molecular functioning of the brain in a living human [27]. ^{18}F-FDG was developed to assess brain glycometabolism, which led to the original application of PET in epilepsy [28]. Although ^{18}F-FDG is widely used in patients with epilepsy, unfortunately, it is not a desired tracer: the distribution of glucose hypometabolism regions is not related accurately to the level of hippocampal sclerosis, as results from MRI or histopathological test [29]. Since the 1990s, plentiful researches have assayed the implementation of ^{11}C-FMZ PET in the field of epilepsy [25]. Interestingly, it was demonstrated that the increase of seizure frequency correlated inversely with the tracer intake in the frontalis piriform cortex in an ^{11}C-FMZ PET study in epilepsy patients [30]. The site was inconsistent with the location of seizure onset and has been consistent with the results of morphometric MRI and EEG-fMRI researches [31]. Nevertheless, the tracer has not seen widely clinical utility, mainly due to its short half-life.

For decades, endeavors have been made to compare the utility of ^{18}F-FDG and ^{11}C-FMZ in the localization of epileptogenic zone [18, 32–37]. Nonetheless, the conclusions were less powerful to be extrapolated to clinical practice due to limited sample sizes and heterogeneity of different studies. We performed a meta-analysis to generate a more precise effect size of performances of FDG and FMZ in epilepsy localization and to provide a convincing evidence for healthcare professionals in counseling patients with epilepsy.

In this meta-analysis, we did a detailed literature search to improve the potential to capture all relevant studies as we can. Data extraction was conducted by two independent investigators using a pre-designed form. Furthermore, we assessed the heterogeneity between studies included, source of heterogeneity, quality of each study, and publication bias. The quality of individual study included in this meta-analysis was evaluated as high according to the QUADAS-2 scale. Furthermore, no significant heterogeneity between studies was observed; the analysis of threshold indicated that the results of studies can be consolidated with sufficient reasons. The influence analysis showed no single study had significant impact on the overall results. However, as we performed subgroup analysis, the results revealed that as for ^{11}C-FMZ-PET, there was statistically significant difference in the TLE patients and adults. This contradiction may be attributed to the small numbers of studies in subgroups. Deeks' funnel plot asymmetry tests indicated that publication bias may not affect the results between studies in either ^{18}F-FDG or ^{11}C-FMZ PET. This meta-analysis showed higher sensitivity of FDG-PET over FMZ-PET for the localization of epilepsy; however, the specificity of FDG-PET was lower than that of FMZ-PET. With respect to the type of epilepsy, both modalities showed better performance in patients with TLE compared with other epilepsy types. In consideration of clinical applications, given the positive and negative LRs of FMZ-PET (2.3 (95% CI: 1.3–4.0) and 0.52 (95% CI: 0.36–0.77)), it might help in excluding and confirming the localization of epilepsy foci in contrast to relevant indicators of FDG-PET. With respect to concordant

Fig. 5 Forest plots of studies included in the meta-analysis for localization of epilepsy with ^{18}F-FDG PET (**a**) and ^{11}C-FMZ PET (**b**). FDG-PET demonstrated an overall sensitivity of 0.66 and specificity of 0.71; heterogeneity for pooled sensitivity and specificity was statistically insignificant. FMZ-PET demonstrated an overall sensitivity of 0.62 and specificity of 0.73; heterogeneity for pooled sensitivity and specificity was statistically insignificant ▶


a
Study ID
SENSITIVITY (95% CI)
Szelies1996 0.64 [0.35 - 0.87]
Debets1997 0.89 [0.52 - 1.00]
Juhasz1999 0.50 [0.12 - 0.88]
Szelies2000 0.70 [0.35 - 0.93]
DellaBadia2002 0.83 [0.59 - 0.96]
Padma2004 0.69 [0.39 - 0.91]
Kumar2010 0.80 [0.28 - 0.99]
Komoto2015 0.70 [0.35 - 0.93]
Yankam2015 0.50 [0.16 - 0.84]
Lascano2015 0.66 [0.49 - 0.80]
Sharma2018 0.29 [0.04 - 0.71]
Duez2019 0.59 [0.39 - 0.76]
COMBINED 0.66[0.58 - 0.73]
Q = 11.82, df = 11.00, p = 0.38
I-squared = 6.94 [0.00 - 88.37]
0.0
1.0
SENSITIVITY
Study ID
SPECIFICITY (95% CI)
Szelies1996 0.67 [0.22 - 0.96]
Debets1997 0.67 [0.22 - 0.96]
Juhasz1999 0.67 [0.22 - 0.96]
Szelies2000 1.00 [0.48 - 1.00]
DellaBadia2002 0.59 [0.33 - 0.82]
Padma2004 0.81 [0.62 - 0.94]
Kumar2010 0.80 [0.52 - 0.96]
Komoto2015 0.60 [0.26 - 0.88]
Yankam2015 0.63 [0.24 - 0.91]
Lascano2015 0.59 [0.33 - 0.82]
Sharma2018 0.40 [0.05 - 0.85]
Duez2019 0.82 [0.63 - 0.94]
COMBINED 0.71[0.63 - 0.78]
Q = 11.65, df = 11.00, p = 0.39
I-squared = 5.56 [0.00 - 88.20]
0.1
1.0
SPECIFICITY
b
Study ID
SENSITIVITY (95% CI)
Szelies1996 0.64 [0.35 - 0.87]
Debets1997 0.67 [0.30 - 0.93]
Juhasz1999 0.50 [0.12 - 0.88]
Szelies2000 0.67 [0.38 - 0.88]
Padma2004 0.69 [0.39 - 0.91]
Komoto2015 0.22 [0.03 - 0.60]
Yankam2015 0.88 [0.47 - 1.00]
COMBINED 0.62[0.49 - 0.73]
Q = 9.13, df = 6.00, p = 0.17
I-squared = 34.29 [0.00 - 90.81]
0.0
1.0
SENSITIVITY
Study ID
SPECIFICITY (95% CI)
Szelies1996 0.67 [0.22 - 0.96]
Debets1997 0.67 [0.22 - 0.96]
Juhasz1999 0.33 [0.04 - 0.78]
Szelies2000 1.00 [0.54 - 1.00]
Padma2004 0.85 [0.66 - 0.96]
Komoto2015 0.73 [0.39 - 0.94]
Yankam2015 0.63 [0.24 - 0.91]
COMBINED 0.73[0.59 - 0.84]
Q = 9.85, df = 6.00, p = 0.13
I-squared = 39.07 [0.00 - 91.84]
0.0
1.0
SPECIFICITY

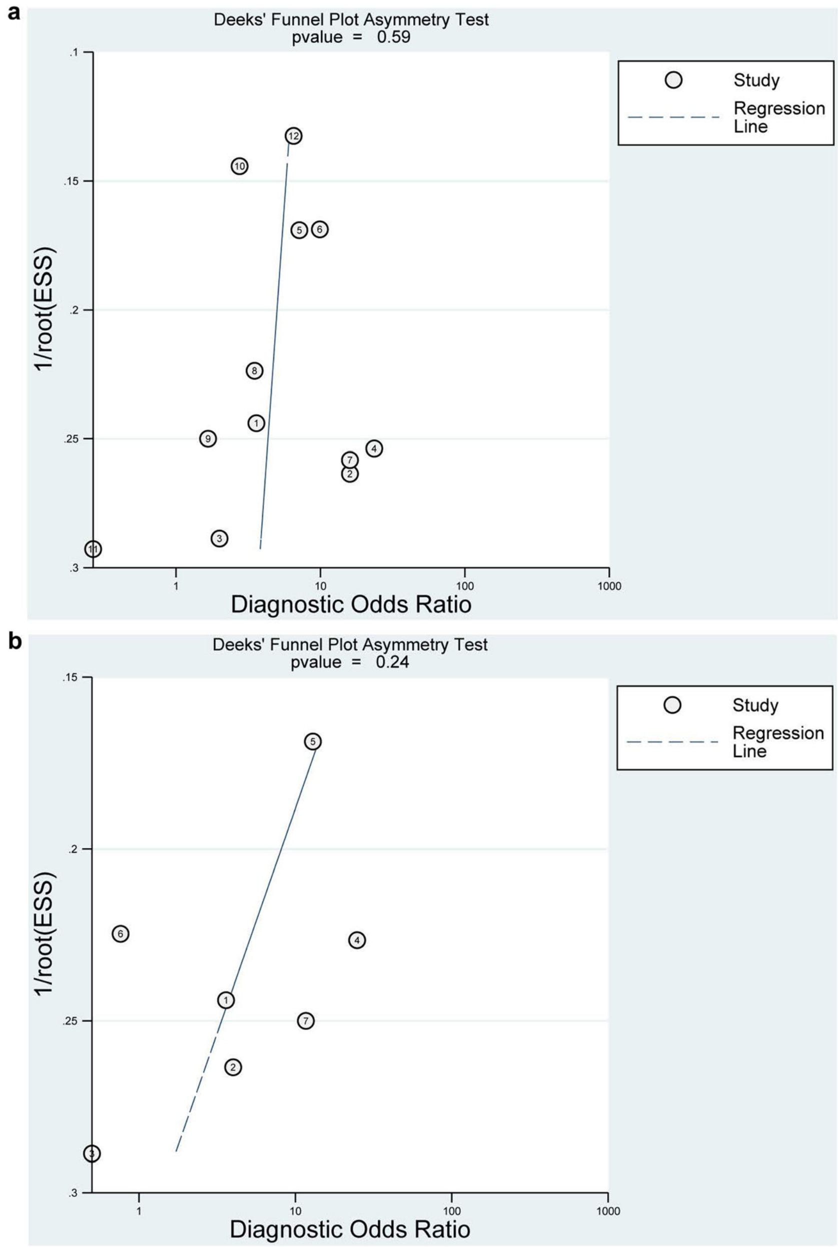


Fig. 6 Funnel plots for the pooled analysis of ^{18}F-FDG PET (**a**) and ^{11}C-FMZ PET (**b**) in the localization of epilepsy. Deeks' funnel plot asymmetry tests yielded a p value of 0.59 for ^{18}F-FDG PET and a p value of 0.24 for ^{11}C-FMZ PET

detection results compared with reference standards (EEG/surgery outcome), FDG-PET/MRI coregistration reached a concordance rate of 93%; FMZ-PET manifested superior concordance rate over FDG-PET imaging. FMZ-PET showed higher concordance rate than FDG-PET.

Nevertheless, there are limitations in this meta-analysis. All analysis was performed at the study level, so we were unable to extract information at individual level based on the information in each study. Therefore, the division of subgroups for age of participants and the duration of epilepsy was deemed to be less specific. Although we detailed the inclusion and exclusion criteria, heterogeneity in studies still existed. Even though the subgroup analysis was conducted, the corresponding interpretation should be made with caution.

On the basis of our findings in this analysis, we may conclude that both ^{11}C-FMZ PET and ^{18}F-FDG PET can provide helpful complementary information for the localization of epileptogenic zone, especially when combined with other non-invasive technologies such as MRI. Interestingly, the recent development of ^{18}F-FMZ, an alternative tracer of ^{11}C-FMZ, might overcome the issues including short half-life [38]. Further assessments of potentially powerful tracers such as ^{18}F-FMZ are needed.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00330-020-07645-4.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Li Huo (huoli@pumch.cn).

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was not required for this study because this was a meta-analysis using the studies in published literature and did not analyze specific human subjects.

Ethical approval Institutional Review Board approval was not required because this was a meta-analysis using the studies in published literature and did not analyze specific human subjects.

Study subjects or cohorts overlap Information of study's subjects or cohorts was extracted from previously published studies which were cited in the article.

Methodology
• meta-analysis

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