Original Article

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Diagnostic Performance of FAPI PET/CT vs. ^{18}F-FDG PET/CT in Evaluation of Liver Tumors: A Systematic Review and Meta-analysis

Karaciğer Tümörlerinin Değerlendirilmesinde FAPI PET/BT ve ^{18}F-FDG PET/BT'nin Tanısal Performanslarının Karşılaştırılması: Sistematik Bir Derleme ve Meta-analiz

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Abstract

Objectives: Primary liver tumors constitute one of the most common tumors. These are aggressive tumors with poor survival. Fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT), most commonly used functional imaging, shows limited tracer retention and poor tumor to background ratios (TBR). Novel ^{68}Ga-fibroblast-activation-protein inhibitor (FAPI) PET/CT has shown better tracer uptake and detection efficacy in liver tumors. However, most of the available literature is limited to single center studies with limited number of patients. So, we tried to review and analyze the head-to-head comparison of ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT in evaluation of liver tumors.

Methods: Literature available on head to head comparison of diagnostic accuracy of ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT was searched in databases like PubMed, SCOPUS, EMBASE and Google Scholar for published original studies till April 2023. The relevant studies were selected and assessed using the Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies-2 checklist. A random-effect model was used for calculating pooled sensitivity and specificity. They were represented with 95% confidence intervals (95% CI) and demonstrated in Forest plots. I-square statistic was used to assess heterogeneity in the studies.

Results: Pooled sensitivity and specificity of FAPI PET/CT and ^{18}F-FDG PET/CT for detection of primary liver tumors was 94.3% (95% CI: 90.6-96.8%); 89.3% (95% CI: 71.8-97.7%) and 56.1% (95% CI: 49.7-62.5%); 96.4% (95% CI: 81.7-99.9%) respectively. Pooled sensitivity for detection of extrahepatic metastatic disease was 92.2% (range: 88.1-100%; 95% CI: 87.8-95.4%) and 72.4% (range: 69.8-76.5; 95% CI: 65.9-78.2%) respectively. Also, the maximum standardized uptake value (SUV_{max}) and TBR were higher for FAPI PET/CT than ^{18}F-FDG PET/CT in the included studies.

Conclusion: Overall, FAPI PET/CT showed higher sensitivity for detection of liver tumors with better SUV_{max} and TBR than ^{18}F-FDG PET/CT.

Keywords: Positron emission tomography/computed tomography, ^{18}F-fluorodeoxyglucose, fibroblast-activation-protein inhibitors, liver cancers, hepatocellular cancer, cholangiocarcinoma

Öz

Amaç: Primer karaciğer tümörleri en sık görülen tümörlerdendir. Bunlar hayatta kalma oranı düşük olan agresif tümörlerdir. En sık kullanılan fonksiyonel görüntüleme olan florodeoksiglukoz (FDG) pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT), sınırlı radyofarmasötik tutulumu ve zayıf tümör/arka plan oranları (TBR) gösterir. Yeni ^{68}Ga-fibroblast aktivasyon protein inhibitörü (FAPI) PET/BT, karaciğer tümörlerinde daha iyi radyofarmasötik tutulumu ve tespit etkinliği göstermiştir. Ancak mevcut literatürün çoğu, sınırlı hasta sayısıyla yapılan tek merkezli çalışmalarla sınırlıdır. Bu nedenle, karaciğer tümörlerinin değerlendirilmesinde ^{18}F-FDG PET/BT ve ^{68}Ga-FAPI PET/BT'nin birebir karşılaştırmasını gözden geçirip analiz etmeye çalıştık.

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Yöntem: ^{18}F-FDG PET/BT ve ^{68}Ga-FAPI PET/BT'nin tanısal doğruluğunun birebir karşılaştırılması konusunda mevcut literatür, Nisan 2023'e kadar yayınlanmış araştırma makaleleri için PubMed, SCOPUS, EMBASE ve Google Scholar gibi veritabanlarında tarandı. İlgili çalışmalar Tanısal Doğruluk Çalışmalarının Kalite Değerlendirmesi için Gözden Geçirilmiş Araç-2 kontrol listesi kullanılarak seçilmiş ve değerlendirilmiştir. Birleştirilmiş duyarlılığı ve özgüllüğü hesaplamak için rastgele etki modeli kullanıldı. Bunlar %95 güven aralıklarıyla (%95 GA) temsil edildi ve Orman grafiklerinde gösterildi. Çalışmalardaki heterojenliği değerlendirmek için I-kare istatistiği kullanıldı.

Bulgular: Primer karaciğer tümörlerinin tespiti için FAPI PET/BT'nin havuzlanmış duyarlılığı ve özgüllüğü sırasıyla %94,3 (%95 GA: %90,6-96,8) ve %89,3 (%95 GA: %71,8-97,7); ^{18}F-FDG PET/BT'nin havuzlanmış duyarlılığı ve özgüllüğü sırasıyla %56,1 (%95 GA: %49,7-62,5) ve %96,4 (%95 GA: %81,7-99,9) idi. Ekstrahepatik metastatik hastalığın saptanması için havuzlanmış duyarlılık FAPI PET/BT ve ^{18}F-FDG PET/BT için sırasıyla %92,2 (aralık: %88,1-100; %95 GA: %87,8-95,4) ve %72,4 (aralık: 69,8-76,5; %95 GA: %65,9-78,2) idi. Ayrıca, dahil edilen çalışmalarda FAPI PET/BT için maksimum standardize tutulum değeri (SUV_{maks}) ve TBR, ^{18}F-FDG PET/BT'den daha yüksekti.

Sonuç: Genel olarak, FAPI PET/BT, karaciğer tümörlerinin tespitinde ^{18}F-FDG PET/BT'ye göre daha iyi SUV_{maks} ve TBR ile daha yüksek duyarlılık gösterdi.

Anahtar kelimeler: Pozitron emisyon tomografisi/bilgisayarlı tomografi, ^{18}F-florodeoksiglukoz, fibroblast aktivasyon protein inhibitörleri, karaciğer kanserleri, hepatoselüler kanser, kolanjiokarsinom

Introduction

Primary liver tumor comprises of two major histological types of cancers i.e., hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC). HCC arises from the hepatocytes and is the most common type, comprising of ~75 % of all liver tumors. While CC arises from biliary tree with in the liver and is the second most common liver cancer (~12-15% of all liver cancer). Overall, Liver tumors are fairly common and constitutes the 6th most commonly diagnosed cancer worldwide with an incidence of 4.7%. These are aggressive with 5-year survival as low as 18%. Liver cancer is the 4th most common cause of cancer-associated mortality worldwide (1,2).

Liver tumors are usually diagnosed late, especially in countries like India where liver tumor screening is not common with only 13.6-23.7% of cases presenting at stages where curative treatment could be offered (3,4).

Imaging plays a very important role in the evaluation of liver tumors. Unlike other malignancies, liver tumors, especially HCC can be diagnosed non-invasively without biopsy without histopathological confirmation. Diagnostic imaging modalities used in the staging and workup of liver tumors include ultrasonography, contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), and functional/hybrid (functional + anatomical) imaging modalities like ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) and recently introduced ^{68}Ga-fibroblast-activation-protein inhibitor (FAPI) PET/CT (5).

Functional imaging targets physiological functions which are hyper-represented in tumors compared to normal tissues. FDG targets glucose metabolism and enters the cell via GLUT transporters but is not metabolized like glucose and remains trapped in cells while FAPI is an inhibitor of FAP highly expressed on cancer-associated fibroblasts which constitute as high as 90% of gross tumor mass in some malignancies (6,7).

^{18}F-FDG PET/CT is the most commonly used functional imaging and has established its central role in a wide variety of malignant and non-malignant conditions. However, its role in liver tumors is limited mainly due to the presence of glucose-6-phosphatase, high expression of P-glycoprotein, lower expression of GLUT1 or GLUT2 especially in well to moderately-differentiated HCC and high background activity in the liver, thus limiting the FDG avidity of these tumors. Glucose-6-phosphatase present in high concentration in hepatocytes, can dephosphorylate glucose-6-phosphate and FDG-6-phosphate and this FDG then can exit from the cell. These reduces the tumor to background ratios (TBR) for liver tumors (8,9). Liver tumors have high amount of stromal component and desmoplastic reaction and thus, FAPI avidity. This high FAPI avidity together with the low liver background results in better TBRs and sensitivity (6). Recent literature suggests a higher sensitivity of FAPI ~87-100% compared to 65-92% for ^{18}F-FDG PET/CT (10). However, the limited literature available that compared the diagnostic performance of FDG vs. FAPI is mainly from single-center studies with a limited number of patients. Thus, we tried to meta-analyse these studies to highlight the diagnostic performance of ^{18}F-FDG PET/CT vs ^{68}Ga-FAPI PET/CT.

Materials and Methods

We did this meta-analysis by following the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) statement which describes an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses (9). Ethical approval has been taken from the All India Institute of Medical Sciences Bhubaneswar Ethics Committee with approval number T/IM-NF/Nucl. Med/23/19 (date: 15.05.2023). As this is a meta-analysis

of the already published articles and no patient is directly involved, so taking consent is no applicable.

Literature Search Strategy

A comprehensive literature search of PubMed, SCOPUS, Embase and Google Scholar databases was carried out to find relevant published articles performing head-to-head comparison of diagnostic accuracy of ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT in evaluation of hepatic tumors. We used a search string made of following keywords: (1) "^{18}F-FDG PET/CT" or "fluorodeoxyglucose PET" (2) "^{68}Ga-FAPI PET/CT" or "fibroblast activating protein inhibitor" (3) "HCC" or "hepatic tumors" or "hepatocellular carcinoma" or "cholangiocarcinoma" or "liver tumors".

The literature was searched with an upper time bracket up to 26th April 2023 with no lower time bracket or language restriction. Also, relevant references from the retrieved studies were screened for additional articles.

Selection Criteria

Studies fulfilling the following inclusion criteria were included: (a) original studies where both ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT were performed in patients with hepatic tumors; (b) sufficient data to reassess sensitivity and specificity of both ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT in patients with hepatic tumors; (c) appropriate reference standard was used (viz histopathological assessment and/or follow up); (d) the time interval between the ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT ≤10 days.

The exclusion criteria were: a) articles not within the field of interest of this review; b) articles without head-to-head comparison of ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT; c) the time interval between the ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT >10 days; d) review articles, letters or editorials, comments, abstracts presented at conference; e) case reports or small case series (<5 patients), f) data overlap.

Quality Assessment and Data Extraction

The methodological quality of the selected studies was assessed by two investigators independently. Any disagreements were resolved through consultation or intervention by the third reviewer.

Quality of studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool which primarily evaluates the risk of bias in patient selection, index test, reference standard, and the timing and flow of reference test (11).

For each study, following details were extracted: Basic details like first author, year of publication, country of origin, study design (retrospective, prospective); characteristics of study population like gender and age, sample size, and technical aspects (injected activity of ^{18}F-FDG and ^{68}Ga-FAPI, time between injections and image acquisition); reference standard, clinical results or other diagnostic methods used (CT and MRI).

For each study, we tried to extract the number of True Positive, True Negative, False Positive, and False Negative findings for ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT in the staging of hepatic tumors.

Statistical Analysis

We tried to obtain the sensitivity, specificity, from individual studies on a per-patient and per-lesion based analysis. Pooled data was presented with 95% confidence intervals (95% CI) and displayed using forest plots. Heterogeneity was estimated using the I-square index (I^2). The area under the summary receiver operating characteristics curve was calculated to measure the accuracy of these methods.

Results

Literature Search

The primary electronic search of PubMed, SCOPUS, Embase and Google Scholar resulted in 175 relevant articles. Of these, 38 were duplicates. The titles of 137 articles were reviewed, out of which 112 were excluded due to following reasons: (i) not related to the topic (106); (ii) case report (3); (iii) review articles (3). Remaining 25 articles were selected, abstracts of which were reviewed by two reviewers PS and TS. Twenty-five full-text articles were selected for review. After screening the 25 full-text articles, we excluded 16 articles for the following reasons: (i) no head to head comparison was available; (ii) studies which included different types of tumors but data for liver cancer patients was not provided separately; (iii) studies included only patients with tumors negative on ^{18}F-FDG PET/CT; (iv) the time interval between the ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT >10 days. Finally, 9 eligible studies were included in this review. The process of selection of studies in the meta-analysis is depicted in PRISMA flowchart (Figure 1).

Study Characteristics

The basic characteristics of the studies included in the final analysis are summarized in Table 1. A total of 9 studies were analysed, of these 7 studies were prospective while 2 were retrospective. Among the included studies, 3 studies compared the utility of FAPI PET/CT and FDG PET/CT in multiple malignancies. Chen et al. (12) included 75 patients, of which 11 were liver tumors and were included in the meta-analysis. Similarly, Pang et al. (13) included 64 patients with 15 types of malignancies, of which only 12 were liver tumors. While Lan et al. (14) evaluated 123 patients (102 oncologic and 21 non-oncologic), of

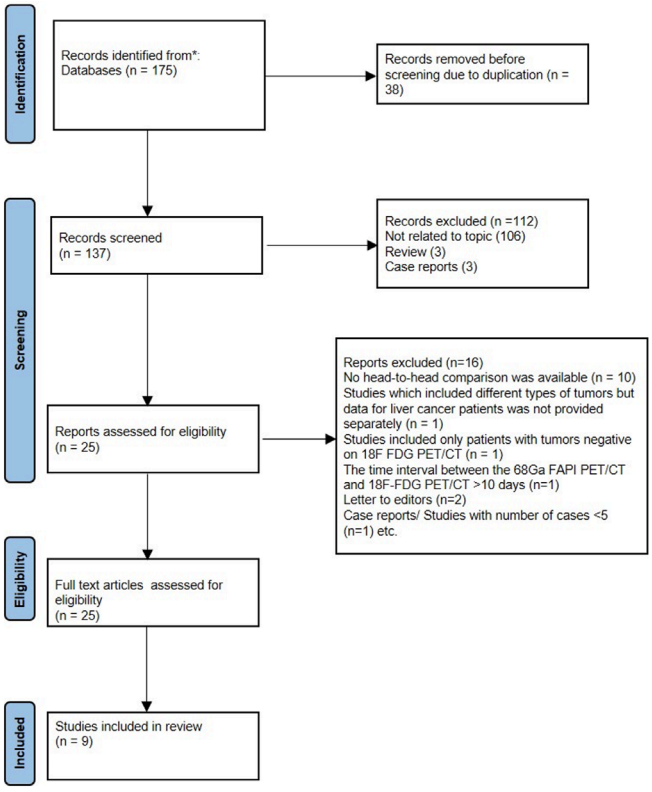

Figure 1. PRISMA flow chart depicting the search for studies on head to head comparison of ^{68}Ga-FAPI and ^{18}F-FDG PET/CT in patients of with liver tumors. Nine studies were selected for final the current meta-analysis FAPI: Fibroblast-activation-protein inhibitors, ^{18}F-FDG: Fluorine-18-fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

which only 16 were liver tumors. The prospective pilot study for dedicated primary HCC was conducted by Shi et al. (15). This study included 20 patients with primary HCC. Following this, Wang et al. (16) and Siripongsatian et al. (17) evaluated the utility of FAPI PET/CT in 25 and 27 liver tumor patients, respectively. Jinghua et al. (18) evaluated 47 patients with biliary tract tumors, of which 9 were excluded from the meta-analysis (5 benign and 4 gallbladder carcinoma) and the remaining 11 were included. Rajaraman et al. (19) evaluated 41 patients with suspected liver tumors, of which 7 had a final diagnosis of non-hepatic malignancies (6 gallbladder carcinoma and 1 peri-ampullary carcinoma) and the remaining 34 were included in the meta-analysis. Similarly, in study by Guo et al. (20) including 34 patients, 2 were benign while 9 had no histological proof, thus only 23 patients were included in the meta-analysis.

All studies used ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT. The technical details of the included studies are given in Table 2. All the included studies performed both qualitative (visual analysis) and semi-quantitative analysis. Semi-quantitative parameters of the included studies are given in Table 3.

Quality Assessment

The quality assessment of the included studies was performed using QUADAS-2 (11). The quality of the included studies is demonstrated in Table 4 and Figure 2, respectively.

Quantitative Analysis (Meta-analysis)

A total of 9 studies were included for the systematic review,

Table 1. Basic characteristics of the studies included in the systematic review

Authors	Year	Country	Study design	No. of patients	Imaging purpose	Blinding	Imaging analysis	Mean age (year)	Diagnostic criteria
Chen et al. (12)	2020	China	P	11	Initial staging, relapsed	yes	V+Q	Median =61.5	Histopathology
Guo et al. (20)	2021	China	P	23	Initial staging	Yes	V+Q	Mean-60.6	Histopathology
Shi et al. (15)	2021	China	P	20	Initial staging	NR	V+Q	Mean-58	Histopathology/ follow-up
Siripongsatian et al. (17)	2022	Thailand	R	27	Initial staging, relapsed	Yes	V+Q	Median =61.5	Follow-up/MRI
Wang et al. (16)	2021	China	R	25	Initial staging	Yes	V+Q	Mean-59.4	Histopathology
Pang et al. (13)	2022	China	P	12	Initial staging, relapsed	No	V+Q	Median =57.5	Histopathology/ follow up
Lan et al. (14)	2021	China	P	16	Initial staging, relapsed	Yes	V+Q	Mean-56.1	CECT/MRI/ follow up
Rajaraman et al. (19)	2023	India	P	34	Initial staging	NR	V+Q	NR	Histopathology/ MRI
Jinghua et al. (18)	2023	China	P	38	Initial staging, relapsed	Yes	V+Q	Mean-59.09	Histopathology/ follow up

FAPI: Fibroblast-activation-protein inhibitors, 18F-FDG: Fluorine-18-fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, NR: Not reported

Table 2. For technical characteristics of the studies included in the systematic review

Author	PET scanner	^{68}Ga-FAPI mean injected dose (MBq)	^{18}F-FDG mean injected dose (MBq)	Time interval between two scans	Scanning scope
Chen et al. (12)	Discovery MI, GE Healthcare	^{68}Ga-FAPI-04 (1.8-2.2 MBq)	^{18}F-FDG (3.7 MBq/kg)	Within 1 week	From the head to the upper thighs
Guo et al. (20)	Discovery MI, GE Healthcare	^{68}Ga-FAPI-04 (148-259 MBq)	^{18}F-FDG (3.7 MBq/kg)	Within 1 week	From the head to the upper thighs
Shi et al. (15)	PoleStar m660, Sinounion Healthcare	68Ga-FAPI-04 (3.59±0.47 MBq/kg)	^{18}F-FDG (3.7 MBq/kg)	Within 3 days	NG
Siripongsatian et al. (17)	64-slice Siemens Biograph vision scanner	^{68}Ga-FAPI-46 (2.59 MBq/kg)	^{18}F-FDG (2.59 MBq/kg)	Within 1 week	NG
Wang et al. (16)	FAPI: mMI510, Union imaging FDG: Biograph mCT Flow scanner, Siemens	^{68}Ga-FAPI-04 (185 MBq)	^{18}F-FDG (NG)	Within 1 day	NG
Pang et al. (13)	Discovery MI, GE Healthcare	Ga-FAP-2286 (1.8-2.2 MBq/kg) Ga-FAP-2286 (dose NG)	288.1±28.4 MBq (227.5-332.4	Within 1 week	NG
Lan et al. (14)	uMI780, United Imaging Healthcare	^{68}Ga-FAPI-04 (1.85 MBq/kg)	^{18}F-FDG (3.7 MBq/kg)	Within 3 days	Skull base to upper thigh + separate head scan
Rajaraman et al. (19)	Discovery DR, GE Healthcare	^{68}Ga-FAPI-04 (185- 370 MBq)	^{18}F-FDG (3.7 MBq/kg)	Within 1 week	NG
Jinghua et al. (18)	NG	^{68}Ga-FAPI-04 (2.04 ± 0.22 MBq/kg)	^{18}F-FDG (3.7±0.19 MBq/kg)	Within 1 week	From the head to the upper thighs

FAPI: Fibroblast-activation-protein inhibitors, ^{18}F-FDG: Fluorine-18-fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, MRI: Magnetic resonance imaging, NG: Not given

Table 3. Semi-quantitative parameters of FAPI PET/CT and 18F FDG PET/CT for the studies included in the systematic review

Study	Tumor	No. of patients	SUV_{max} mean/median		TBR mean/median	
			FAPI	FDG	FAPI	FDG
Chen et al. (12)	HCC + CC	11	Median: 16.18 (7.24-25.97)	3.34 (2.08-10.7)	NR	NR
Guo et al. (20)	HCC	16	Median: 11.47 (4.66-21.03)	4.28 (3.25-10.81)	4.97 (1.05-10.49)	1.16 (0.96-4.21)
	CC	7	Median: 16.51 (8.34-23.21)	4.22 (2.63-11.26)	6.95 (2.15-10.62)	1.49 (0.89-4.41)
Shi et al. (15)	HCC	14	Mean: 8.47±4.06	4.86±3.58	7.13±5.5	2.39±2.21
	CC	3	Mean: 14.14±2.2	9.19±3.6	26.46±4.94	4.42±1.94
Siripongsatian et al. (17)	HCC	7	Median: 9.65 (4.98-18.89)	5.53 (3.37-23.23)	7.9 (2.03-13.54)	1.96 (1.25-6.95)
	CC	12	Median: 19.82 (5.27-30.25)	4.89 (3.38-23.23)	21.08 (3.59- 35.18)	1.47 (0.98-7.74)
Wang et al. (16)	HCC only	25	Mean: 6.96±5.01	5.89±3.38	11.9±8.35	3.14±1.59
Pang et al. (13)	HCC + CC	11	Median: 11.3 (2.5-28.9)	4.8 (3.1-9.7)	5.2 (1.5-9.4)	1.5 (1-3.5)
Lan et al. (14)	HCC + CC	16	Mean: 10.22±5.32	6.16±5.07	NR	NR
Rajaraman et al. (19)	HCC	6	Median: 11.47 (10.8-12.07)	13.4 (8.68-18.12)	2.15 (2.04-2.27)	4.72 (3.53-5.92)
	CC	18	Median: 17.7 (6.54-20.53)	7.26 (4.42-16.3)	7.15 (1.53-21.14)	3.01 (1.86-5.66)
Jinghua et al. (18)	HCC	38	17.25±6.72	10.80±5.22	NR	NR

FAPI: Fibroblast-activation-protein inhibitors, ^{18}F-FDG: Fluorine-18-fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, MRI: Magnetic resonance imaging, NR: Not reported, HCC: Hepatocellular carcinoma, CC: Cholangiocarcinoma, SUV_{max}: Maximum standardized uptake value

however, complete data for quantitative analysis was not available for the included studies. The sensitivity and specificity for primary tumor detection was analysed on per-patient and per lesion basis as well as in terms of different histotypes i.e., HCC and intrahepatic cholangiocellular carcinoma separately. Diagnostic accuracy of FAPI PET/CT and ^{18}F-FDG PET/CT in individual studies is given in Table 5.

For primary liver tumors (staging as well as recurrent tumors), per lesion analysis was performed in 9 studies and overall pooled sensitivity for FAPI PET/CT vs ^{18}F-FDG PET/CT was 94.3% (range: 85.4-100%; 95% CI: 90.6-96.8%; I^2: 62%) and 56.1 (range: 39.0-84.2%; 95% CI: 49.7-62.5%; I^2: 65.8%) respectively (Figure 3). While data for calculation of pooled specificity was available for 5 studies only and revealed a pooled specificity of 89.3% (range: 75-100%, 95% CI: 71.8-97.7%) for FAPI PET/CT and 96.4% (range 87.5-100%; 95% CI: 81.7-99.9%; I^2: 0%) for ^{18}F-FDG PET/CT (Figure 4). The area under the curve (AUC) of ^{68}Ga-FAPI was 0.956 while for ^{18}F-FDG PET/CT was 0.682.

Per patient analysis for pooled sensitivity and specificity could be performed only in 8 and 4 studies, respectively. Sensitivity and specificity for FAPI PET/CT were 98.1% (range: 95.7-100%; 95% CI: 94.6-99.6%; I^2: 0%) and 86.4% (range: 75-100%; 95% CI: 65.1-97.1%; I^2: 0%) (Figure 5A, 5B, 6A, 6B) while for ^{18}F-FDG PET/CT these were 62.9% (range: 45.5-84.2%; 95% CI: 54.9-70.4%; I^2: 56.6%) and 95.5% (range: 87.5-100%; 95% CI: 77.2-99.9%; I^2: 0%) respectively (Figure 5C, 5D, 6C, 6D). The AUC of ^{68}Ga-FAPI was 0.989 while for ^{18}F-FDG PET/CT was 0.702 (Figure 7). The mean difference in the pooled sensitivity was statistically significant (p=0.02).

For evaluation of individual histotypes, only 6 studies provided required information. For HCC patient-based analysis revealed a pooled sensitivity of 98.5% (range: 93.8-100%; 95% CI: 91.7%-100%; I^2: 0%) for FAPI PET/CT and 60.9% (range: 40-75%; 95% CI: 47.9-72.9%; I^2: 0%) for FDG PET/CT (Figure 8). For CC, pooled Sn was 97.6% (range: 94.4-100%; 95% CI: 91.6-99.7%; I^2: 0%) for FAPI PET/CT and 67.5% (range: 40-100%; 95% CI: 56.3-77.4%; I^2: 63.5%) for FDG PET/CT (Figure 9). The per-lesion analysis for the same is given in Figure 10 and 11.

For detection of recurrent tumors, FAPI PET/CT showed much higher pooled sensitivity than ^{18}F-FDG PET/CT. Pooled Sn for FAPI PET/CT was 100% (95% CI: 82.4-100%; I^2: 0%),

Table 4. Quality Assessment of Diagnostic Accuracy Studies-2

Study, year	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Chen et al. (12)	Low	Low	Low	Low	Low	Low	Low
Guo et al. (20)	Low	Low	Low	Low	Low	Low	Low
Shi et al. (15)	Low	Unclear	Low	Low	Low	Unclear	Low
Siripongsatian et al. (17)	Low	Low	Low	Low	Low	Low	Low
Wang et al. (16)	Low	Low	Low	Low	Low	Low	Low
Pang et al. (13)	Low	High	Low	Low	Low	Unclear	Low
Lan et al. (14)	Low	Low	Low	Unclear	Low	Low	Low
Rajaraman et al. (19)	Low	Unclear	Low	Low	Low	Unclear	Low
Jinghua et al. (18)	Low	Low	Low	Low	Low	Low	Low

FAPI: Fibroblast-activation-protein inhibitors, ^{18}F-FDG: Fluorine-18-fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, MRI: Magnetic resonance imaging, NR: Not reported

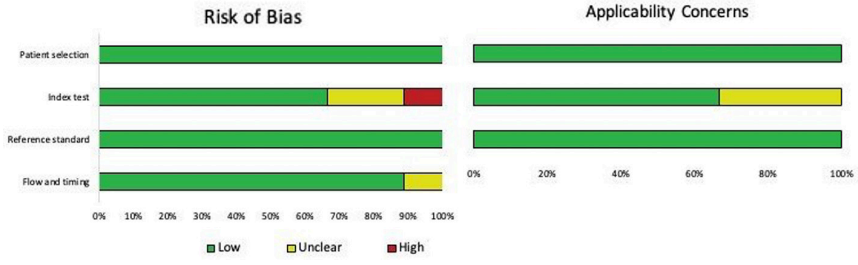

Figure 2. Summary of quality of the studies, risk of bias and applicability concerns of the included studies as per the QUADAS-2
QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies-2

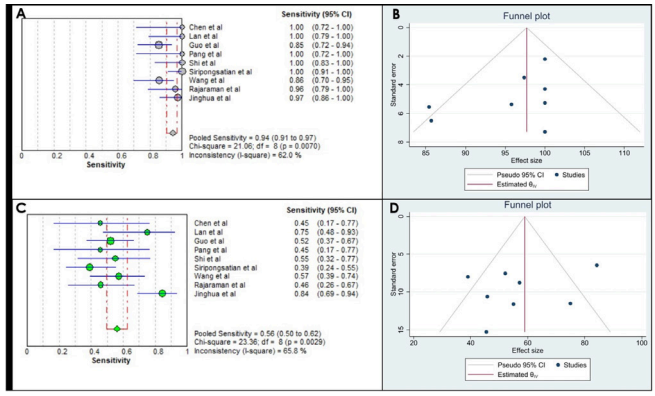

Figure 3. Forest and funnel plots showing pooled sensitivity of FAPI PET/CT (A, B) vs. ^{18}F-FDG PET/CT (C, D) in detection of liver malignancies on per lesion analysis

FAPI: Fibroblast-activation-protein inhibitors, ^{18}F-FDG: Fluorine-18-fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, CI: Confidence interval

Table 5. Diagnostic performance of FAPI PET/CT and ^{18}F-FDG PET/CT in for evaluation of liver tumors

Author	No. of patients	FAPI PET/CT				^{18}F-FDG PET/CT			
		Sensitivity (%)		Specificity (%)		Sensitivity (%)		Specificity (%)	
		Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI
Chen et al. (12)	11	100	71.5-100	NR	NR	45.5	16.7-76.6	NR	NR
Guo et al. (20)	23	95.7	78.1-99.9	NR	NR	65.2	42.7-83.6	NR	NR
Shi et al. (15)	20	100	80.5-100	100	29.2-100	58.8	32.9-81.6	100	29.2-100
Siripongsatian et al. (17)	27	100	82.4-100	75	34.9-96.8	52.6	28.9-75.6	87.5	47.3-99.7
Pang et al. (13)	12	100	71.5-100	100	25-100	45.5	16.7-17.6	100	25-100
Lan et al. (14)	16	100	79.4-100	NR	NR	75	47.6-92.7	NR	NR
Rajaraman et al. (19)	34	95.8	78.9-99.9	90	55.5-99.7	45.8	25.6-67.2	100	69.2-100
Jinghua et al. (18)	38	97.4	86.2-99.9	NR	NR	84.2	68.7-94	NR	NR

FAPI: Fibroblast-activation-protein inhibitors, ^{18}F-FDG: Fluorine-18-fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, CI: Confidence interval

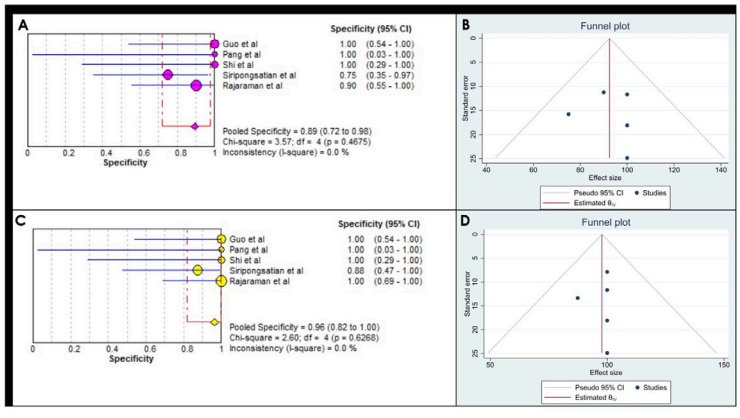

Figure 4. Forest and funnel plots showing pooled specificity of FAPI PET/CT (A, B) vs. ^{18}F-FDG PET/CT (C, D) in detection of liver malignancies on per lesion analysis

FAPI: Fibroblast-activation-protein inhibitors, ^{18}F-FDG: Fluorine-18-fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, CI: Confidence interval

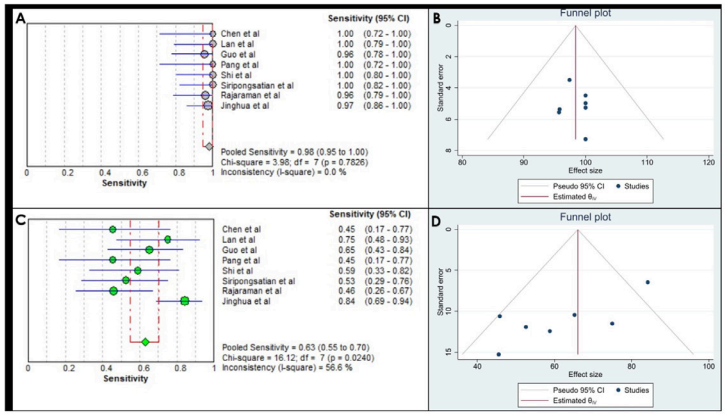

Figure 5. Forest and funnel plots showing pooled sensitivity of FAPI PET/CT (A, B) vs. ^{18}F-FDG PET/CT (C, D) in detection of liver malignancies on per patient analysis

FAPI: Fibroblast-activation-protein inhibitors, ^{18}F-FDG: Fluorine-18-fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, CI: Confidence interval

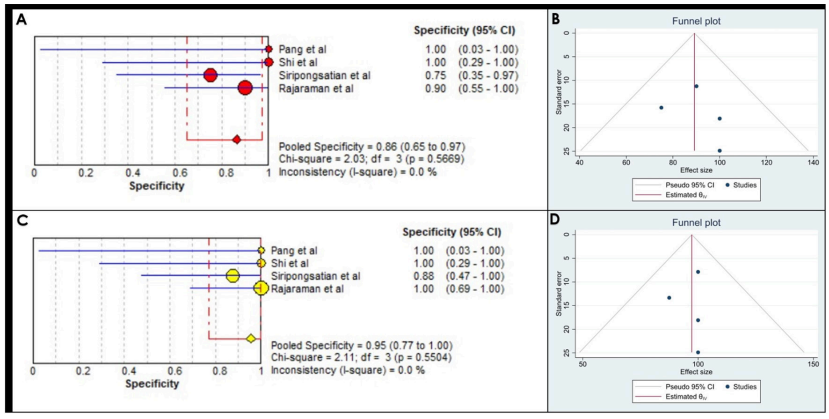

Figure 6. Forest and funnel plots showing pooled specificity of FAPI PET/CT (A, B) vs. ^{18}F-FDG PET/CT (C, D) in detection of liver malignancies on per patient analysis

FAPI: Fibroblast-activation-protein inhibitors, ^{18}F-FDG: Fluorine-18-fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, CI: Confidence interval

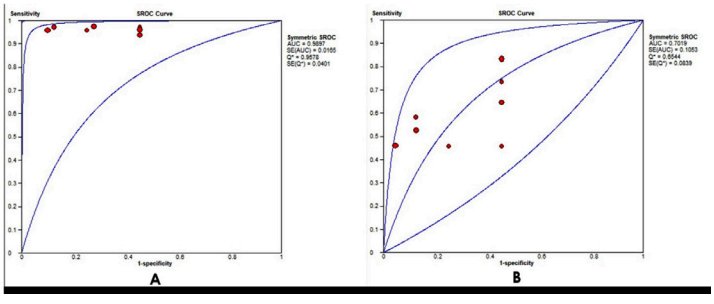

Figure 7. Summary receiver operating characteristics for ^{18}F-FDG (A) and FAPI (B)

FAPI: Fibroblast-activation-protein inhibitors, ^{18}F-FDG: Fluorine-18-fluorodeoxyglucose, ROC: Receiver operating characteristic, AUC: Area under the curve

compared to 32% (95% CI: 13-57%; I^2: 65.2%) for ^{18}F-FDG PET/CT (Figure 12). For primary tumor staging, FAPI PET/CT revealed pooled Sn of 97.7% (range: 95.7-100%; 95% CI: 91.9-99.7%; I^2: 0%) while ^{18}F-FDG PET/CT had pooled Sn of 58.1% (range: 45.8-66.7%; 95% CI: 47.0-68.7%; I^2: 0%) (Figure 13) (Table 6). For detection of extrahepatic metastatic disease, pooled sensitivity could be evaluated only in 3 studies (Table 7). FAPI PET/CT had a pooled Sn of 92.2% (range: 88.1-100%; 95% CI: 87.8-95.4%; I^2: 77.4%) while for FDG PET/CT pooled Sn was 72.4% (range: 69.8-76.5%; 95% CI: 65.9-78.2%; I^2: 0%) (Figure 14).

All the studies included in the meta-analyses have compared the maximum standardized uptake value (SUV_{max}) and/or TBR values of ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT in primary liver tumors. Overall, mean/median SUV_{max} was found to be higher in ^{68}Ga-FAPI PET/CT compared to ^{18}F-FDG PET/CT.

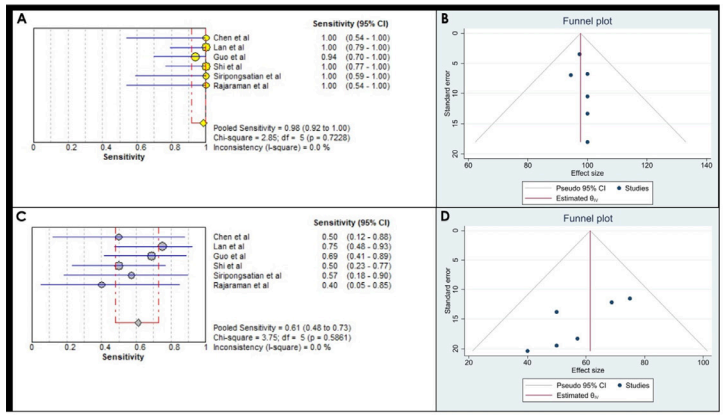

Figure 8. Forest and funnel plots showing pooled sensitivity of FAPI PET/CT (A, B) vs. ^{18}F-FDG PET/CT (C, D) in detection of hepatocellular carcinoma on per patient analysis

FAPI: Fibroblast-activation-protein inhibitors, ^{18}F-FDG: Fluorine-18-fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, CI: Confidence interval

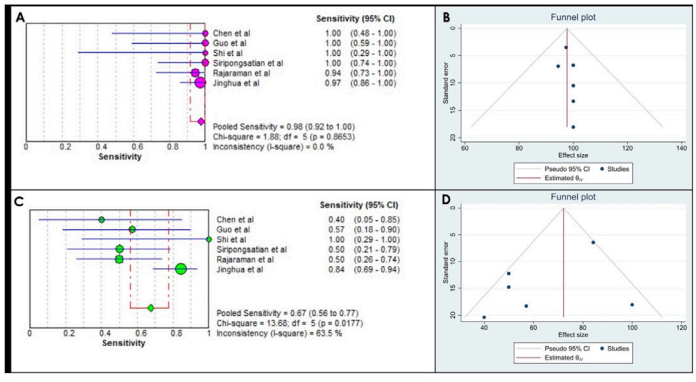

Figure 9. Forest and funnel plots showing pooled sensitivity of FAPI PET/CT (A, B) vs. ^{18}F-FDG PET/CT (C, D) in detection of cholangiocarcinoma on per patient analysis

FAPI: Fibroblast-activation-protein inhibitors, ^{18}F-FDG: Fluorine-18-fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, CI: Confidence interval

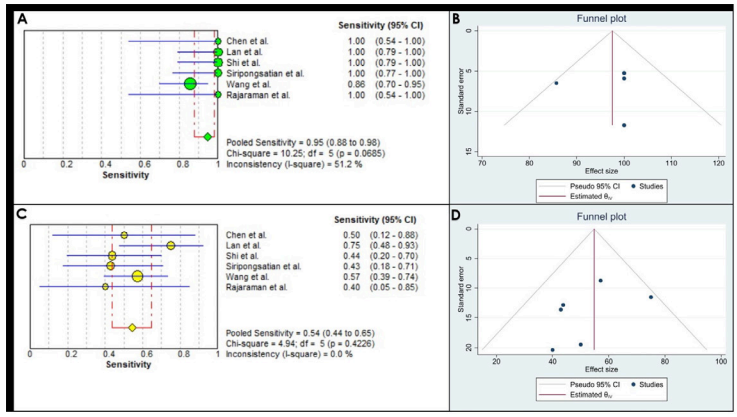

Figure 10. Forest and funnel plots showing pooled sensitivity of FAPI PET/CT (A, B) vs. ^{18}F-FDG PET/CT (C, D) in detection of hepatocellular carcinoma on per lesion analysis

FAPI: Fibroblast-activation-protein inhibitors, ^{18}F-FDG: Fluorine-18-fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, CI: Confidence interval

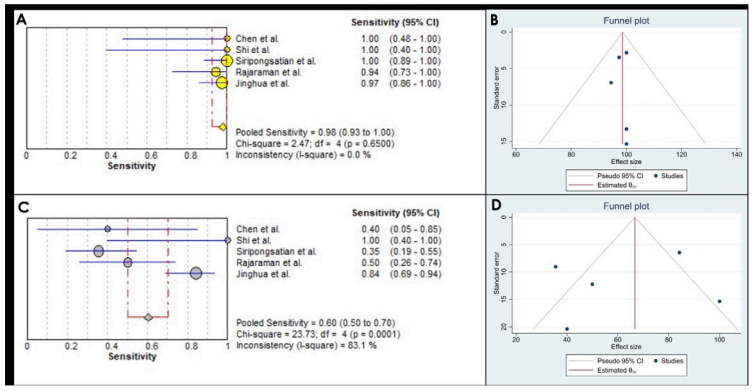

Figure 11. Forest and funnel plots showing pooled sensitivity of FAPI PET/CT (A, B) vs. ^{18}F-FDG PET/CT (C, D) in detection of cholangiocarcinoma on per lesion analysis

FAPI: Fibroblast-activation-protein inhibitors, ^{18}F-FDG: Fluorine-18-fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, CI: Confidence interval

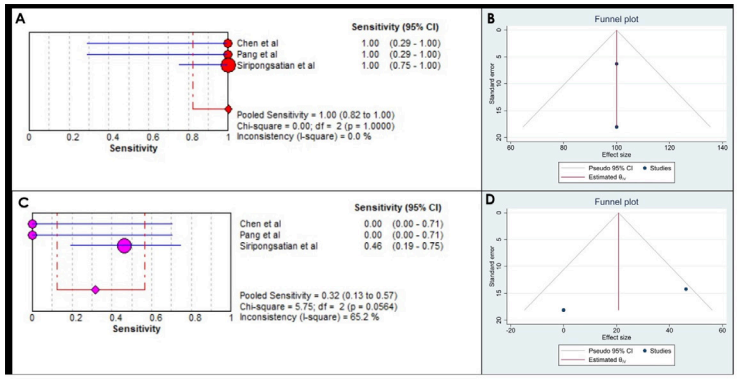

Figure 12. Forest and funnel plots showing pooled sensitivity of FAPI PET/CT (A, B) vs. ^{18}F-FDG PET/CT (C, D) in detection of recurrent liver tumors on per patient analysis

FAPI: Fibroblast-activation-protein inhibitors, ^{18}F-FDG: Fluorine-18-fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, CI: Confidence interval

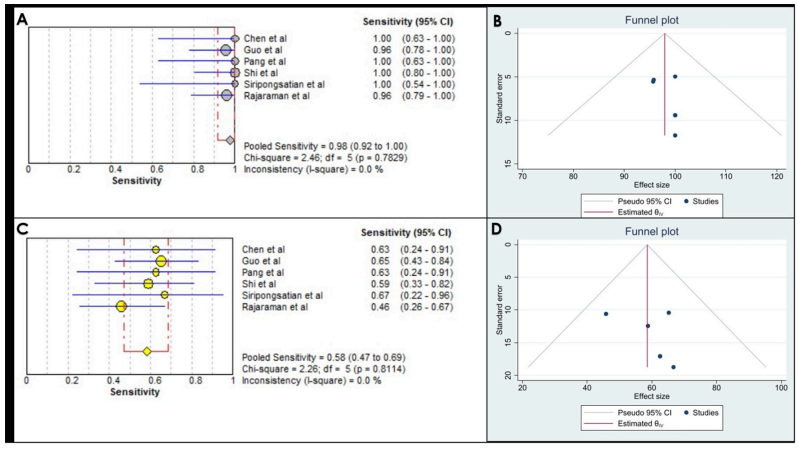

Figure 13. Forest and funnel plots showing pooled sensitivity of FAPI PET/CT (A, B) vs. ^{18}F-FDG PET/CT (C, D) in staging liver malignancies on per patient analysis

FAPI: Fibroblast-activation-protein inhibitors, ^{18}F-FDG: Fluorine-18-fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, CI: Confidence interval

Table 6. Pooled diagnostic sensitivity and specificity of the analysed data						
		No. of studies	FAPI PET/CT	95%CI	^{18}F-FDG PET/CT	95% CI
Per patient analysis	Pooled Sn	8	98.1%	94.6-99.6	62.9%	54.9-70.4
	Pooled Sp	4	86.4%	65.1-97.1	95.5%	77.2-99.9
Per lesion analysis	Pooled Sn	9	94.3%	90.6-96.8	56.1%	49.7-62.5
	Pooled Sp	5	89.3%	71.8-97.7	96.4%	81.7-99.9
Staging	Pooled Sn	6	97.7%	91.9-99.7	58.1%	47-68.7
Recurrent disease	Pooled Sn	3	100%	82.4-100	32%	13-57
HCC per patient	Pooled Sn	6	98.5%	91.7-100	60.9%	47.9-72.9
HCC per lesion	Pooled Sn	6	95%	88.0-98.0	54%	44.0 -65.0
CC per patient	Pooled Sn	6	97.6%	91.6-99.7	67.5%	56.3-77.4
CC per lesion	Pooled Sn	5	98%	93.0-100	60%	50.0-70.0
For extrahepatic metastasis	Pooled Sn	3	92.2%	87.8-95.4	72.4%	65.9-78.2

FAPI: Fibroblast-activation-protein inhibitors, ^{18}F-FDG: Fluorine-18-fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, Sn: Sensitivity, Sp: Specificity, CI: Confidence interval, HCC: Hepatocellular carcinoma, CC: Cholangiocarcinoma

Table 7. Diagnostic performance of FAPI PET/CT and ^{18}F-FDG PET/CT in for evaluation of extrahepatic metastasis					
Author	No. of extrahepatic lesions	FAPI PET/CT Sensitivity (%)		^{18}F- FDG PET/CT Sensitivity (%)	
		Value	95% CI	Value	95% CI
Guo et al. (20)	126	88.1	81.1-93.2	69.8	61-77.7
Shi et al. (15)	17	100	80.5-100	76.5	50.1-93.2
Siripongsatian et al. (17)	74	97.3	90.6-99.7	75.7	64.3-84.9

FAPI: Fibroblast-activation-protein inhibitors, ^{18}F-FDG: Fluorine-^{18}-fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, CI: Confidence interval

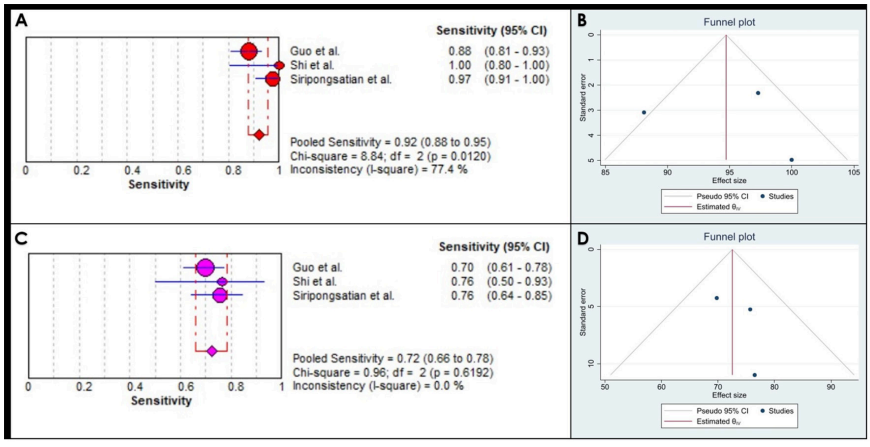

Figure 14. Forest and funnel plots showing pooled sensitivity of FAPI PET/CT (A, B) vs. ^{18}F-FDG PET/CT (C, D) in detection of extrahepatic metastatic disease on per lesion analysis

FAPI: Fibroblast-activation-protein inhibitors, ^{18}F-FDG: Fluorine-18-fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, CI: Confidence interval

However, in study by Rajaraman et al. (19) SUV_{max} when compared among different histotypes, SUV_{max} of HCC was higher for FDG PET/CT than FAPI PET/CT which was in contrast to the rest of the studies. No adverse event to FAPI or FDG PET/CT was reported in any of the included studies. No pharmacological or physiological effects occurred in responses to FAPI administration. None of the articles had declared any conflicts of interest.

Discussion

Liver malignancies represent one of the most common malignancies worldwide. Liver cancers are generally associated with poor prognosis. HCC, the most common liver tumor, carries a 5-year survival and disease-free survival as low as 15.6 and 21.5% respectively (21). The survival depends on the stage at diagnosis with median survival of early, intermediate and advanced stages with preserved hepatic function being ~36, ~16 and ~6 months, respectively (1). Some recent studies have reported improved survival reaching as high as 70% in early stages where curative treatment options are feasible, thereby making early diagnosis and accurate staging utmost important (21).

FDG PET/CT is most common function modality used for oncological imaging. However, it has limited role in detection of primary liver tumors, especially in HCC where sensitivity is 40-68% compared to 68% for CECT (16,22). Similarly, in CC, FDG PET/CT fails to offer any significant advantage over conventional imaging for primary tumor detection. FDG PET/CT is found advantageous mainly in detection of extra-hepatic metastatic disease where it has sensitivity of 77-100% compared to 51.3% for conventional imaging (23). Current meta-analysis revealed a pooled sensitivity of 60.9% (95% CI: 47.9-72.9) for primary HCC and 67.5% (95% CI: 56.3-77.4) for primary CC with an overall sensitivity of 62.9% (95% CI: 54.9-70.4) for all primary liver tumors (12-20). For extrahepatic metastasis, our meta-analysis revealed a sensitivity of 72.4% (95% CI: 65.9-78.2) (12-20). Recent National Comprehensive Cancer Network guideline for hepatobiliary malignancies do not routinely recommend FDG PET/CT owing to its limited sensitivity, however, it is recommended in cases with equivocal findings due to its high specificity and predictive value (24). To overcome these limitations of functional imaging, various strategies have been adopted including use of diagnostic CECT with FDG PET (^{18}F-FDG PET/CECT) and use of novel radiotracers like ^{11}C-acetate, ^{68}Ga-FAPI, ^{8}F-fluorocholine, ^{11}C-choline, ^{68}Ga-labeled asparagine-glycine-arginine etc.

FAPI targets the fibroblast activating protein, a type II transmembrane serine protease, present on cancer associated fibroblasts. These are overexpressed in majority of epithelial tumours as well as in tumors with prominent desmoplastic response like CC. The high expression of FAPs in liver tumors combined with low background liver activity improves the detection rate of liver cancer. FAPI PET/CT has shown sensitivity as high as 100% for detection of primary liver tumors as well as extrahepatic metastasis in some studies (6). In our study, we found a pooled sensitivity of 98.5% (95% CI: 91.7-100) for primary HCC and 97.6% (95% CI: 91.6-99.7) for primary CC with an overall sensitivity of 98.1% (95% CI: 94.6-99.6) for all primary liver tumors. For extrahepatic metastasis, our meta-analysis revealed a sensitivity of 92.2% (95% CI: 87.7-95.4) (12-20).

Recently, Liu et al. performed a meta-analysis comparing the diagnostic performance of FAPI PET/CT and ^{18}F-FDG PET/CT in abdominopelvic malignancies. The authors also found higher primary lesion detection rate of 0.98 (95% CI: 0.95-1.00; I^2 =22.58%, p=0.23) with FAPI PET/CT compared to 0.76 (95% CI: 0.63-0.87; I^2 =82.48%, p=0.00) for FDG PET/CT. Similar to our study, the author found higher sensitivity for detection of metastatic disease with FAPI PET/CT [Sn-0.918 (95% CI: 0.900-0.933; I^2 =98.2%)] compared to FDG PET/CT [Sn-0.714 (95% CI: 0.686-0.741; I^2 =95.1%)] (10). In the current meta-analysis, we also performed per lesion analysis of the pooled sensitivity and specificity for detection of hepatic lesions which revealed a sensitivity of 56.1% (95% CI: 49.7-62.5) for FDG vs. 94.3% (95% CI: 90.6-96.8) for FAPI PET/CT. These findings were in line with the previously published studies.

There are few short-comings associated with this meta-analysis like heterogeneity among the studies, the publication bias and small number of studies available for the subgroup analysis.

Conclusion

Overall, in the present meta-analysis we found a superior sensitivity of FAPI PET/CT compared to FDG PET/CT in both per patient and per lesion analysis of primary liver tumor detection. Also, sub-group analysis revealed superior sensitivity of FAPI PET/CT for detection of both HCC and CC as well as primary staging, recurrence detection and extrahepatic metastatic disease. Thus, ^{68}Ga-FAPI appears promising and can replace FDG PET/CT for staging and work-up of liver tumors. However, FAPI is still in its naive stages and these results need to be further confirmed by larger, multicentric and prospective studies.

Ethics

Ethics Committee Approval: Ethical approval has been taken from the All India Institute of Medical Sciences Bhubaneswar Ethics Committee with approval number T/IM-NF/Nucl. Med/23/19 (date: 15.05.2023).

Informed Consent: As this is a meta-analysis of the already published articles and no patient is directly involved, so taking consent is no applicable.

Authorship Contributions

Concept: P.S., G.K.P., K.A., Design: P.S., G.K.P., Analysis or Interpretation: T.S., G.K.P., K.A., Literature Search: P.S., A.R., Writing: P.S., T.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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