Accuracy of ^{18}F-FDG PET/CT and CECT for primary staging and diagnosis of recurrent gastric cancer: A meta-analysis

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Abstract. Contrast-enhanced computed tomography (CECT) is commonly used for staging and diagnosing recurrent gastric cancer. Recently, ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET)/CT gained popularity as a diagnostic tool owing to advantages including dual functional and anatomical imaging, which may facilitate early diagnosis. The diagnostic performance of ^{18}F-FDG PET/CT and CECT has been assessed in several studies but with variable results. Therefore, the present meta-analysis aimed to evaluate the accuracy of ^{18}F-FDG PET/CT and CECT for primary TNM staging and the diagnosis of recurrent gastric cancers. A systematic search of the PubMed Central, Medline, Scopus, Cochrane and Embase databases from inception until January 2020 was performed. The Quality Assessment of Diagnostic Accuracy Study-2 tool was used to determine the quality of the selected studies. Pooled estimates of sensitivity and specificity were calculated. A total of 58 studies comprising 9,997 patients were included. Most studies had a low risk of bias. The sensitivity and specificity for nodal staging of gastric cancer were 49% (95% CI, 37-61%) and 92% (95% CI, 86-96%) for ^{18}F-FDG PET/CT, respectively, and 67% (95% CI, 57-76%) and 86% (95% CI, 81-89%) for CECT, respectively. For metastasis staging, the sensitivity and specificity were 56% (95% CI, 40-71%) and 97% (95% CI, 87-99%) for ^{18}F-FDG PET/CT, respectively, and 59% (95% CI, 41-75%) and 96% (95% CI, 83-99%) for CECT, respectively. For diagnosing cancer recurrence, the pooled sensitivity and specificity were 81% (95% CI, 72-88%) and 83% (95% CI, 74-89%) for ^{18}F-FDG PET/CT, respectively, and 59% (95% CI, 41-75%) and 96% (95% CI, 83-99%) for CECT, respectively. Both ^{18}F-FDG PET/CT and CECT were deemed highly useful for diagnosing recurrent gastric cancer due to their high sensitivities and specificities. However, these techniques cannot be used to exclude or confirm the presence of lymph node metastases or recurrent gastric cancer tumors, but can be used for the confirmation of distal metastasis.

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Introduction

The global burden of gastric cancer has drastically decreased over the last few decades (1). However, the disease remains a leading cause of cancer-associated mortality with an overall poor prognosis (2,3). One of the major factors increasing the mortality of gastric cancer is late diagnosis. It is estimated that ~80% of cases are diagnosed in the late stages of malignancy (1,3). Thus, early and accurate diagnosis along with appropriate TNM staging of all the gastric cancers is essential (4-7). Early detection enables the clinician to appropriately select the treatment strategy and correctly predict overall prognosis (8).

Several imaging modalities, including endoscopic ultrasound (EUS), contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI) and ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET)/CT may be used for the diagnosis and TNM staging of gastric cancers (9). However, no specific guidelines exist regarding the most appropriate diagnostic modality for the staging of gastric cancer (10). In addition, there are limitations to each diagnostic tool for assessing gastric cancer. EUS cannot be used to evaluate the greater curvature wall, the fundus or the lymphatic spread (11,12) and it is highly dependent on the body habitus of the patient (13). CECT scans have limitations detecting flat lesions and feature poor contrast resolution for soft tissues (14,15). This may result in inaccurate assessments of lymph nodes, as CECT cannot detect microscopic nodal invasion and cannot exclude malignancy from normal large reactive nodes (14). MRI also has limitations including respiratory motion artifacts, high costs, long examination times and lack of standard gastric cancer protocols (16,17). Furthermore, nodal assessments via MRI are also limited by size criteria and the body coverage of a single examination is not suitable for metastasis staging (18). ^{18}F-FDG PET/CT is a semi-quantitative method that assesses the FDG uptake in gastric tumors (19). However, standardized uptake values depend on numerous factors, including the time interval post-FDG injection, tumor size, technical parameters and normoglycemia (20,21). In addition, uptake values vary with pathological cancer types and mucinous cancers may provide false-negative results (22).

Such limitations associated with each imaging modality preclude the accurate preoperative staging of gastric cancer. Furthermore, ~50% of patients with advanced gastric cancers develop recurrences after treatment (23,24). Early detection of recurrence is also essential to reduce mortality associated with the disease. Out of the several imaging modalities, CECT and ^{18}F-FDG PET/CT have been commonly used for the diagnosis and staging of gastric cancer. Studies have assessed the accuracy of each imaging tool in different settings with variable results. There is a requirement for high-quality evidence to determine the accuracy of these imaging modalities to guide clinical practice. Hence, the present systematic review and meta-analysis was performed to assess the accuracy of the diagnostic performance of ^{18}F-FDG PET/CT and CECT for TNM staging of primary tumors and diagnosis of recurrences in patients with gastric cancer.

Materials and methods

Inclusion criteria. All types of studies examining the accuracy of CECT or ^{18}F-FDG PET/CT for diagnosing and staging primary and recurrent gastric cancer were included. Studies were to compare the diagnostic accuracy of ^{18}F-FDG PET/CT or CECT (screening tests) with the histopathological examination result, which was considered the 'reference standard'. Full-text articles that reported on the sensitivity and specificity or provided information to calculate these values were included. Studies with sample sizes of <10 patients were excluded.

Search strategy. A systematic electronic search was performed in the databases PubMed Central, Medline, Scopus, Cochrane Library and Embase. The following medical subject headings and free-text terms were used for the search: 'Validation studies', 'gastric carcinoma', 'staging', 'prognosis', 'gastric cancer', 'recurrence', 'sensitivity', 'specificity', 'diagnosis', 'computed tomography', 'positron emission tomography', 'fluorodeoxyglucose' and 'diagnostic accuracy studies'. The search included entries from the inception of the databases up to 1st January 2020 without any language restrictions. The reference lists of primary trials were also examined to further identify any relevant articles for inclusion in the present review.

Selection of studies. A total of two authors (ZZ and BZ) independently performed the primary screening of titles, key words and abstracts. Full texts of relevant studies were then retrieved. Secondary screening of the retrieved articles was then performed to select studies meeting the inclusion criteria. All disagreements were resolved in discussion with a third investigator (WC).

Data extraction and management. The primary investigators (ZZ and BZ) extracted the relevant data from the studies, which included the following: Study setting, design, inclusion and exclusion criteria, sample size, comorbidities, the mean age of participants, index test, and sensitivity and specificity values of the imaging modality. The data extracted were double-checked during the review and the study reports to ensure correctness. The study outcomes were as follows: Sensitivity, specificity, diagnostic odds ratio (DOR), positive likelihood ratio (LR+), negative likelihood ratio (LR-).

Risk of bias assessment. The Quality Assessment of Diagnostic Accuracy Studies-2 tool was used to assess the risk of bias for each study (25). The tool comprises the following domains: Patient selection bias, conduct and interpretation of index tests and reference standards, as well as time interval of outcome assessments. The studies in each domain were graded as having unclear, high or low risk of bias.

Statistical analysis. The present meta-analysis was performed using the STATA 14.2 software (StataCorp). The pooled values for sensitivity, specificity, LR-, LR+ and DOR for each the ^{18}F-FDG PET/CT and the CECT imaging techniques were obtained using the bivariate meta-analysis method. A summary receiver operating characteristic (SROC) curve was generated and the area under the curve (AUC) was obtained. An AUC value closer to 1 indicated better diagnostic accuracy. Study-specific and pooled values of sensitivity and specificity were graphically represented using forest plots. The clinical values for both ^{18}F-FDG PET/CT and CECT were determined by generating LR scattergrams. In addition, the probability that a patient with gastric cancer had nodal or distant metastases or recurrences was tested using Fagan plots. Bivariate boxplots were generated and heterogeneity was tested using the χ^2 and I^2 statistics (I^2<25%, mild; I^2=25-75%, moderate; and I^2>75%, substantial heterogeneity). Publication bias was assessed graphically by funnel plots and also by Deek's test. The 'Midas' command package in STATA 14.2 software (StataCorp, LP) was used for all analyses.

Results

Selection of studies. In the database search, a total of 2,934 records were identified, of which, 1,388 studies were from Medline, 880 from Scopus, 557 from Embase and 109 from the Cochrane library. After the first stage of screening, 247 studies were retrieved based on relevance. The full texts of these articles were extracted and it was assessed whether they fulfilled the inclusion criteria. Finally, a total of 58 studies met the inclusion criteria and were included in the review (Fig. 1).

Characteristics of the included studies. Table I lists the characteristics of the included studies (14,23,26-81). The majority of them (37/58) were retrospective in nature. Data from a total of 9,997 participants were analyzed in the included studies. The sample sizes of individual studies varied from 18 to 1,964 patients. All of the included studies used histopathology as the reference standard. Among the studies using ^{18}F-FDG PET/CT as the index test, 11 reported data on lymph node metastases and 8 reported on distant metastases, while 16 reported on the accuracy of the imaging modality for detecting recurrent gastric cancer tumors. Among the studies using CECT as the index test, 37 studies reported data on lymph node metastases, 7 on distant metastasis and 4 on recurrent gastric cancer tumors.

Methodological quality. Fig. 2 depicts the risk of bias assessments for the included studies. A high risk of patient selection bias was present in almost 20% of the studies. Furthermore, >40% of the studies had a high risk of bias for conduct and interpretation of the index test. All of the studies had a low risk

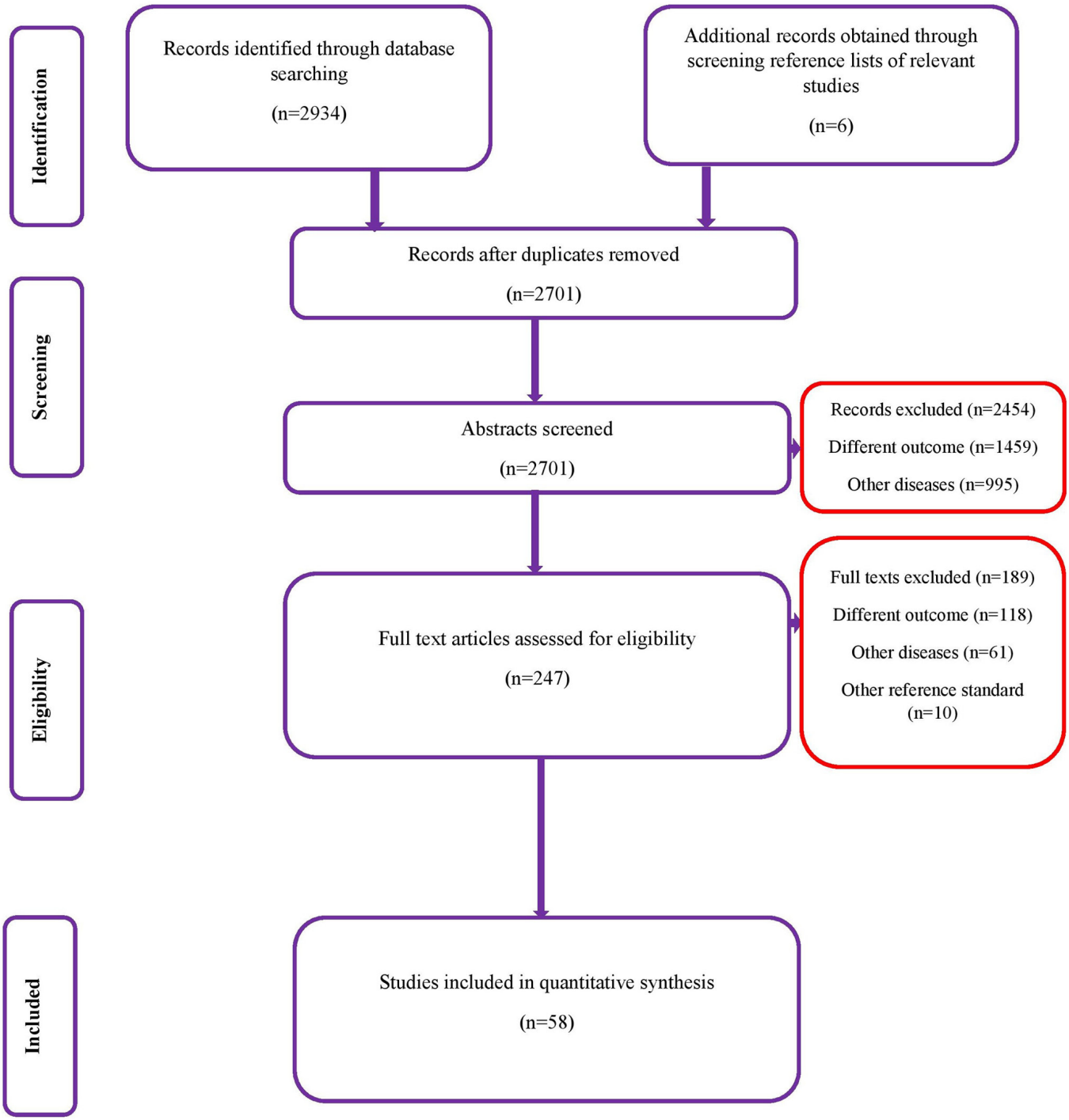

Figure 1. Search strategy.

of bias for conduct and interpretation of reference standards. In addition, ~70% of the studies had low risks of bias for patient flow and interval between index tests and reference standards.

Diagnostic performance of ^{18}F-FDG PET/CT

Lymph node metastasis. Overall, 11 studies evaluated the accuracy of ^{18}F-FDG PET/CT for diagnosing lymph node metastases (N staging) among patients with gastric cancer. The pooled sensitivity and specificity were 49% (95% CI, 37-61%) and 92% (95% CI, 86-96%), respectively (Fig. 3). The DOR was 11 (95% CI, 6-21). The LR+ was 6.1 (95% CI, 3.5-10.6) and the LR- was 0.56 (0.44-0.70). The LR+ and LR- values were in the right lower quadrant of the LR scattergram, indicating that the ^{18}F-FDG PET/CT cannot be used for confirmation or exclusion (Fig. 4). Fig. 5 presents the SROC curve for diagnosing nodal metastases using ^{18}F-FDG PET/CT. The AUC was 0.84 (95% CI, 0.66-0.94), indicating a high diagnostic performance for ^{18}F-FDG PET/CT. Fagan's nomogram indicated an average clinical utility of ^{18}F-FDG PET/CT for diagnosing nodal metastasis, as the post-test probability (positive, 85%; negative, 35%) differed slightly from the pre-test probability (49%; Fig. 6).

Table I. Characteristics of the included studies (n=58).

Study number	First author and year	Country	Study design	Sample size	Type of diagnostic modality	Gold standard comparator	Outcomes reported	Sensitivity and specificity	(Refs)
1	Ahn *et al*, 2009	South Korea	Retrospective	434	CECT	Histopathology	Lymph node metastasis	Sensitivity=17.0% Specificity=91.6%	(26)
2	Bilici *et al*, 2011	Turkey	Retrospective	34	18F-FDG PET/CT and CECT	Histopathology	Recurrent gastric cancer	Sensitivity (FDG-PET)=95.8% Specificity (FDG-PET)=100.0% Sensitivity (CECT)=62.5% Specificity (CECT)=100.0%	(27)
3	Blackshaw *et al*, 2003	United Kingdom	Prospective	100	CECT	Histopathology	Distant metastasis	Sensitivity (CECT)=46.2% Specificity (CECT)=100.0%	(28)
4	Bosch *et al*, 2020	United Kingdom	Retrospective	105	CECT	Histopathology	Distant metastasis	Sensitivity (CECT)=40.0% Specificity (CECT)=73.3%	(29)
5	Cayvarlı *et al*, 2014	Turkey	Retrospective	130	18F-FDG PET/CT and CECT	Histopathology	Recurrent gastric cancer	Sensitivity=91.2% Specificity=61.5%	(30)
6	Chen *et al*, 2005	South Korea	Prospective	68	18F-FDG PET/CT and CECT	Histopathology	Lymph node and distant metastasis	FDG PET (LN): Sensitivity=56.0% Specificity=92.0% FDG PET (Distant): Sensitivity=30.0% Specificity=98.0% CECT (Distant): Sensitivity=80.0% Specificity=91.0% CECT (LN): Sensitivity=78.0% Specificity=61.0%	(31)
7	Chen *et al*, 2007	Taiwan	Retrospective	64	CECT	Histopathology	Lymph node metastasis	Sensitivity=88.0% Specificity=80.0%	(32)
8	Chen *et al*, 2006	Taiwan	Prospective study	55	CECT	Histopathology	Lymph node metastasis	Sensitivity=86.0% Specificity=77.0%	(14)
9	De Potter *et al*, 2002	Belgium	Retrospective study	33	18F-FDG PET/CT	Histopathology	Recurrent gastric cancer	Sensitivity=70.0% Specificity=69.0%	(33)
10	D'Elia F *et al*, 2000	Italy	Prospective	107	CECT	Histopathology	Lymph node metastasis	Sensitivity=97.0% Specificity=65.0%	(34)

Table I. Continued.

Study number	First author and year	Country	Study design	Sample size	Type of diagnostic modality	Gold standard comparator	Outcomes reported	Sensitivity and specificity	(Refs)
11	Feng *et al*, 2013	China	Prospective	610	CECT	Histopathology	Lymph node metastasis	Sensitivity=84.9% Specificity=61.0%	(35)
12	Filik *et al*, 2015	Turkey	Retrospective	25	18F-FDG PET/CT and CECT	Histopathology	Lymph node metastasis	FDG PET: Sensitivity=82.0% Specificity=75.0% CECT: Sensitivity=64.0% Specificity=100.0%	(36)
13	Fujikawa *et al*, 2014	Japan	Prospective	525	CECT	Histopathology	Lymph node metastasis	Sensitivity=4.0% Specificity=98.0%	(37)
14	Giganti *et al*, 2016	Italy	Prospective	55	CECT	Histopathology	Lymph node metastasis	Sensitivity=90.0% Specificity=91.0%	(38)
15	Graziosi *et al*, 2011	Italy	Retrospective	50	18F-FDG PET/CT and CECT	Histopathology	Recurrent gastric cancer	Sensitivity=89.0% Specificity=85.0%	(39)
16	Ha *et al*, 2011	South Korea	Retrospective	78	18F-FDG PET/CT and CECT	Histopathology	Lymph node metastasis	FDG PET: Sensitivity=89.0% Specificity=85.0% CECT: Sensitivity=69.0% Specificity=86.0%	(40)
17	Hasegawa *et al*, 2013	Japan	Prospective	315	CECT	Histopathology	Lymph node metastasis	Sensitivity=46.4% Specificity=96.0%	(41)
18	Hwang *et al*, 2010	South Korea	Prospective	247	CECT	Histopathology	Lymph node metastasis	Sensitivity=44.5% Specificity=85.3%	(42)
19	Jadvar *et al*, 2003	United States of America	Retrospective	18	18F-FDG PET/CT	Histopathology	Recurrent gastric cancer	Sensitivity=77.7% Specificity=77.7%	(43)
20	Joo *et al*, 2015	South Korea	Prospective	47	CECT	Histopathology	Lymph node metastasis	Sensitivity=43.3% Specificity=100.0%	(44)
21	Karakoyun *et al*, 2014	Turkey	Prospective	55	CECT	Histopathology	Lymph node metastasis	Sensitivity=97.5% Specificity=73.3%	(45)

Table I. Continued.

Study number	First author and year	Country	Study design	Sample size	Type of diagnostic modality	Gold standard comparator	Outcomes reported	Sensitivity and specificity	(Refs)
22	Kawanaka *et al*, 2016	Japan	Retrospective study	101	18F-FDG PET/CT and CECT	Histopathology	Lymph node and distant metastasis	FDG PET (LN): Sensitivity=80.0% Specificity=70.0% CECT (Distant): Sensitivity=75.0% Specificity=97.0% FDG PET (Distant): Sensitivity=81.0% Specificity=100.0% CECT (LN): Sensitivity=84.0% Specificity=70.0%	(46)
23	Kim *et al*, 2005	South Korea	Prospective	106	CECT	Histopathology	Lymph node metastasis	Sensitivity=71.7% Specificity=63.3%	(47)
24	Kim *et al*, 2009	South Korea	Retrospective	102	CECT	Histopathology	Lymph node metastasis	Sensitivity=50.0% Specificity=91.0%	(48)
25	Kim *et al*, 2011	South Korea	Retrospective	71	18F-FDG PET/CT	Histopathology	Lymph node metastasis and recurrent gastric cancer	Lymph node metastasis: Sensitivity=40.0% Specificity=100.0% Recurrent gastric cancer: Sensitivity=51.0% Specificity=84.0%	(49)
26	Kim *et al*, 2013	South Korea	Retrospective	171	CECT	Histopathology	Lymph node metastasis	Sensitivity=60.0% Specificity=89.0%	(50)
27	Kim *et al*, 2017	South Korea	Retrospective	600	CECT	Histopathology	Recurrent gastric cancer	Sensitivity=75.9% Specificity=98.4%	(51)
28	Kudou *et al*, 2018	Japan	Retrospective	117	18F-FDG PET/CT and CECT	Histopathology	Lymph node and distant metastasis	FDG PET (LN): Sensitivity=22.6% Specificity=90.0% CECT (Distant): Sensitivity=60.8% Specificity=67.6% FDG PET (Distant): Sensitivity=80.0% Specificity=64.0% CECT (LN): Sensitivity=52.0% Specificity=71.0%	(52)

Table I. Continued.

Study number	First author and year	Country	Study design	Sample size	Type of diagnostic modality	Gold standard comparator	Outcomes reported	Sensitivity and specificity	(Refs)
29	Lee *et al*, 2010	South Korea	Retrospective	148	CECT	Histopathology	Lymph node metastasis	Sensitivity=26.3% Specificity=98.8%	(53)
30	Lee *et al*, 2011	South Korea	Retrospective	93	18F-FDG PET/CT and CECT	Histopathology	Recurrent gastric cancer	FDG PET: Sensitivity=42.0% Specificity=57.0% CECT: Sensitivity=85.0% Specificity=87.0%	(54)
31	Lee *et al*, 2014	South Korea	Retrospective	46	18F-FDG PET/CT	Histopathology	Recurrent gastric cancer	Sensitivity=100.0% Specificity=88.0%	(55)
32	Lim *et al*, 2006	South Korea	Retrospective	112	CECT	Histopathology	Lymph node and distant metastasis	Sensitivity=35.0% Specificity=98.9%	(56)
33	Marrelli *et al*, 2011	Italy	Prospective	92	CECT	Histopathology	Lymph node metastasis	Sensitivity=84.6% Specificity=95%	(57)
34	Mochiki *et al*, 2004	Japan	Prospective	85	18F-FDG PET/CT and CECT	Histopathology	Lymph node metastasis	FDG PET: Sensitivity=35.0% Specificity=100.0% CECT: Sensitivity=65.0% Specificity=77.0%	(23)
35	Nakamoto *et al*, 2009	Japan	Retrospective	92	18F-FDG PET/CT	Histopathology	Recurrent gastric cancer	Sensitivity=77.2% Specificity=91.7%	(58)
36	Namikawa *et al*, 2014	Japan	Retrospective	90	18F-FDG PET/CT	Histopathology	Lymph node metastasis	Sensitivity=64.0% Specificity=85.0%	(59)
37	Pan *et al*, 2013	China	Prospective	96	CECT	Histopathology	Lymph node metastasis	Sensitivity=91.0% Specificity=60.0%	(60)
38	Park *et al*, 2009	South Korea	Retrospective	105	18F-FDG PET/CT	Histopathology	Recurrent gastric cancer	Sensitivity=74.0% Specificity=76.0%	(61)
39	Park *et al*, 2010	South Korea	Retrospective	1964	CECT	Histopathology	Lymph node metastasis	Sensitivity=57.0% Specificity=80.0%	(62)
40	Park *et al*, 2014	South Korea	Retrospective	74	CECT	Histopathology	Lymph node metastasis	Sensitivity=51.0% Specificity=81.0%	(63)

Table I. Continued.

Study number	First author and year	Country	Study design	Sample size	Type of diagnostic modality	Gold standard comparator	Outcomes reported	Sensitivity and specificity	(Refs)
41	Perlaza *et al*, 2018	Spain	Prospective	50	18F-FDG PET/CT and CECT	Histopathology	Distant metastasis	FDG PET: Sensitivity=63.0% Specificity=92.0% CECT: Sensitivity=65.0% Specificity=100.0%	(64)
42	Ren *et al*, 2007	China	Retrospective	77	CECT	Histopathology	Lymph node metastasis	Sensitivity=83.0% Specificity=75.0%	(65)
43	Saito *et al*, 2015	Japan	Retrospective	90	CECT	Histopathology	Lymph node metastasis	Sensitivity=55.0% Specificity=86.0%	(66)
44	Sharma *et al*, 2012	India	Retrospective	93	18F-FDG PET/CT	Histopathology	Recurrent gastric cancer	Sensitivity=95.0% Specificity=79.0%	(67)
45	Shinohara *et al*, 2005	Japan	Prospective	451	CECT	Histopathology	Lymph node metastasis	Sensitivity=67.0% Specificity=90.0%	(68)
46	Sim *et al*, 2009	South Korea	Retrospective	52	18F-FDG PET/CT	Histopathology and CECT	Recurrent gastric cancer	FDG PET: Sensitivity=68.0% Specificity=71.0% CECT: Sensitivity=89.0% Specificity=64.0%	(69)
47	Smyth *et al*, 2012	United States of America	Prospective	113	18F-FDG PET/CT	Histopathology	Distant metastasis	Sensitivity=35.0% Specificity=98.7%	(70)
48	Stell *et al*, 1996	United Kingdom	Prospective	65	CECT	Histopathology	Lymph node and distant metastasis	LN: Sensitivity=26.0% Specificity=100.0% Distant: Sensitivity=7.6% Specificity=100.0%	(71)
49	Sun *et al*, 2008	China	Retrospective	23	18F-FDG PET/CT	Histopathology	Distant metastasis	Sensitivity=85.0% Specificity=77.7%	(72)
50	Tsujimoto *et al*, 2010	Japan	Prospective	205	18F-FDG PET/CT	Histopathology	LN metastasis	Sensitivity=21.0% Specificity=89.0%	(73)

Table I. Continued.

Study number	First author and year	Country	Study design	Sample size	Type of diagnostic modality	Gold standard comparator	Outcomes reported	Sensitivity and specificity	(Refs)
51	Turlakow A *et al*, 2003	United States of America	Retrospective	37	18F-FDG PET/CT	Histopathology	Distant metastasis	Sensitivity=56.0% Specificity=93.0%	(74)
52	Yan *et al*, 2009	China	Prospective	670	CECT	Histopathology	Lymph node metastasis	Sensitivity=86.0% Specificity=76.0%	(75)
53	Yan *et al*, 2010	China	Prospective	61	CECT	Histopathology	Lymph node metastasis	Sensitivity=77.0% Specificity=73.0%	(76)
54	Yang *et al*, 2008	Japan	Retrospective	44	CECT	Histopathology	Lymph node metastasis	Sensitivity=84.0% Specificity=84.0%	(77)
55	Yoon *et al*, 2012	South Korea	Retrospective	372	18F-FDG PET/CT and CECT	Histopathology	Lymph node metastasis	FDG PET: Sensitivity=59.0% Specificity=88.0% CECT: Sensitivity=70.0% Specificity=82.0%	(78)
56	Yun *et al*, 2005	South Korea	Retrospective	30	18F-FDG PET/CT	Histopathology	Recurrent gastric cancer	Sensitivity=94.0% Specificity=69.0%	(79)
57	Yun *et al*, 2005	South Korea	Retrospective	81	18F-FDG PET/CT and CECT	Histopathology	Lymph node metastasis	FDG PET: Sensitivity=50.0% Specificity=98.0% CECT: Sensitivity=50.0% Specificity=98.0%	(80)
58	Zhong *et al*, 2012	China	Retrospective	115	CECT	Histopathology	Lymph node metastasis	Sensitivity=87.0% Specificity=75.0%	(81)

CECT, contrast-enhanced computed tomography; ^{18}F-FDG PET, ^{18}F-fluorodeoxyglucose positron emission tomography.

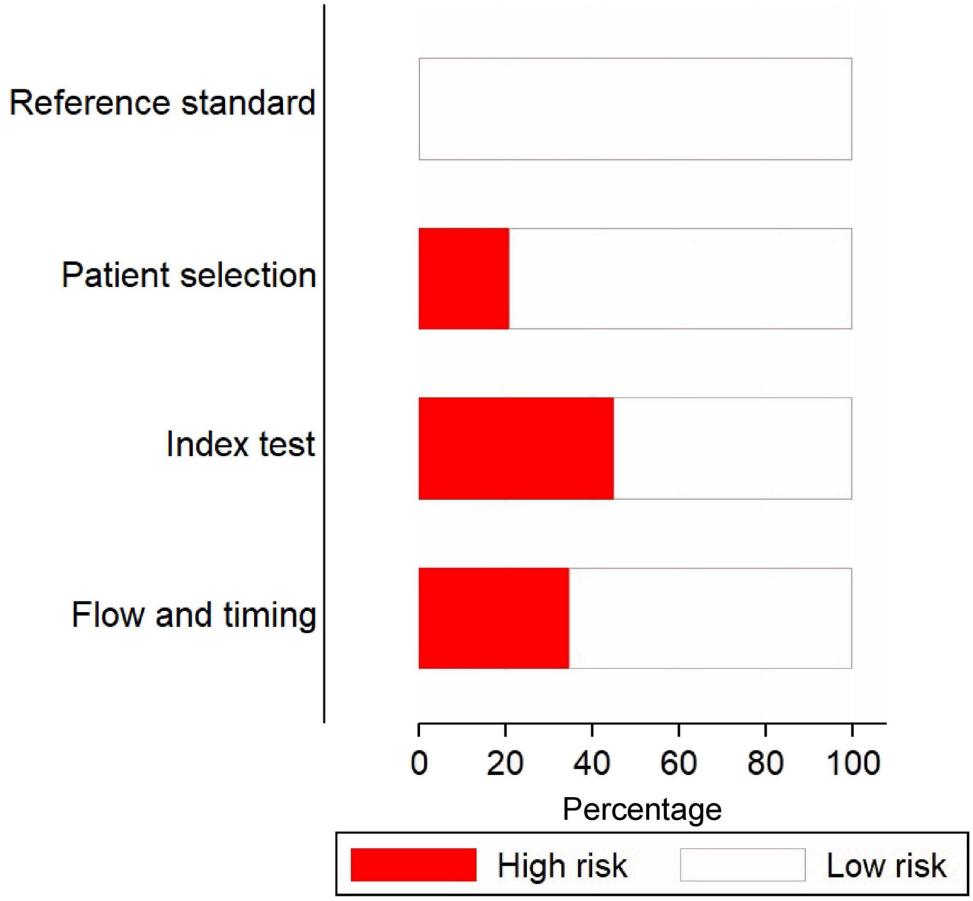

Figure 2. Quality assessment for the included studies (n=59) using the Quality Assessment of Diagnostic Accuracy Study-2 tool.

Considerable heterogeneity with a significant χ^2 test (P<0.001) and an I^2 value of 87.6% for pooling the sensitivity and 64.2% for specificity was determined, indicating substantial heterogeneity (Fig. 3). Of note, two studies were outside the circle of the bivariate box plot, indicating the possibility of between-study heterogeneity (Fig. 7). The funnel plot was symmetrical, indicating the absence of publication bias (Fig. S1), which was confirmed with a non-significant Deek's test (P=0.44).

Distant metastasis. In total, 8 studies evaluated the accuracy of ^{18}F-FDG PET/CT for diagnosing distant metastases (M staging) among patients with gastric cancer. The pooled sensitivity and specificity were 56% (95% CI, 40-71%) and 97% (95% CI, 87-99%), respectively (Fig. 3). The DOR was 41 (95% CI, 8-206). The LR+ was 18.5 (95% CI, 4.1-83.6) and the LR- was 0.45 (0.32-0.65). LR+ and LR- values were in the right upper quadrant of the LR scattergram, indicating that the ^{18}F-FDG PET/CT may be used for confirmation only (Fig. 4). Fig. 5 presents the SROC curve for diagnosing distant metastases using ^{18}F-FDG PET/CT. The AUC of 0.83 (95% CI, 0.74-0.89) suggested a high diagnostic performance of ^{18}F-FDG PET/CT. Fagan's nomogram indicated a good clinical utility for ^{18}F-FDG PET/CT for diagnosing distant metastasis, as the post-test probability (positive, 91%; negative, 20%) was significantly different from the pre-test probability (35%) (Fig. 6).

Considerable heterogeneity with a significant Chi-square test (P<0.001) and an I^2 value of 83.5% for pooling the sensitivity and 94.1% for specificity was determined, indicating substantial heterogeneity (Fig. 3). Of note, 1 study was outside of the bivariate box plot circle, indicating the possibility of between-study heterogeneity (Fig. 7). Publication bias was not assessed, as <10 studies reported on this outcome.

Recurrent gastric cancer. In total, 16 studies evaluated the accuracy of ^{18}F-FDG PET/CT for diagnosing recurrent gastric cancer. The pooled sensitivity and specificity were 81% (95% CI, 72-88%) and 83% (95% CI, 74-89%), respectively (Fig. 3). The DOR was 21 (95% CI, 10-45). The LR+ was 4.8 (95% CI, 3-7.5) and the LR- was 0.23 (0.15-0.35). The LR+ and LR- values were in the right lower quadrant of the LR scattergram, indicating that the ^{18}F-FDG PET/CT should not be used for confirmation or exclusion (Fig. 4). Fig. 5 presents the SROC curve for diagnosing recurrent gastric cancer tumors using ^{18}F-FDG PET/CT. The AUC was 0.89 (95% CI, 0.73-0.96), indicating a high diagnostic performance of ^{18}F-FDG PET/CT. Fagan's nomogram suggested a good clinical utility of ^{18}F-FDG PET/CT for recurrent gastric cancer diagnosis, as the post-test probability (positive, 73%; negative, 11%) differed from the pre-test probability (36%; Fig. 6).

Considerable heterogeneity was determined with a significant Chi-square test (P<0.001) and an I^2 value of 75.7% for pooling the sensitivity and 89.7% for specificity, indicating substantial heterogeneity (Fig. 3). A total of 4 studies were outside of the bivariate box plot circle, implying the possibility of between-study heterogeneity (Fig. 7). The funnel plot

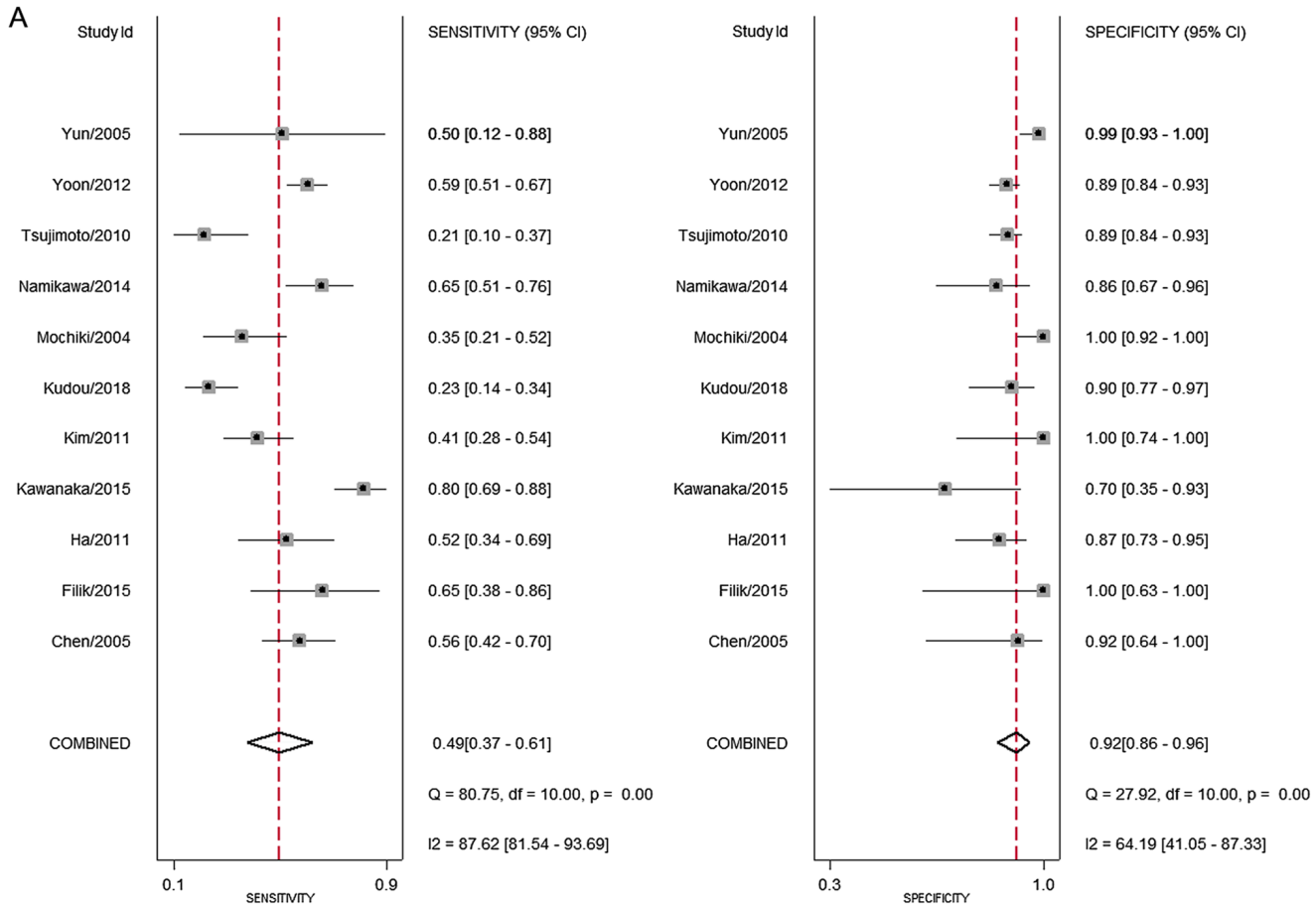

Figure 3. Continued.

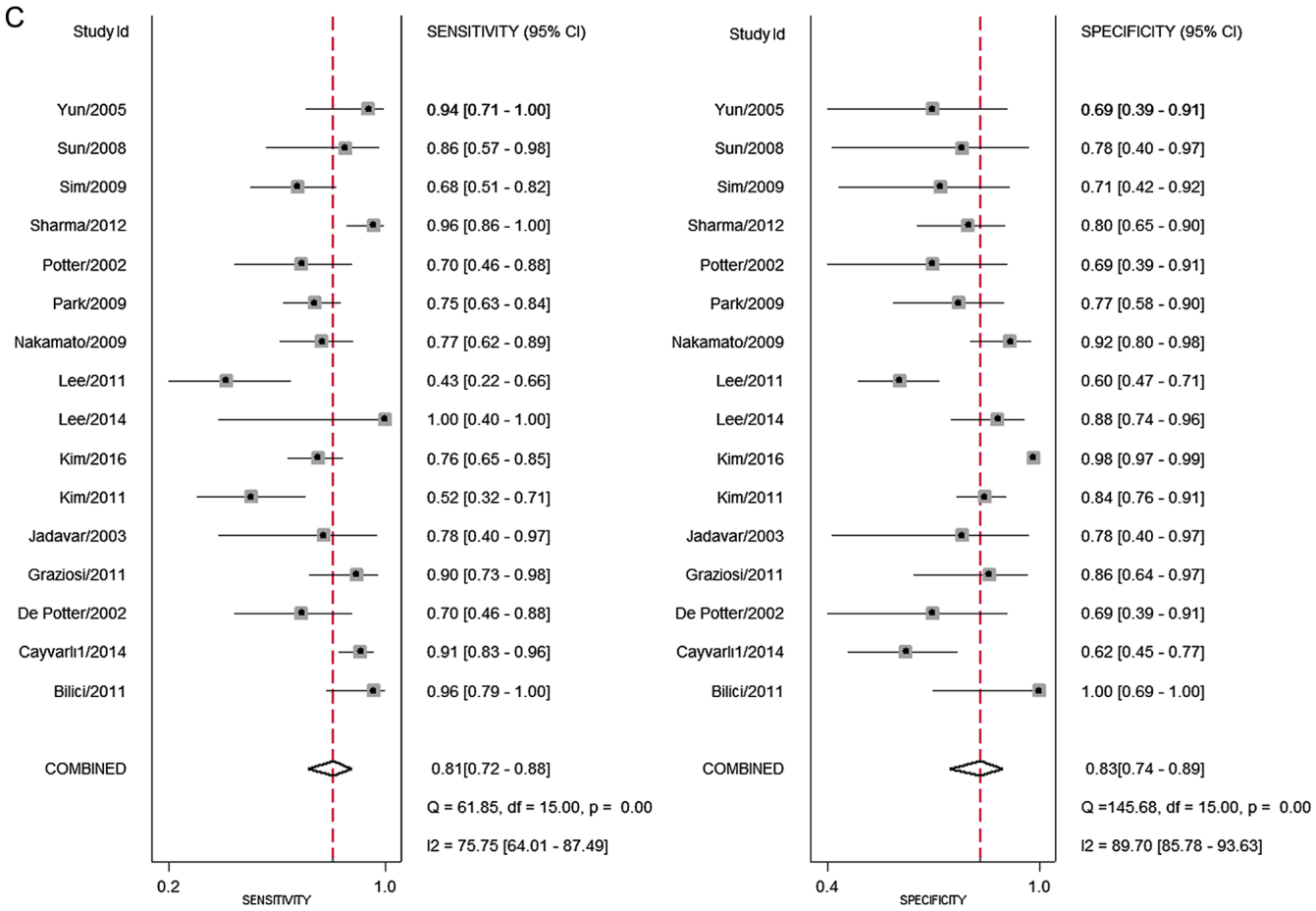

Figure 3. Continued.

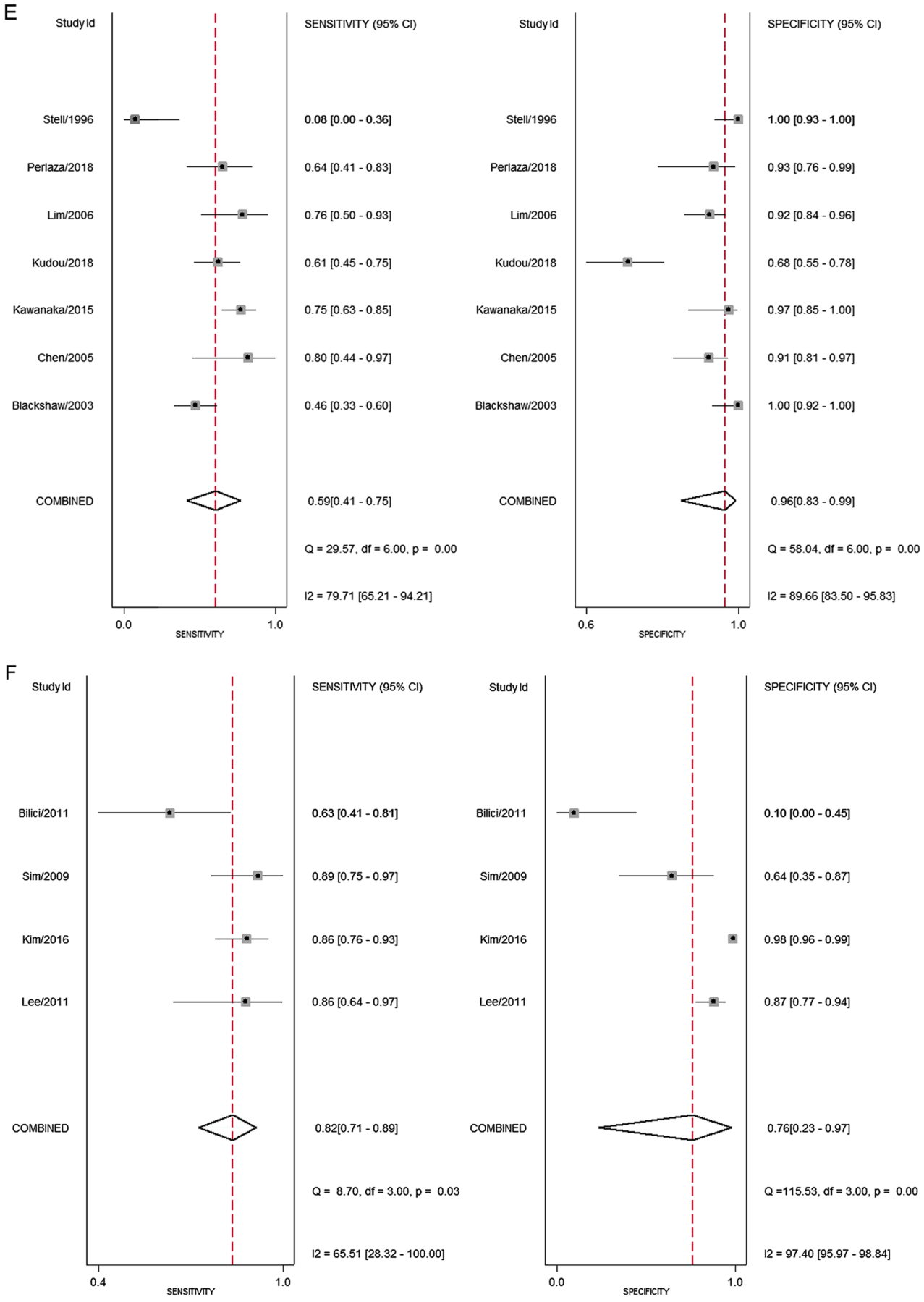

Figure 3. Pooled sensitivities and specificities of different imaging techniques for malignancy detection in patients with gastric cancer. Forest plot indicating the pooled sensitivity and specificity of (A) FDG PET for lymph node metastasis; (B) FDG PET for distant metastasis; (C) FDG PET for recurrent gastric cancer; (D) CECT for lymph node metastasis; (E) CECT for distant metastasis; and (F) CECT for recurrent gastric cancer. CECT, contrast-enhanced computed tomography; FDG PET, fluorodeoxyglucose positron emission tomography; df, degrees of freedom.

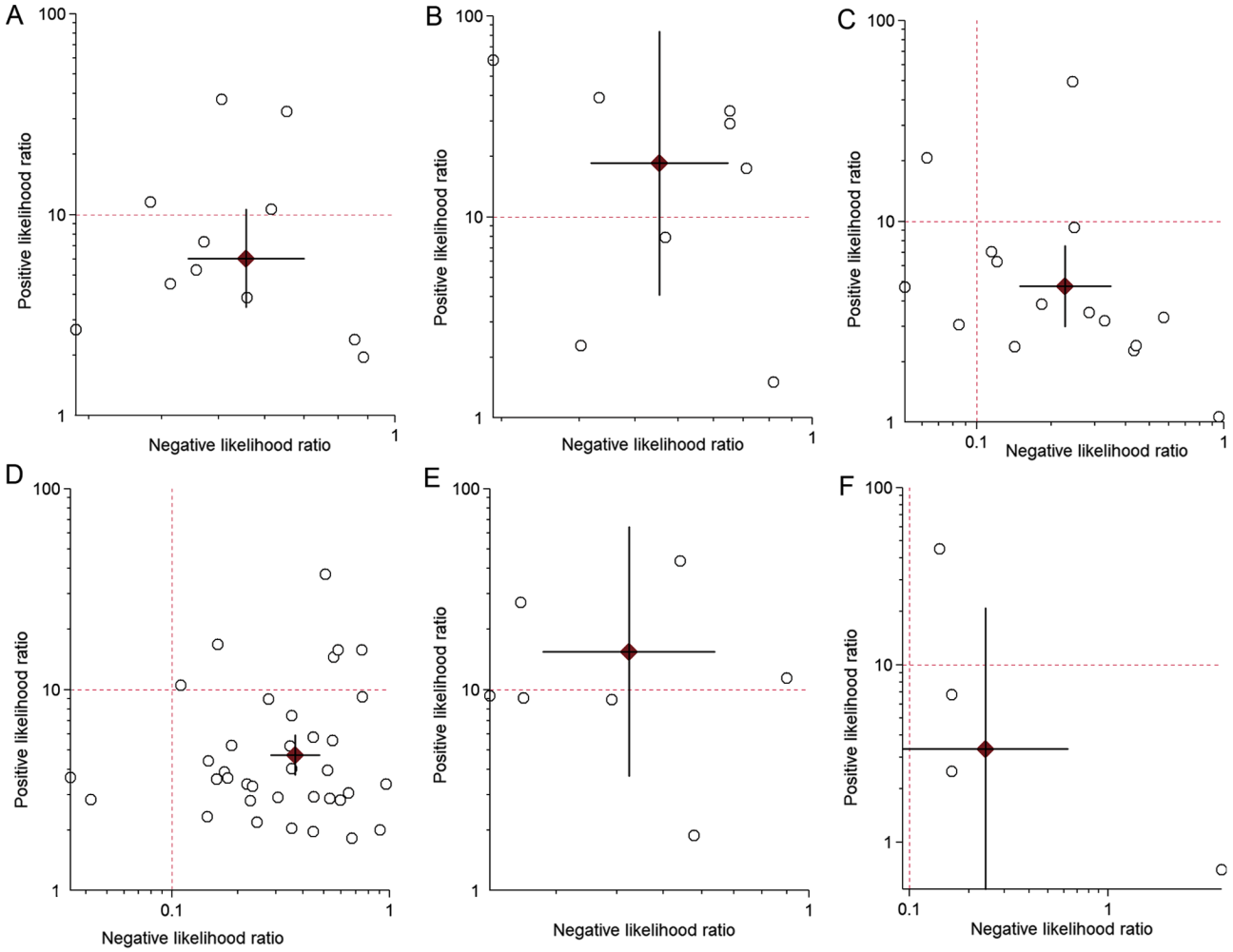

Figure 4. Likelihood scattergrams. Scatter plots of (A) FDG PET for lymph node metastasis; (B) FDG PET for distant metastasis; (C) FDG PET for recurrent gastric cancer; (D) CECT for lymph node metastasis; (E) for CECT on distant metastasis; and (F) CECT for recurrent gastric cancer. Upper left quadrant: Exclusion and confirmation; LR+ >10, LR- <0.1. Upper right quadrant: Confirmation only; LR+ >10, LR- >0.1. Lower left quadrant: Exclusion or confirmation; LR+ <10, LR- <0.1. Lower right quadrant: No exclusion or confirmation; LR+ <10, LR- >0.1. Summary LR+ and LR- for index test with 95% confidence intervals. LR+/-, positive/negative likelihood ratio; CECT, contrast-enhanced computed tomography; FDG PET, fluorodeoxyglucose positron emission tomography.

was symmetrical, indicating the absence of publication bias (Fig. S2). This was confirmed with a non-significant Deek's test (P=0.10).

Diagnostic performance of CECT.

Lymph node metastasis. In total, 37 studies evaluated the accuracy of CECT for diagnosing lymph node metastases (N staging) among patients with gastric cancer. The pooled sensitivity and specificity were 69% (95% CI, 59-77%) and 85% (95% CI, 81-89%), respectively (Fig. 3). The DOR was 12 (95% CI, 9-17). The LR+ was 4.7 (95% CI, 3.8-5.8) and the LR- was 0.38 (0.30-0.50). The LR+ and LR- values were in the right lower quadrant of the LR scattergram, indicating that the CECT cannot be used for confirmation or exclusion (Fig. 4). Fig. 5 presents the SROC curve for diagnosing nodal metastases using CECT. The AUC was 0.86 (95% CI, 0.81-0.90), indicating a high diagnostic performance for CECT. Fagan's nomogram suggested an average clinical utility of CECT for nodal metastasis diagnosis, as the post-test probability (positive, 77%; negative, 14%) differed slightly from the pre-test probability (42%; Fig. 6).

Considerable heterogeneity with a significant Chi-square test (P<0.001) and an I^2 value of 94.6% for pooling the sensitivity and 91.7% for specificity was determined, indicating substantial heterogeneity (Fig. 3). A total of six studies were outside the bivariate box plot circle, implying the possibility of between-study heterogeneity (Fig. 7). The funnel plot was found to be asymmetrical according to Deeks' test (P=0.02), indicating the presence of publication bias (Fig. S3).

Distant metastasis. A total of 7 studies evaluated the accuracy of CECT for diagnosing distant metastasis (M staging) among patients with gastric cancer. The pooled sensitivity and specificity were 59% (95% CI, 41-75%) and 96% (95% CI, 83-99%), respectively (Fig. 3). The DOR was 36 (95% CI, 9-147). The LR+ was 15.4 (95% CI, 3.7-64.3) and the LR- was 0.42 (0.28-0.64). The LR+ and LR- values were in the right upper quadrant of the LR scattergram, indicating that the CECT may be used for confirmation only (Fig. 4). Fig. 5 presents the SROC curve for diagnosing distant metastases using CECT. The AUC was 0.85 (95% CI, 0.77-0.91), indicating a high diagnostic performance of CECT. Fagan's nomogram suggested a good clinical utility

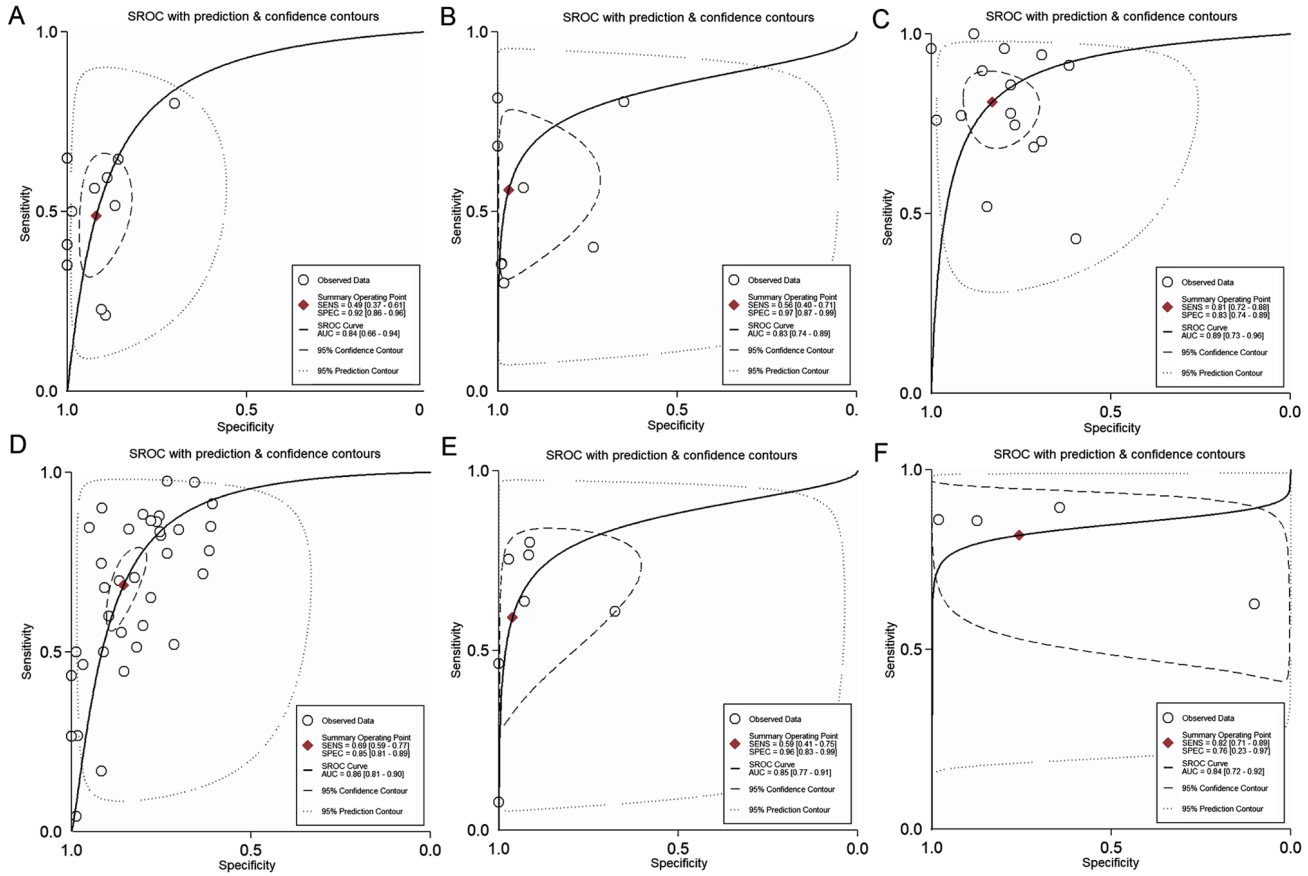

Figure 5. SROC curves. (A) FDG PET for lymph node metastasis; (B) FDG PET for distant metastasis; (C) FDG PET for recurrent gastric cancer; (D) CECT for lymph node metastasis; (E) CECT for distant metastasis; and (F) CECT for recurrent gastric cancer. CECT, contrast-enhanced computed tomography; FDG PET, fluorodeoxyglucose positron emission tomography; SROC, summary receiver operating characteristic; SENS, sensitivity; SPEC, specificity; AUC, area under the curve.

of CECT for distant metastasis diagnosis, as the post-test probability (positive, 90%; negative, 20%) differed significantly from the pre-test probability (37%) (Fig. 6).

Considerable heterogeneity with a significant Chi-square test (P<0.001) and an I^2 value of 79.7% for pooling the sensitivity and 89.7% for specificity was determined, indicating substantial heterogeneity (Fig. 3). A total of 2 studies were outside the bivariate box plot circle, suggesting between-study heterogeneity (Fig. 7). Publication bias was not assessed, as <10 studies reported on this outcome.

Recurrent gastric cancer. In total, 4 studies evaluated the accuracy of CECT for diagnosing patients with recurrent gastric cancer. The pooled sensitivity and specificity were 82% (95% CI, 71-89%) and 76% (95% CI, 23-97%), respectively (Fig. 3). The DOR was 14 (95% CI, 0.89-217). The LR+ was 3.4 (95% CI, 0.54-21) and the LR- was 0.24 (0.09-0.63). The LR+ and LR- values were in the right lower quadrant of the LR scattergram, indicating that the CECT cannot be used for confirmation or exclusion (Fig. 4). Fig. 5 presents the SROC curve for diagnosing recurrent gastric cancer using CECT. The AUC was 0.84 (95% CI, 0.72-0.92), indicating a high diagnostic performance of CECT. Fagan's nomogram suggested a good clinical utility of CECT for diagnosing recurrent gastric cancer, as the post-test probability (positive, 66%; negative, 12%) differed from the pre-test probability (37%) (Fig. 6).

Considerable heterogeneity was determined with a significant Chi-square test (P<0.001) and an I^2 value of 65.5% for pooling the sensitivity and 95.4% for specificity, indicating substantial heterogeneity (Fig. 3). Of note, one study was outside the bivariate box plot circle, indicating the possibility of between-study heterogeneity (Fig. 7). Publication bias was not assessed, as <10 studies reported on this outcome.

Discussion

Various imaging modalities are available for the staging of primary gastric cancers and diagnosing recurrent lesions. For several years, CECT scans have been routinely used for preoperative staging of gastric cancer around the world. However, ^{18}F-FDG PET/CT is a relatively new technique that is being incorporated for the pre-operative staging of several malignant lesions (19,20). An important advantage offered by ^{18}F-FDG PET/CT is that it combines functional images from PET and anatomical details of the CT scan, thereby overcoming the limitations of the individual imaging modalities (21). Both PET and CT are acquired in the same session for ^{18}F-FDG PET/CT and the modality allows for the accurate anatomical localization of malignant lesions. Evidence suggests that ^{18}F-FDG PET/CT may also facilitate early diagnosis, particularly for recurrent lesions with negative findings on conventional imaging (19-21). In order to present high-level

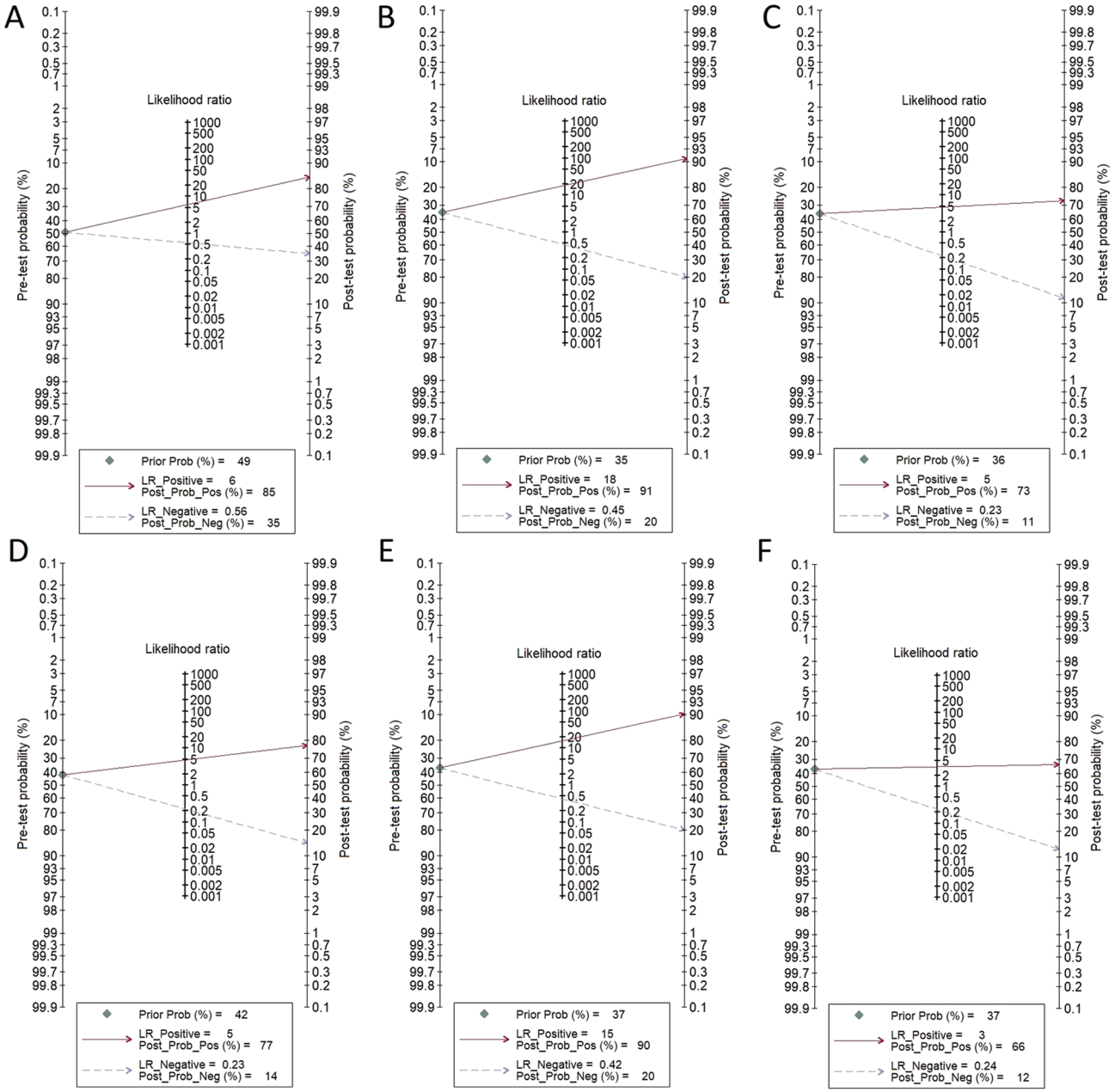

Figure 6. Fagan nomogram evaluating the overall value of (A) FDG PET for lymph node metastasis; (B) FDG PET for distant metastasis; (C) FDG PET for recurrent gastric cancer; (D) CECT for lymph node metastasis; (E) CECT for distant metastasis; and (F) CECT for recurrent gastric cancer. CECT, contrast-enhanced computed tomography; FDG PET, fluorodeoxyglucose positron emission tomography; LR, likelihood ratio; Pos, positive; Neg, negative; Prob, probability.

evidence to guide clinical practice, the current literature was reviewed to analyze the diagnostic accuracies of both [18]F-FDG PET/CT and CECT for patients with primary and recurrent gastric cancers.

The present study provided a pooled analysis of data from a large number of studies comprising a total of 9,997 participants. Initially, the diagnostic accuracy of both imaging modalities for lymph node metastases was assessed and it was revealed that [18]F-FDG PET/CT had a pooled sensitivity of 49% and specificity of 92% with a high diagnostic performance (AUC=0.84). On the other hand, CECT had a better pooled sensitivity (69%) but lower specificity (85%) and higher diagnostic accuracy (AUC=0.86) for the same. For distant metastasis, the diagnostic accuracies of both techniques (sensitivity and specificity) were similar. Furthermore, for recurrent gastric cancer, the pooled sensitivities were similar for both techniques, but the pooled specificity was higher for [18]F-FDG PET/CT than for CECT. The results of the present study concur with previous reviews conducted by Zhong *et al* (81) in 2012 and Li *et al* (82) in 2016, which demonstrated that [18]F-FDG PET/CT had a higher diagnostic performance than CECT for recurrent gastric cancer but CECT is better for preoperative staging of nodal metastasis. These studies also suggested that both techniques are equally accurate in detecting distant metastases among patients with gastric cancer.

The LR scattergrams of both techniques had the LR+ and LR- in the right lower quadrant, indicating that these techniques cannot be used to exclude or confirm the presence

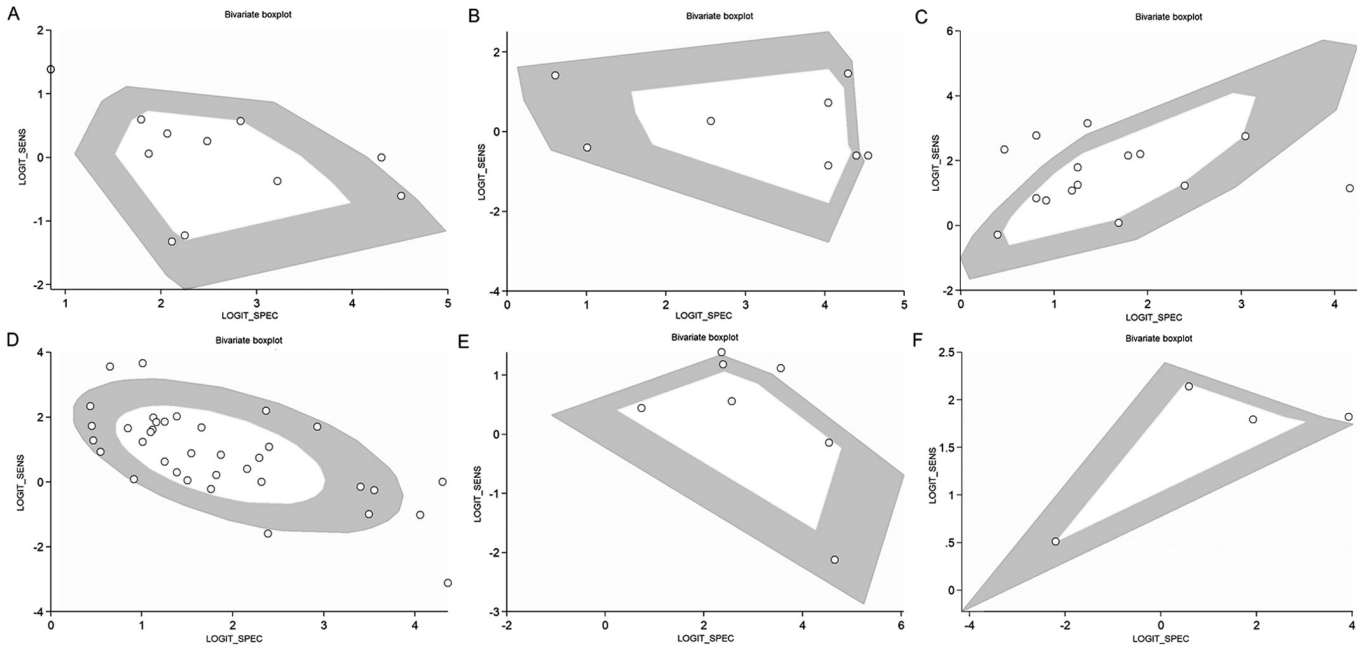

Figure 7. Bivariate boxplot of the sensitivities and specificities in the included studies. (A) FDG PET for lymph node metastasis; (B) FDG PET for distant metastasis; (C) FDG PET for recurrent gastric cancer; (D) CECT for lymph node metastasis; (E) CECT for distant metastasis; and (F) CECT for recurrent gastric cancer. SENS, sensitivity; SPEC, specificity.

of lymph node metastases or recurrent gastric cancer tumors. However, both ^{18}F-FDG PET/CT and CECT had LR scattergrams occupying the right upper quadrant for distant metastases, indicating that both techniques may be used for confirming the M staging of gastric cancer. The clinical values of both ^{18}F-FDG PET/CT and CECT for all the outcomes were high, as Fagan's nomogram exhibited a significant increase in the post-test probabilities compared to the pre-test probabilities. However, while inferring these results, the quality and methodology differences between the included studies should be considered, as these may potentially influence the conclusions. There was significant inter-study heterogeneity among the included studies as indicated by a significant Chi-square test and I^2 statistic results. Furthermore, Deek's test and the funnel plots indicated the possibility of publication bias among the studies reporting on the diagnostic accuracy of CECT for lymph node metastasis. Publication bias for other outcomes for CECT was not assessed due to an insufficient number of studies in the analysis. However, there was no evidence of publication bias among the studies reporting on the outcomes for ^{18}F-FDG PET/CT.

The present study has the following strengths: As compared with previous reviews on the subject (81,82), the present study provided comprehensive and updated evidence on the accuracy of ^{18}F-FDG PET/CT and CECT for primary gastric cancer TNM staging and detection of recurrence. The lack of publication bias for the ^{18}F-FDG PET/CT analysis in the present review adds credibility to the overall results. However, the present study also has certain limitations. First, there was a high risk of bias in certain studies assessing the accuracy of CECT, which may have influenced the final estimates. In addition, significant inter-study heterogeneity was identified between the studies included in the present review. This may have influenced the accuracy of the pooled results. Finally, no meta-regression was performed to explore the sources of heterogeneity among the included studies.

Despite these limitations, the present study provided valuable insight regarding the diagnostic performance of two important non-invasive imaging modalities for screening patients with gastric cancer for preoperative TNM staging and postoperative recurrence. ^{18}F-FDG PET/CT has a sensitivity well below the acceptable threshold for N staging for gastric cancer, indicating that it cannot be used for diagnosing nodal metastasis in patients with gastric cancer. Although CECT had a satisfactory sensitivity and specificity for all the outcomes, it did not meet the SnNout triage test criteria for sensitivity and the SpPin criteria for the specificity of a diagnostic test for N staging of gastric cancer and recurrent gastric cancer (83). This means that CECT cannot be used to confirm or rule out nodal metastases or recurrent gastric cancer tumors in patients. However, both ^{18}F-FDG PET/CT and CECT meet the SpPin criteria for the specificity of a diagnostic test for gastric cancer M staging, which indicates that both techniques may be used to confirm distant metastasis with a high level of confidence in patients with gastric cancer. The present results may prompt a change in clinical practices for the diagnosis and staging of gastric cancer. Both ^{18}F-FDG PET/CT and CECT may be used as first-line imaging modalities for M staging of the disease. However, further studies from different geographical regions of the world are also required, as current evidence from low- and middle-income regions is limited. With more generalizable data, new global guidelines and practices may be generated for patients with gastric cancer irrespective of the setting. Affordability of the tests should also be considered by cost-effectiveness analyses to choose the best and the most cost-effective technique for gastric cancer diagnosis and staging.

In conclusion, the present study indicated that both FDG PET/CT and CECT are highly useful imaging modalities for

diagnosing recurrent gastric cancer due to their high sensitivities and specificities. These techniques cannot be used to exclude or confirm the presence of lymph node metastases or recurrent gastric cancer tumors, but can be used for the confirmation of distal metastasis.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

ZZ, BZ and CJ designed the project; WC and HX were involved in data collection and data analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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