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ORIGINAL ARTICLE

State-of-the-art of FAPI-PET imaging: a systematic review and meta-analysis

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Abstract

Introduction Fibroblast activation protein-α (FAPα) is overexpressed on cancer-associated fibroblasts in approximately 90% of epithelial neoplasms, representing an appealing target for therapeutic and molecular imaging applications. [^{68} Ga] Ga-labelled radiopharmaceuticals—FAP-inhibitors (FAPI)—have been developed for PET. We systematically reviewed and meta-analysed published literature to provide an overview of its clinical role.

Materials and methods The search, limited to January 1st, 2018–March 31st, 2021, was performed on MedLine and Embase databases using all the possible combinations of terms "FAP", "FAPI", "PET/CT", "positron emission tomography", "fibroblast", "cancer-associated fibroblasts", "CAF", "molecular imaging", and "fibroblast imaging". Study quality was assessed using the QUADAS-2 criteria. Patient-based and lesion-based pooled sensitivities/specificities of FAPI PET were computed using a random-effects model directly from the STATA "metaprop" command. Between-study statistical heterogeneity was tested (I^2-statistics).

Results Twenty-three studies were selected for systematic review. Investigations on staging or restaging head and neck cancer ($n=2$, 29 patients), abdominal malignancies ($n=6$, 171 patients), various cancers ($n=2$, 143 patients), and radiation treatment planning ($n=4$, 56 patients) were included in the meta-analysis. On patient-based analysis, pooled sensitivity was 0.99 (95% CI 0.97–1.00) with negligible heterogeneity; pooled specificity was 0.87 (95% CI 0.62–1.00), with negligible heterogeneity. On lesion-based analysis, sensitivity and specificity had high heterogeneity ($I^2=88.56\%$ and $I^2=97.20\%$, respectively). Pooled sensitivity for the primary tumour was 1.00 (95% CI 0.98–1.00) with negligible heterogeneity. Pooled sensitivity/specificity of nodal metastases had high heterogeneity ($I^2=89.18\%$ and $I^2=95.74\%$, respectively). Pooled sensitivity in distant metastases was good (0.93 with 95% CI 0.88–0.97) with negligible heterogeneity.

Conclusions FAPI-PET appears promising, especially in imaging cancers unsuitable for [^{18}F]FDG imaging, particularly primary lesions and distant metastases. However, high-level evidence is needed to define its role, specifically to identify cancer types, non-oncological diseases, and clinical settings for its applications.

Keywords Fibroblast activation protein alpha · FAPI-PET Imaging · Meta-analysis · Systematic review · PET/CT

Martina Sollini and Margarita Kirienko contributed equally to the present work.

This article is part of the Topical Collection on Miscellanea

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Introduction

The tumour microenvironment (TME) is a complex and dynamic framework that plays a crucial role in malignant cells' survival, proliferation, spread, and drug resistance through pro-tumorigenic signalling pathways [1, 2]. This evidence has led to re-focus research and drug development that shifted from the "tumour" to TME elements, which gained interest for potential therapeutic and molecular imaging applications [3, 4].

Among others, cancer-associated fibroblasts (CAFs) have emerged as appealing TME targets. CAFs constitute

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an extremely heterogeneous and plastic cell population, characterised by different origins, functions, and surface markers [4–6]. In particular, fibroblast activation protein-α (FAPα)—a dipeptidyl peptidase—is overexpressed on CAFs' cell membrane and stroma in approximately 90% of epithelial neoplasms [7, 8]. FAPα is also a marker of wound healing and other active extracellular matrix remodelling processes, including liver cirrhosis and myocardial infarction [9–11]. In cancer pathogenesis, FAPα is present on functionally crucial TME stromal cells, contributes to CAFs' tumorigenic effect, and might be associated directly with the malignant phenotype of transformed cells [12, 13], and additionally, tumour cells in osteosarcoma, glioblastoma, and other neoplasms [14, 15].

Therefore, FAPα appears to be a suitable target both for oncological and non-oncological imaging. [^{68} Ga]Ga-labelled radiopharmaceuticals—FAP-inhibitors (FAPI)—have been developed for in vivo positron emission tomography/computed tomography (PET/CT) or PET/magnetic resonance imaging (MRI). [^{68} Ga]Ga-FAPI-02 and [^{68} Ga]Ga-FAPI-04—the most investigated—showed excellent biodistribution properties and a high tumour-to-background ratio [8, 16, 17]. The clinical and scientific interest in [^{68} Ga]Ga-FAPI imaging has shown an explosive increase, as shown by the number of publications and the number of active trials (Fig. 1).

Indeed, in recent years, [^{68} Ga]Ga-FAPI imaging has been explored for various purposes in different clinical settings with promising results. The present work aimed to systematically review and meta-analyse published literature on [^{68} Ga]Ga-FAPI imaging to provide evidence-based indications on the potential role of these tracers.

Materials and methods

Literature search and study selection

Once conceptualised, the project has been registered in PROSPERO (https://www.crd.york.ac.uk/prospero/) (registration number CRD42020222886). The systematic review was carried out following the PRISMA statement (the checklist is available as Supplementary material). A four-step search and evaluation strategy was adopted and executed independently by two reviewers (MS and FF). The first step consisted of identifying sentinel studies within the PubMed database by applying multiple combinations of the following keywords: [^{68} Ga]Ga-FAPI, PET, cancer-associated fibroblasts. In the second step, specific keywords and MeSH terms were defined, as follows: "FAP", "FAPI", "PET/CT", "positron emission tomography", "fibroblast", "cancer-associated fibroblasts", "CAF", "molecular imaging", and "fibroblast imaging". In the third step, the MedLine and Embase databases were searched with all the possible combinations of these terms and the resulting lists of matching manuscripts were exported in.csv format. The search was limited to the January 1st, 2018–March 31st, 2021 period. The application of a starting date was related to the first publication on radiopharmaceutical in 2018 [18]. In the last step, the lists were fused and screened to identify papers describing the use of [^{68} Ga]Ga-FAPI PET in humans.

For article selection, the list was first screened for duplicates, which were removed. Then, the list was screened to identify specific keywords that identified papers outside the scope of the present review, such as "animal", "preclinical", "phantom", "osteomalacia", and "brown fat". These terms were used to highlight papers potentially out of the scope of

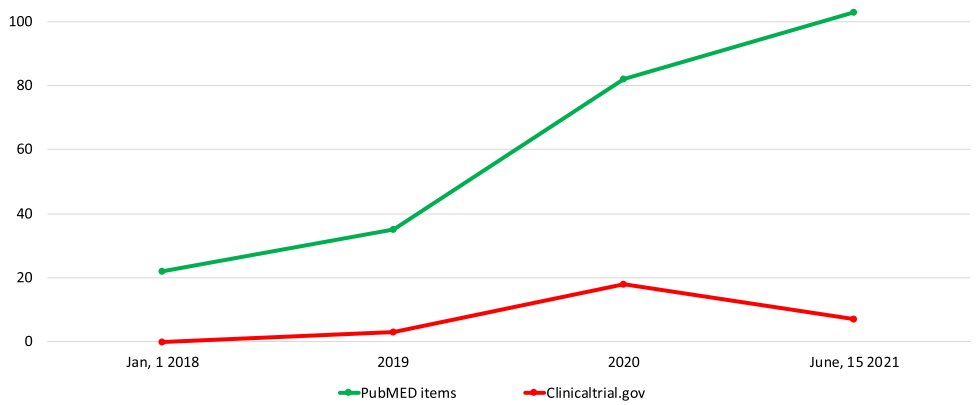

Fig. 1 The number of publications (PubMed) and the number of active trials (ClinicalTrials.gov) on [Ga^{68}]Ga-/[F^{18}]F-FAPI imaging. Search criteria for PubMed were (((((("POSITRON EMISSION TOMOGRAPHY" AND "FAPI") OR ("POSITRON EMISSION TOMOGRAPHY" AND "FAP")) OR ("POSITRON EMISSION TOMOGRAPHY" AND "FIBROBLAST")) OR ("PET/CT" AND "FAPI")) OR ("PET/CT" AND "FAP")) OR ("PET/CT" AND "FIBROBLAST"). Search criteria for ClinicalTrials.gov were "FAPI" OR "Fibroblast PET/CT" OR "FAP PET/CT"

the analysis. Then, the title and the abstracts of these studies were screened to confirm the exclusion.

Subsequently, the following exclusion criteria were defined: (a) full-text not in the English language; (b) out of the scope of the present review and meta-analysis; (c) preclinical studies without translational aspects (i.e. not involving human subjects); (d) phantom, analytical, or simulation studies; (e) single-patient case report; (f) editorials, commentaries, and reviews; (g) conference proceedings. Titles and abstracts of the identified articles were reviewed, applying the exclusion criteria mentioned above, and selected articles were retrieved in full-text. In the case of publications from the same research group/institution that presented significant overlap in terms of aim(s) and population, the study with the largest cohort was included. A reference list of selected articles retrieved in full-text was screened for potentially eligible studies. Additionally, the reference list of case reports, editorials, commentaries, and reviews was screened.

Quality assessment

The quality of each study was assessed independently by two reviewers (MS and FF) using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) criteria [19]. As per the QUADAS-2 scoring design, for the "patient selection", "index test", and "reference standard" domains, the risk of bias and applicability were evaluated, whereas in the "flow and timing" domain, only the risk of bias was assessed.

Based on the signalling questions and the evaluation of the match of the considered paper with the review purpose, we defined both the "risk of bias" and the "applicability" as "unclear", "low", or "high". We assigned 0.5 points in case of an "unclear" score, 1 point in case of "high risk of bias/low applicability", and "zero" in case of "low risk of bias/high applicability". Studies were excluded if they totalled 4 points or more across the seven QUADAS-2 sub-domains. A third reviewer (MK) assessed the paper blinded to previous assessments in case of discordancy, and majority voting was used for the final decision.

Data collection

For each study, we collected the following information: (1) general features (name of the authors, year of publication, journal, country, study design, sample size, funding, conflict of interest), (2) study broad category (oncology, cardiology, immunology) and sub-category (e.g. heart remodelling, GI malignancies), (3) imaging technical aspects (patient preparation, acquisition modality and protocols, injected activity, uptake time, FAPI molecule, radiopharmaceutical/imaging modality used as comparator if any, interpretation criteria), and (4) type of image analysis (qualitative, semi-quantitative, or quantitative); (5) reference standard (pathological, morphological, functional, hybrid), and (6) finally, we collected metrics used to assess [^{68} Ga]Ga-FAPI imaging performance. Detection rate, sensitivity, specificity, and accuracy were recorded or calculated whenever possible (i.e. available number of true/false positive and true/false-negative cases according to reference standard) at a per patient and per lesion level. For studies not strictly dealing with diagnosis, we collected metrics used to evaluate the diagnostic performance of [^{68} Ga]Ga-FAPI imaging according to the specific aim. The corresponding author of the studies was contacted in case of missing data. Data were cross-checked, and any discrepancy was discussed to reach a consensus (MS, FF, and MK).

Statistical analysis

Descriptive statistics and frequency tables were used to summarise data. We classified the papers according to the topic in oncological and non-oncological and then performed the analysis. Because of the objective of the present study, which was to provide evidence-based data on [^{68} Ga]Ga-FAPI-PET imaging, we included in the meta-analysis only those studies (at least three per sub-category) that provided sensitivity and/or specificity or complete data to construct a confusion matrix. Sensitivity, specificity, and their 95% confidence intervals (CIs) were calculated from each study. The upper confidence interval was cropped to 1 [20]. Forest plots of the estimated pooled sensitivities and specificities (with 95% confidence intervals) were created. The weight of each study was calculated from the random-effects model directly from the STATA "metaprop" command [21]. Freeman-Tukey double arcsine transformation was performed to stabilise variances before pooling [21]. Between-study statistical heterogeneity was tested to assess data consistency (the higher the inconsistency, the larger uncertainty in meta-analysis results) using I2 and Cochran's Q homogeneity test. We scored heterogeneity as low, moderate, and high. Heterogeneity may be biased by several factors [22, 23], and no recommendation exists on which value is adequate to go further with the analysis. We fixed as acceptable a low/moderate level of heterogeneity (i.e. $I_2 < 75\%$) [23]. In case of high heterogeneity between studies, other options for data analysis (e.g. sub-groups meta-analysis) were preferred as recommended by Higgins et al. [23]. Per lesion, analysis was further stratified according to the type and/or the disease site (e.g. primary tumour, nodal involvement, and/or distant metastases). Publication and other potential bias were assessed using funnel plots. The Egger method was applied to assess funnel plot asymmetry. A p-value ≤ 0.05 was considered statistically significant. Statistical analyses

were performed using STATA (STATA version 16.1 StataCorp LP, College Station, TX, USA).

Results

Study selection

The search of the PubMed/MEDLINE and EMBASE databases returned a total of 1278 studies. Duplicates' removal eliminated 322 papers. The screening of titles and abstracts applying the criteria mentioned above resulted in selecting 36 papers, which were retrieved in full-text. Two articles, not fulfilling the selection criteria (one case report and one with overlapping population), were excluded after reviewing the full text.

Thirty-four articles were finally assessed for quality (Supplementary Fig. 1), and 23/34 (70%) were assessed as having an acceptable QUADAS-2 score (< 4). Figure 2 details the selection process. Supplementary Table 1 summarises the main characteristics of articles assessed for quality and included in the systematic review.

Systematic review

Twenty-three articles were included in the systematic review analysis. The main issues related to the quality of these studies were related to patient selection and reference standard

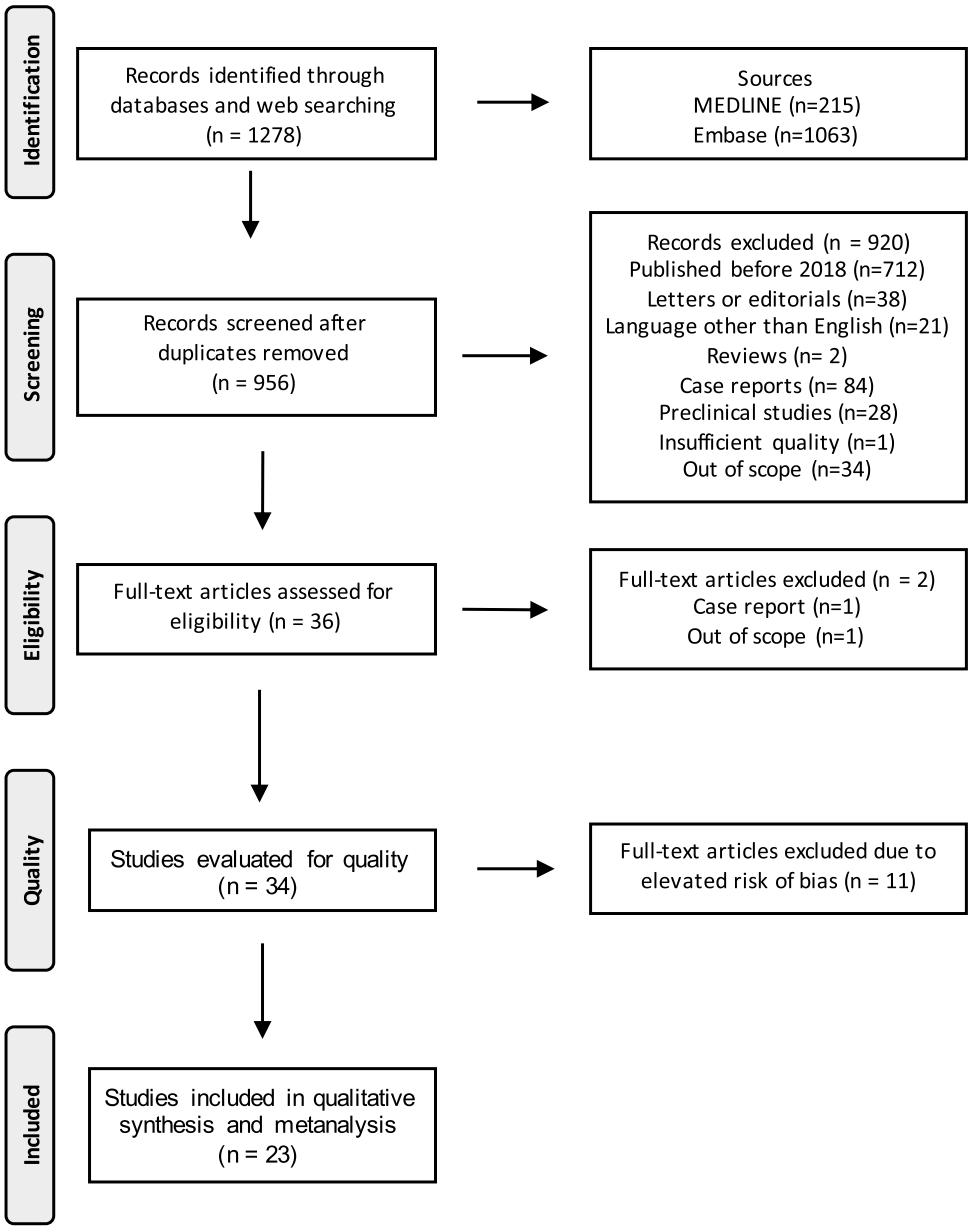

Fig. 2 Paper selection process

(Fig. 3). None of the studies, not even the prospective ones, reported power or sample size justification. One study was designed as a phase I investigation [24]. In 12/23 studies, [^{68} Ga]Ga-FAPI was offered as a compassionate drug according to the German Medicinal Product Act §13(2b) [25–36]. In the remaining 10/23 papers, the trial phase was not specified or designated as "not applicable" [37–46]. Fifteen out of 23 studies (65%) were financed by non-profit organisations [24, 26, 27, 30, 34, 37–40, 42–47]. None of the included studies received funding from industry or private entities. Authors declared a conflict of interest in 14/23 articles (ten related and four unrelated to work, respectively) [25–36, 45, 47]. Conflict of interest related to the work consisted of a patent application for quinoline-based FAP-targeting in 9/10 cases.

Non-oncological studies

Non-oncological studies included six papers (Table 1). Three out of 6 papers were focused on cardiovascular conditions (287 patients), one on systemic sclerosis (21 patients), and the remaining two evaluated patients with IgG-4-related disease (53 patients).

Non-oncological studies focused on cardiovascular diseases Siebermair et al. [25] demonstrated a significant correlation between myocardial [^{68} Ga]Ga-FAPI uptake and coronary artery disease, age, and left ventricular ejection fraction in patients who received [^{68} Ga]Ga-FAPI PET/CT for tumour staging. Heckmann et al. [29] showed a significant correlation between left ventricular [^{68} Ga]Ga-FAPI uptake and elevated thyroid-stimulating hormone (TSH) level (> 4 uU/mL), cardiovascular risk factors (high body mass index and diabetes), history of platinum-based chemotherapies, and previous radiation to the chest in 185 patients suffering from metastasised cancer. Data were confirmed in a validation cohort of 44 patients. Finke et al. [35] found a higher myocardial [^{68} Ga]Ga-FAPI uptake in patients with suspected checkpoint inhibitor-associated myocarditis ($n = 3$) than in those without any signs of cardiac disease ($n = 23$).

Non-oncological studies focused on rheumatological diseases In a case–control study, Bergmann et al. [34] provided evidence about the dynamic process of fibroblast activation in patients with pulmonary fibrosis, suggesting to assess the risk of progression in systemic sclerosis-associated interstitial lung disease by [^{68} Ga]Ga-FAPI PET/CT. Schmidkonz et al. [26] demonstrated, in a cross-sectional clinical study, the possibility of non-invasively tracking the evolutionary pattern of IgG4-related disease—from inflammation towards fibrosis—using a combined approach that included [^{68} Ga]Ga-FAPI and [^{18}F]FDG imaging. [^{68} Ga]Ga-FAPI uptake was not correlated with [^{18}F]FDG pattern, suggesting that inflammation and fibrosis are not necessarily linked. Specifically, fibrotic lesions showed strong [^{68} Ga]Ga-FAPI uptake, which was missing in inflammatory phenomena. Similarly, Luo et al. [24] compared [^{68} Ga]Ga-FAPI and [^{18}F]FDG PET/CT in patients suffering from IgG4-related disease. On a per lesion analysis, [^{68} Ga]Ga-FAPI PET/CT upstaged half of the patients identifying a greater disease burden compared with [^{18}F]FDG, but failed in detecting all nodal lesions (present in 16/26 patients).

Oncological studies

Seventeen studies described the use of FAPI in oncology (Table 2). Ten out of 17 articles focused on tumour staging and/or restaging: in head and neck cancer (2/10 papers, 29 patients), abdominal malignancies (6/10 papers, 171 patients), and a variety of cancers (2/10 papers, 143 patients). Four out of 17 papers were focused on radiation treatment planning (56 patients), and the remaining 3/17 dealt with biodistribution and kinetics (90 patients).[Edit]

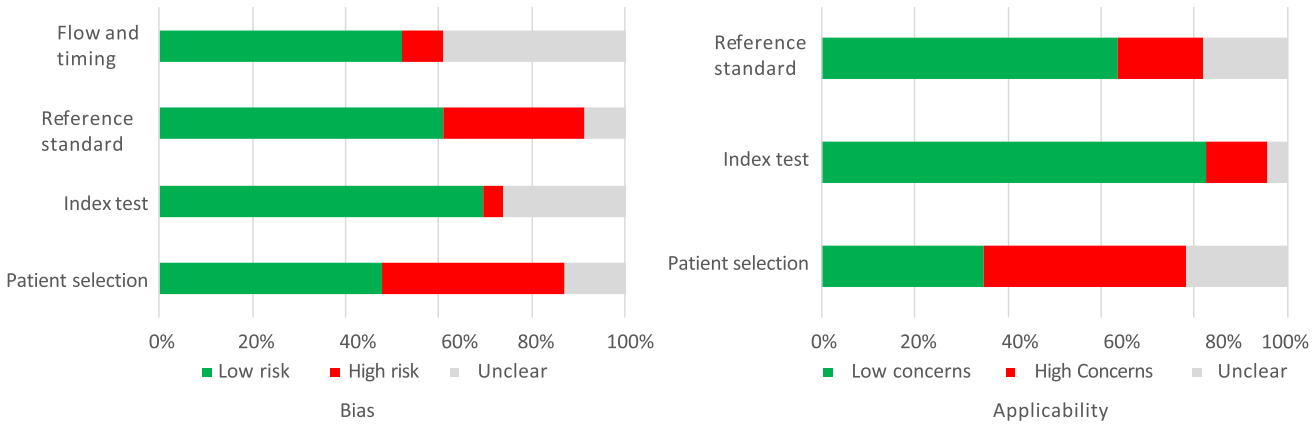

Fig. 3 Quality assessment according to QUADAS-2 of the 23 articles included in the systematic review

Table 1 Main characteristics of non-oncological studies on [^{68} Ga]Ga-FAPI PET imaging included in the systematic review

Reference	Patients, n	Study design	Disease	Molecule	Injected activity (MBq)	Acquisition timing (min)	Image analyses	Reference standard	Comparator	Analysis	[^{68} Ga]Ga-FAPI PET performance	[^{18}F]FDG PET performance
Siebermair et al. [25]	32	R	Myocardial remodelling in CAD	FAPI-04	116–164	12 ± 7	V + S	Clinical data and TTE	-	Per patient	-	-
Heckmann et al. [29]	229	R	Myocardial remodelling in CAD	FAPI-04, FAPI-46, FAPI-21, FAPI-25	122–336	60 (10 and 180 in a subgroup of patients)	V + S	Clinical data	-	Per patient	-	-
Finke et al. [35]	26	R	ICI-associated myocarditis	FAPI-04, FAPI-46, FAPI-21, FAPI-25	122–336	60	V + S	Cardiac catheterization, HP, clinical data and MRI	-	Per patient	3 TP, 23 TN	-
Bergmann C et al. [34]	21	P	Systemic sclerosis-associated ILD	FAPI-04	1.5 MBq/kg	15	V + S	HRCT, clinical data and pulmonary function tests	HRCT	Per lesion	-	-
Schmidkonz et al. [26]	27	P	IgG4-related disease	FAPI-04	116–165	60	V + S	HP, clinical data and MRI	[^{18}F]FDG PET/CT and MRI		NA	
Luo Y et al. [24]	26	P	IgG4-related disease	FAPI-04	55.5–162.8	47–90	V + S	[^{18}F]FDG PET/CT	[^{18}F]FDG PET/CT	Per patient	26/26 TP	24/26 TP, 2/26 TN
										Per lesion	89/107 TP, 18/107 FN	90/107 TP, 17/107 FN

R, retrospective; *P*, prospective; *CAD*, coronary artery disease; *TTE*, trans-thoracic echocardiography; *HP*, histopathology; *DR*, detection rate; *ICI*, immune checkpoint inhibitors; *ILD*, interstitial lung disease; *NA*, not available; *TP*, true positive; *TN*, true negative; *FP*, false positive; *FN*, false negative

Table 2 Main characteristics of oncological studies on [^{68} Ga]Ga-FAPI imaging included in the systematic review

Authors	N. pts	Study design	Tumour type	Clinical setting	Molecule	Injected activity (MBq)	Acquisition timing	Image analyses	Reference standard	Comparator	Analysis	[^{68} Ga]Ga-FAPI PET performance	[^{18}F]FDG PET performance	MRI performance	CT performance
Syed et al. [31]	14	P	H&N cancer	Biodistribution and RT planning	FAPI-02 FAPI-04 FAPI-46	-	30	S	ceCT and MRI	ceCT, MRI	Per patient/ per lesion	T: 14/14 TP	-	-	-
Windisch et al. [28]	13	P	GBM	RT planning	FAPI-02 FAPI-04	150–250	30	S	MRI	MRI	Per patient/ per lesion	T: 14/14 TP	-	T: 14/14 TP	-
Liermann et al. [36]	7	P	Pancreatic carcinoma	RT planning	FAPI-04	NA	40–60	V + S	Imaging (CT)	CeCT	Per patient/ per lesion	T. 7/7 TP	-	-	T. 7/7 TP
Zhao et al. [43]	21	R	Oesophageal cancer	RT planning	FAPI-04	1.8–2.2 MBq/kg	60	V + S	Imaging	ceCT, [^{18}F] FDG PET/ CT, endoscopy	Per patient	21/21 TP	21/21 TP	-	21/21 TP
											Per lesion	T: 21/21 TP	T: 21/21 TP	-	T: 21/21 TP
												N: 25/26 TP, 1/26 FN	N: 20/26 TP, 6/26 FN	-	-
Geist et al. [40]	8	P	Hepatic nodules (ICC, HCC, metastases, benign lesions)	Diagnosis, biodistribution and kinetics	FAPI-04	174–259	60	S	HP	-	Per lesion	-	-	-	-
Shi et al. [45]	17	P	Hepatic nodules (ICC, HCC, metastases)	Staging	FAPI-04	96–260	60	S	HP	ceCT, MRI	Per patient	16/17 TP, 1/17 TN	-	-	-
											Per lesion	T: 27/28 TP, 1/28 TN	-	-	-

Table 2 (continued)

Authors	N. pts	Study design	Tumour type	Clinical setting	Molecule	Injected activity (MBq)	Acquisition timing	Image analyses	Reference standard	Comparator	Analysis	[^{68} Ga]Ga-FAPI PET performance	[^{18}F]FDG PET performance	MRI performance	CT performance
Shi et al. (2)[44]	20	P	Hepatic nodules (ICC, HCC, benign)	Staging	FAPI-04	196–260	40–50	V + S	HP, imaging and clinical FU	[^{18}F]FDG PET/CT	Per patient	17/20 TP, 3/20 TN	7/20 TP, 3, 20 TN, 10/20 FN	-	-
											Per lesion	T: 20/23 TP, 3/23 TN	T: 11/23 TP, 3/23 TN, 9/23 FN	-	-
Guo et al. [46]	34	R	Hepatic nodules (ICC, HCC, benign)	Staging	FAPI-04	148–259	60	V + S	HP and imaging FU	ceCT, MRI, [^{18}F]FDG PET/CT	Per patient	31/34 TP, 2/34 TN, 1/34 FN	-	-	-
											Per lesion	T: 22/25 TP, 2/25 TN, 1/25 FN	T: 15/25 TP, 2/25 TN, 8/25 FN	T: 23/25 TP, 2/25 TN	T: 22/25 TP, 2/25 TN, 1/25 FN
												Intrahepatic lesions: 41/54 TP, 6/54 TN, 7/54 FN	Intrahepatic lesions: 25/54 TP, 6/54 TN, 23/54 FN	Intrahepatic lesions: 48/54 TP, 6/54 TN	-
												N + M: 130/151 TP, 7/151 FP 14/151 FN	N + M: 98/151 TP, 3/151 FP, 50/151 FN	-	-
											Per lesion (HCC)	15/16 TP, 1/16 FN	11/16 TP, 5/16 FN	16/16 TP	15/16 TP, 1/16 FN
											Per lesion (ICC)	7/7 TP	4/7 TP, 3/7 FN	7/7 TP	7/7 TP

Table 2 (continued)

Authors	N. pts	Study design	Tumour type	Clinical setting	Molecule	Injected activity (MBq)	Acquisition timing	Image analyses	Reference standard	Comparator	Analysis	[^{68} Ga]Ga-FAPI PET performance	[^{18}F]FDG PET performance	MRI performance	CT performance
Pang et al. [41]	35	R	GI tract (stomach, duodenum, colorectal)	Staging and restaging	FAPI-04	1.8–2.2 MBq/kg	60	V + S	HP	[^{18}F]FDG PET/CT	Per patient (restaging)	16/16 TP	7/16 TP, 9/16 FN	-	-
											Per lesion	T: 19/19 TP	T: 10/19 TP, 9/19 FN	-	-
												N: 22/84 TP, 46/84 TN, 10/84 FP, 6/84 FN	N: 15/84 TP, 50/84 TN, 6/84 FP, 13/84 FN	-	-
												M: 31/42 TP, 2/42 TN, 5/42 FP, 4/42 FN	M:20/42 TP, 6/42 TN, 1/42 FP, 15/42 FN	-	-
Röhrich et al. [30]	19	R	Pancreatic carcinoma	Staging and restaging	FAPI-04 FAPI-46	150–250	60	V + S	ceCT and clinical FU	CeCT	Per patient	18/19 TP, 1/19 TN	-	-	18/19 TP, 1/19 TN
											Per lesion	T: 18/19 TP, 1/19 TN	-	-	T: 18/19 TP, 1/19 TN
Zhao et al. (2) [38]	46	R	Peritoneal carcinomatosis	Staging and restaging	FAPI-04	1.8–2.2 MBq/kg	60	V + S	HP, clinical data and imaging	[^{18}F]FDG PET/CT	Per patient	42/46 TP, 3/46 TN, 1/46 FN	31/46 TP, 3/46 TN, 12 FN	-	-
											Per lesion (nodular pattern)	115/124 TP, 9/124 FN	49/124 TP, 75/124 FN	-	-

Table 2 (continued)

Authors	N. pts	Study design	Tumour type	Clinical setting	Molecule	Injected activity (MBq)	Acquisition timing	Image analyses	Reference standard	Comparator	Analysis	[^{68} Ga]Ga-FAPI PET performance	[^{18}F]FDG PET performance	MRI performance	CT performance
Chen et al. [42]	68	P	Various cancer	Staging and restaging	FAPI-04	1.8–2.2 MBq/kg	60	V + S	HP, imaging and clinical FU	[^{18}F]FDG PET/CT	Per lesion	T: 19/22 TP, 3/22 FN	-	-	-
												N + M: 72/99 TP, 23/99 FP, 4/99 FN	-	-	-
Chen et al. [37]	75	P	Various cancer	Staging and restaging	FAPI-04	1.8–2.2 MBq/kg	60	V + S	HP	[^{18}F]FDG PET/CT	Per lesion	T: 55/56 TP, 1/56 FN	T: 46/56 TP, 10/56 FN	-	-
												N: 19/39 TP, 10/39 TN, 7/39 FP, 3/39 FN	N: 10/39 TP, 13/39 TN, 4/39 FP, 12/39 FN	-	-
												M: 31/49 TP, 5/49 TN, 7/49 FP, 6/49 FN	M: 22/49 TP, 7/49 TN, 5/49 FP, 15/49 FN	-	-
Ferdinandus et al. [32]	69	R	Various cancer	Diagnosis, biodistribution and kinetics	FAPI-46	58–221	2–34 (early); 57–92 (late)	V + S	Imaging	-	Per lesion (early time-point)	400/400 TP	-	-	-
											Per lesion (late time-point)	398/400 TP, 2/400 FN	-	-	-

Table 2 (continued)

Authors	N. pts	Study design	Tumour type	Clinical setting	Molecule	Injected activity (MBq)	Acquisition timing	Image analyses	Reference standard	Comparator	Analysis	[^{68} Ga]Ga-FAPI PET performance	[^{18}F]FDG PET performance	MRI performance	CT performance
Röhrich et al. [27]	13	R	GBM	Diagnosis, biodistribution and kinetics	FAPI-02 FAPI-04	150–250	30 min (FAPI-04); 10, 60 and 180 (FAPI-02)	S	MRI	MRI	Per lesion	-	-	-	-
Qin C et al., 2021 [39]	15	P	Nasopharyngeal carcinoma	Staging and restaging	FAPI-04	1.85–3.7 MBq/kg	30–60	V + S	Imaging (MRI)	[^{18}F]FDG PET/MRI, MRI	Per lesion	T: 15/15 TP	T: 15/15 TP	-	-
												N: 48/100 TP, 52/100 FN	N: 100/100 TP	-	-
												M: 4/4 TP	M: 4/4 FN	-	-
Serfling S et al., 2020 [33]	8	R	H&N squamous cell carcinoma (Waldeyer's tonsillar ring)	Staging	FAPI-04	260–324	60	V + S	HP	[^{18}F]FDG PET/CT	Per lesion	T: 8/8 TP	T: 8/8 TP	-	-
												N: 9/173 TP, 156/173 TN, 8/173 FN	N: 14/173 TP, 156/173 TN, 3/173 FP	-	-

R, retrospective; *P*, prospective; *V*, visual analyses; *S*, semi-quantitative analyses; *HP*, histopathology; *FU*, follow-up; *GBM*, glioblastoma; *NA*, not available; *GTV*, gross tumour volume; *T*, primary tumour; *N*, lymph node(s); *M*, distant metastases; *TP*, true positive; *TN*, true negative; *FP*, false positive; *FN*, false negative

Oncological studies focused on staging and restaging Qin et al. [39] reported excellent performance of [^{68} Ga]Ga-FAPI, [^{18}F]FDG, and MRI to detect primary nasopharyngeal carcinoma. [^{68} Ga]Ga-FAPI outperformed other imaging modalities to delineate skull base and invasive intracranial disease. [^{18}F]FDG was superior to [^{68} Ga]Ga-FAPI in nodal staging, but as expected, missed skull metastases correctly identified on [^{68} Ga]Ga-FAPI-PET. Serfling et al. [33] demonstrated excellent performance of both [^{68} Ga]Ga-FAPI and [^{18}F]FDG PET/CT to detect primary Waldeyer's tonsillar ring tumour. [^{18}F]FDG was superior to [^{68} Ga]Ga-FAPI in nodal staging. Shi et al. [44] demonstrated the higher sensitivity of [^{68} Ga]Ga-FAPI compared to [^{18}F]FDG PET/CT in patients with suspected primary hepatic tumours. The same group showed excellent results for both [^{68} Ga]Ga-FAPI and MRI in detecting primary liver tumours and metastases [45]. Guo et al. [46] compared [^{68} Ga]Ga-FAPI PET/CT with contrast-enhanced CT (ceCT), MRI, and [^{18}F]FDG-PET/CT in patients with hepatic nodules (hepatocellular carcinoma (HCC) $n=20$, intrahepatic cholangiocarcinoma $n=12$, and benign hepatic nodules $n=2$). MRI resulted as the most accurate technique for intra-hepatic lesion detection. Although [^{68} Ga]Ga-FAPI-04 PET/CT failed in identifying some intrahepatic lesions, it had high sensitivity in diagnosing all malignant lesions—including extrahepatic localisations. Pang et al. [41] compared [^{68} Ga]Ga-FAPI PET/CT with [^{18}F]FDG PET/CT in gastrointestinal malignancies. [^{68} Ga]Ga-FAPI outperformed [^{18}F]FDG in detecting primary tumour, nodal and distant metastases even if it resulted less specific. Röhrich et al. [30] compared the diagnostic performance of [^{68} Ga]Ga-FAPI-PET/CT to ceCT in newly diagnosed or recurrent pancreatic tumour patients. [^{68} Ga]Ga-FAPI PET/CT changed the stage in 10/19 patients. Zhao et al. [38] demonstrated the superiority of [^{68} Ga]Ga-FAPI PET/CT compared with [^{18}F]FDG in the diagnosis of peritoneal carcinomatosis, regardless of the pattern (omental-cake-type and nodular-type). Chen et al. [37] demonstrated the superiority of [^{68} Ga]Ga-FAPI PET/CT in comparison with [^{18}F]FDG in the diagnosis of primary tumours, nodal disease, and distant metastases from various cancers. The same group [42] explored the role of [^{68} Ga]Ga-FAPI PET/CT in patients with negative or inconclusive [^{18}F]FDG findings. [^{68} Ga]Ga-FAPI was highly sensitive but moderately specific, identifying suspicious mass lesions in 12/18 cases, upstaging 7/21 patients, and detecting the primary tumour site and disease recurrence in 4/6 and 20/23 patients, respectively.

Oncological studies focused on radiation treatment planning Windisch et al. [28] compared the gross tumour volume (GTV) delineated on [^{68} Ga]Ga-FAPI with the MRI-based one in glioblastoma patients. The combination of MRI and [^{68} Ga]Ga-FAPI PET findings led to a significant increase of the GTV compared to MRI-based GTV. Similarly, Syed et al. [31] analysed the GTV delineated on [^{68} Ga]Ga-FAPI PET/CT and ceCT in patients with head and neck cancer. The ceCT-GTV resulted smaller than the [^{68} Ga]Ga-FAPI-GTV; in several patients, [^{68} Ga]Ga-FAPI-avid primary tumour areas were included in the [^{68} Ga]Ga-FAPI-GTV but not in the ceCT-GTV. Zhao et al. [43] compared the GTV drawn on [^{68} Ga]Ga-FAPI, [^{18}F]FDG, and ceCT in oesophageal cancer patients. [^{68} Ga]Ga-FAPI- and [^{18}F]FDG-GTV extension was similar to that measured by endoscopy. The favourable tumour-to-background ratio of [^{68} Ga]Ga-FAPI was helpful in delineating the GTV accurately, and when ceCT-GTV was complemented with the information derived from [^{68} Ga]Ga-FAPI and [^{18}F]FDG-PET imaging, size changed in 4/21 and 1/21 cases, respectively. Liermann et al. [36] compared the GTV manually contoured by six radiation oncologists on ceCT to that automatically delineated on [^{68} Ga]Ga-FAPI PET/CT in locally recurrent pancreatic cancer patients. The manual segmentation variability observed among radiation oncologists resulted larger in size and volume geometry with a mean DICE score coefficient ranging between 0.55 and 0.65. On the other hand, the automatically contoured [^{68} Ga]Ga-FAPI-GTV was similar in size to four out of six manually drawn ceCT-GTV, and when reviewing cases, the [^{68} Ga]Ga-FAPI-GTV matched convincingly well the GTV drawn by the six radiation oncologists.

Oncological studies focused on biodistribution and kinetics Röhrich et al. 2020 [27] found a moderately positive correlation between FAP-specific signals and relative cerebral blood volume values, but not with the apparent diffusion coefficient in MRI, suggesting the independence of [^{68} Ga]Ga-FAPI uptake from perfusion and cell density. Geist et al. [40] evaluated through different models the time-activity curves extracted from eight dynamic [^{68} Ga]Ga-FAPI-04 PET/CT to assess the discriminant capability of kinetic parameters in differentiating healthy tissue, HCC, and non-HCC lesions. The findings of this preliminary study suggested a two-compartmental model assess [^{68} Ga]Ga-FAPI kinetics. Ferdinandus et al. [32] compared early (~ 10 min p.i.) and late (~ 60 min p.i.) [^{68} Ga]Ga-FAPI-46 imaging in patients with lesions from various cancers. The two time-point analysis did not show a significant difference in lesion detection ability, even if 2/400 lesions were seen in early images but not in the late ones.

Meta-analysis

We excluded from the meta-analysis articles not focused on oncology and the three studies on biodistribution and kinetics. Finally, 392 patients in 14 studies were included in quantitative analysis (Table 2). Papers were included in the

sub-group analysis according to data availability, as detailed in Supplementary Table 2.

Patient-based performance analysis

Estimated pooled sensitivity and specificity of [^{68} Ga]Ga-FAPI imaging were 0.99 (95% CI 0.97–1.00; $I^2 = 0.00\%$ $p = 0.75$) and 0.87 (95% CI 0.62–1.00; $I^2 = 0.00\%$ $p = 0.51$), respectively (Fig. 4).

Lesion-based performance analysis

Estimated pooled lesion-based sensitivity and specificity of [^{68} Ga]Ga-FAPI imaging were not reliable on a per lesion level (data not shown) since they were affected by high heterogeneity ($I^2 = 88.56\%$ $p = 0.001$ and $I^2 = 97.20\%$ $p = 0.001$, respectively). Funnel plots (Supplementary Fig. 2) suggested data bias, even if this finding was not statistically significant in the funnel plot asymmetry test.

Therefore, we performed separated sub-group analyses to evaluate [^{68} Ga]Ga-FAPI imaging ability to identify the primary tumour and detect nodal involvement and/or distant metastases. Estimated pooled sensitivity for the diagnosis of the primary tumour was 1.00 (95% CI 0.98–1.00; $I^2 = 0.00\%$, $p = 0.83$) (Fig. 5). Estimated pooled sensitivity and specificity of [^{68} Ga]Ga-FAPI imaging to identify non-primary tumour (nodal and distant metastases) lesions (data not shown) were biased by high heterogeneity ($I^2 = 92.66\%$ $p = 0.001$ and $I^2 = 95.20\%$ $p = 0.001$, respectively). In particular, when analysing only nodal status, sensitivity and specificity heterogeneity were as follows: $I^2 = 89.18\%$ $p = 0.001$ and $I^2 = 95.74\%$ $p = 0.001$, respectively. Funnel plots (Supplementary Fig. 3) suggested data bias which emerged statistically significant at funnel plot asymmetry test ($p < 0.0001$). Estimated pooled sensitivity of [^{68} Ga]Ga-FAPI imaging in distant tumour metastases detection resulted 0.93 (95% CI 0.88–0.97; $I^2 = 0.00\%$ $p = 0.41$) (Fig. 6).

The estimated pooled sensitivity/specificity and heterogeneity improved when restricting the analysis to papers focused on abdominal malignancies. Specifically, estimated pooled lesion-based sensitivity and specificity resulted 0.96 (95% CI 0.90–1.00; $I^2 = 68.05\%$ $p = 0.01$) and 0.79 (95% CI 0.62–0.93; $I^2 = 18.20\%$ $p = 0.30$) respectively, as shown in Supplementary Fig. 4. Estimated pooled sensitivity for the primary tumour diagnosis substantially confirmed the findings obtained on all studies (1.00 with 95% CI 0.98–1.00, $I^2 = 0.00$ and %, $p = 0.95$) (Supplementary Fig. 5). Estimated pooled sensitivity for diagnosis of non-primary tumour resulted high (0.87 with 95% CI 0.82–0.92, $I^2 = 22.99$ and %, $p = 0.27$) (Supplementary Fig. 6).

Discussion

[^{68} Ga]Ga-FAPI-PET imaging has opened a new chapter in molecular imaging in oncological and non-oncological diseases, but its clinical role and indications are not fully established yet. Initial studies suggested that [^{68} Ga]Ga-FAPI imaging could replace [^{18}F]FDG-PET scans for oncological and non-oncological indications [48–52]. However, from the present systematic review emerged that, at the current stage, [^{68} Ga]Ga-FAPI does not appear capable to undermine the foundations of [^{18}F]FDG yet. Most of the investigations were focused on moderate-to-low [^{18}F]FDG-avid diseases (Tables 1 and 2), and a considerable proportion of

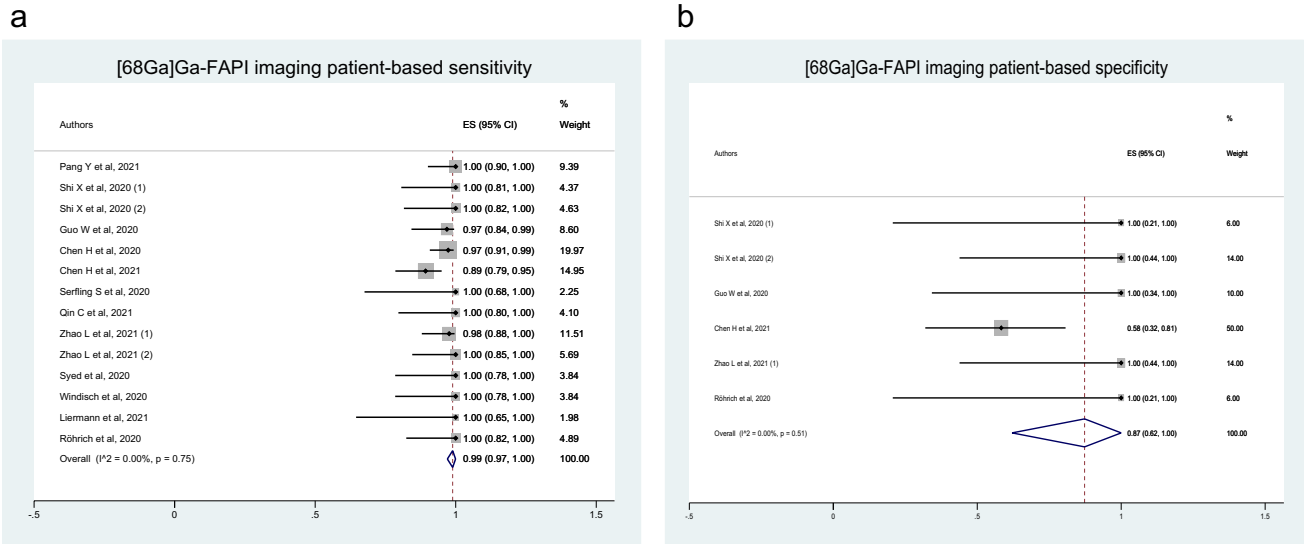

Fig. 4 Estimated pooled sensitivity (panel **a**) and specificity (panel **b**) on patient-based analysis

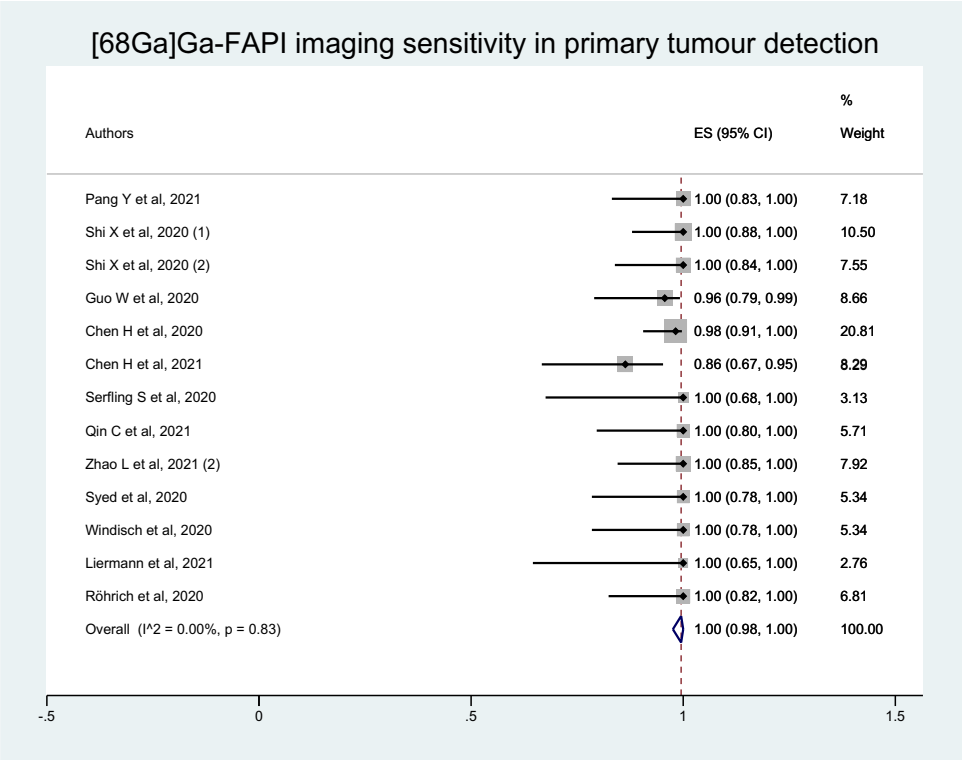

Fig. 5 Estimated pooled sensitivity for the diagnosis of the primary tumour

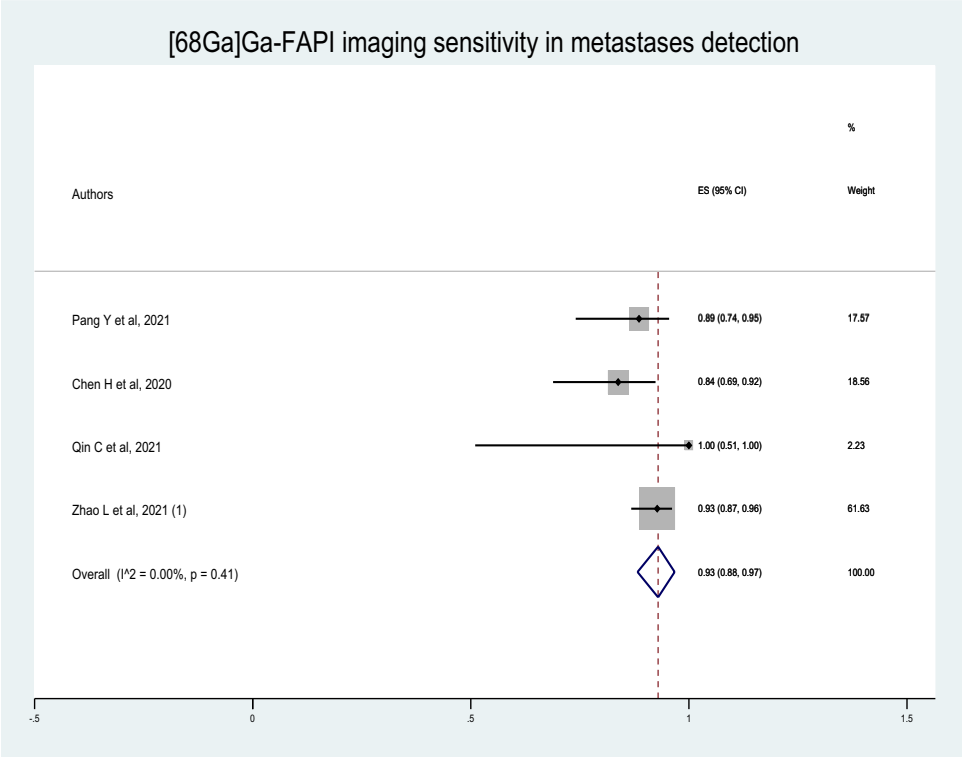

Fig. 6 Estimated pooled sensitivity for distant metastases detection

studies was limited by methodological drawbacks that do not allow to draw definitive conclusions. Still [^{68} Ga]Ga-FAPI PET appears promising in imaging cancers unsuitable for [^{18}F]FDG imaging including: (i) cancers that are well- or moderately differentiated and, thus, present a relatively slow growth and a limited Warburg effect; (ii) tumours

located close to structures/organs with variable physiological/inflammatory/drug-induced uptake, such as liver and gut neoplasms; (iii) tumours in areas with permanently elevated uptake, such as brain and urinary tract malignancies. The first of these categories was explicitly addressed by the studies included in this meta-analysis with excellent results. On the other hand, [^{68} Ga]Ga-FAPI outshone [^{18}F]FDG in the second and third setting [53–56]. The superiority of [^{68} Ga]Ga-FAPI over [^{18}F]FDG was observed in abdominal malignancies in detecting either the primary tumour (96–100% and 53–65%, respectively), or the nodal (79–96% and 54–77%, respectively) and distant metastases (89–93% and 39–57%, respectively). Therefore, [^{68} Ga]Ga-FAPI PET/CT can be successfully used for these purposes (estimated pooled sensitivity of 99% and 92% for the primary and the distant lesions, respectively).

Results in nodal staging were worse than for primary tumour detection. FAPα plays a crucial role in tumour invasion, metastasis, and angiogenesis, and its expression is associated with several factors, including higher local tumour invasion, increased risk of nodal metastases, and poorer outcome [4, 57]. Therefore, the high variability of [^{68} Ga]Ga-FAPI performance in nodal staging assessment (sensitivity 59–100%) could appear unexpected, especially considering that lymph nodes are typically structured by a network constituted by fibroblast reticular cells. However, the exact role(s) exerted by FAPα and FAPα-positive cells in cancer is still to be defined. Evidence suggests a context-dependent functioning and that it is at least in part dictated by tissue-specific environmental cues (i.e. tumour type-specific) [13], as supported by recent data on breast cancer [58] [59]. Moreover, healthy and metastatic lymph nodes are enriched by specific CAFs populations [60]. Notably, two sub-populations (CAF-S1 and CAF-S4) are predominant in lymph nodes invaded by breast tumour. CAF-S1 overexpressed FAPα, while CAF-S4 are characterised by a low to moderate expression of FAPα with significant impact on outcome: CAF-S1 initiates the first steps of epithelial-to-mesenchymal transition and secretes attractive factors for cancer cells. At the same time, CAF-S4 promotes matrix remodelling and cancer cell invasion [60]. Moreover, Serfling et al. [33] suggested a correlation between FAPα lymph node metastases expression and lesion size (weak FAPα expression in lesion < 7 mm, which resulted negative at imaging). Therefore, we can infer that the relatively low performance of [^{68} Ga]Ga-FAPI in detecting nodal metastases reported in some studies may be related to cancer biology and the cell enrichment within lymph nodes. Finally, the radioisotope used for the FAPI labelling could have influenced the resolution, and thus the detectability of smaller tumoural aggregates within the lymph node, given the greater average range in the water of the [^{68} Ga] positron (3.5 mm) compared with that of [^{18}F] (0.6 mm) [61].

Ding et al. [62] demonstrated how the FAPα expression dynamically changed through the different stages of metastasis progression in a breast cancer longitudinal animal model study. In the early stages of tumour metastases development, the sensitivity of [^{68} Ga]Ga-FAPI was higher than [^{18}F]FDG, but with the progress of tumour metastasis, uptake of [^{68} Ga]Ga-FAPI-04 decreased, becoming less sensitive than [^{18}F]FDG.

Data on the role of [^{68} Ga]Ga-FAPI in assessing treatment response are limited [26], especially in patients suffering from tumours [63, 64], preventing the formulation of a clear conclusion. Preclinical data showed that chemo-, immuno-, and/or radiation treatments exert—through different molecular mechanisms and biological pathways—immunogenic, pleiotropic, apoptotic, and tolerogenic effects, finally impacting on FAPα expression [65–69]. Further investigations are necessary to clarify this important topic.

In non-oncological diseases, our findings are in line with those recently published by Windisch et al. [70]. [^{68} Ga]Ga-FAPI imaging suggested new insights on the physiopathology of fibroblasts in acute and chronic heart disease [25]; it could serve as a biomarker, working in synergy with the well-established cardiovascular prognostic risk factors [29], and it might have a role to assess treatment-related cardiotoxicity [35]. In rheumatological studies, [^{68} Ga]Ga-FAPI proved to complement [^{18}F]FDG information targeting fibrosis and inflammation, respectively [24, 26].

However, the [^{68} Ga]Ga-FAPI PET positivity in inflammatory diseases and benign conditions might imply lower specificity for oncological diseases. We excluded case reports from the present systematic review and meta-analysis because of a lower level of evidence. Nonetheless, a wide spectrum of conditions have been described to be positive on [^{68} Ga]Ga-FAPI imaging including infections [71–73], heart disease [74, 75], Crohn's disease [76], Erdheim-Chester disease [77], inflammatory arthritis [64, 78], polymyosytis [79], thyroiditis [80–82], idiopathic retroperitoneal fibrosis [79], renal fibrosis [83], chronic cholecystitis, degenerative osteophyte [84], vertebral body fracture [85], pancreatic pseudocysts, sites of prior pancreatitis, and foci of IgG 4-related disease [86]. This great number of not cancer-related positive sites may represent a challenge for [^{68} Ga]Ga-FAPI imaging and might introduce some limitations in using radionuclide therapy of cancer using FAPα as a target within a theragnostic framework. On the one hand, stromal CAF depletion represents a promising approach to inhibit cancer-supportive functions and disrupt cancer growth [87, 88].

Additionally, stroma barrier alterations induced by radionuclide therapy may foster the effectiveness of other treatments (immunologic, cell-based systemic therapies, radiation or pharmacologic) [89]. On the other hand, cancer may occur in a patient affected by concomitant fibroblast

activating diseases/conditions. Consequently, caution should be made in both diagnostic and therapeutic setting. At image, assessment pitfalls should be identified and proper patient selection for treatment needs to be implemented to prevent possible side effects. Consequently, well-designed studies are needed to clarify the diagnostic performance and safety of FAP-targeted applications.

Although the number of publications focusing on [^{68} Ga]Ga-FAPI and [^{18}F]-FAPI imaging is rising rapidly, the quality of studies is still poor, as proved by our review. From the present meta-analysis emerged that, on a patient-based analysis, [^{68} Ga]Ga-FAPI-PET imaging pooled sensitivity and specificity were high (0.99%, 95% CI 0.97–1.00 and 0.87%, 95% CI 0.62–1.00, respectively). Similarly, on a lesion-based analysis, the pooled sensitivity for diagnosing the primary tumour was extremely high, reaching a value of 1.00 (95% CI 0.98–1.00). However, the estimated pooled sensitivity and specificity of [^{68} Ga]Ga-FAPI PET to detect nodal and distant metastases were biased by high heterogeneity. Notably, the meta-analysis results improved in terms of performance and heterogeneity when we limited the analysis to abdominal malignancies. These findings support the need for well-designed clinical trials [90] to explore the role of [^{68} Ga]Ga-FAPI imaging.

We found that, in approximately 2/3 of the considered studies, at least one co-author declared a conflict of interest, reflecting the growing interest of the pharmaceutical industry in theragnostics. Indeed, the demonstration of the efficacy of [^{177}Lu]Lu-DOTATATE in neuroendocrine neoplasms [91] and of [^{177}Lu]Lu-PSMA-617 in prostate cancer [92] attracted considerable investments in the radiopharmaceutical field [8]. Sponsored trials on FAPα-targeted applications are already ongoing (Fig. 1), and more are expected shortly. Until a few years ago, studies in diagnostic and therapeutic Nuclear Medicine were generally investigator-initiated trials (IIT) rather than industry-sponsored trials (IST) [90]. Consequently, conflict of interest was a much less relevant issue, and we foresee a new research environment soon. A closer industry-academia collaboration may optimise the resources, increase the quality of the studies, and ensure the safety of novel radiopharmaceuticals. Both can contribute to producing high-level evidence and to establishing new recommendations and guidelines. Awareness of the industry interest will enhance the critical appraisal of the investigations. Studies on FAPI-targeted applications are expected to significantly influence clinical practice in the near future [8].

This meta-analysis presents some limitations. Firstly, the relatively small number of published articles in the field is a possible source of bias. Secondly, the sample size and the study design of the studies included in the analysis vastly differed, possibly affecting the reliability of results and preventing the possibility of including all the studies in all sub-group analysis. Thirdly, the study design of papers included in the meta-analysis prevented the estimated pool specificity calculation for both primary tumour and metastases (Tables 1 and 2). Although these aspects may have influenced our results and/or affected statistical power, informative data emerged.

In conclusion, [^{68} Ga]Ga-FAPI-PET imaging opens a new chapter in molecular imaging in oncological and non-oncological diseases. From the meta-analysis, diagnostic performance emerged to be excellent in primary lesions and distant metastasis assessment, while nodal staging was affected by heterogeneity among studies. [^{68} Ga]Ga-FAPI-PET imaging appears promising also for non-oncological indications, in particular cardiovascular and rheumatological diseases. Finally, the role and indications of [^{68} Ga]Ga-FAPI-PET imaging need to be better defined per each disease and clinical setting.

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Author contribution MS, MK and AC conceptualised the project; FF performed literature search; MS, MK, and FF performed articles selection; FG, NG, MS performed the analyses and prepared the figures; NG, FG, FF, MS, MK interpreted the analyses results; MS, FF and MK drafted the paper; NG, FG, and AC critically commented the paper; all the authors critically revised the paper and approved the submitted version of the manuscript.

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Declarations

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