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FAPI-avid nonmalignant PET/CT findings: An expedited systematic review

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Fibroblast activation protein inhibitor (FAPI) is a promising tracer in oncologic positron emission tomography/computed tomography (PET/CT). Numerous studies have demonstrated the superior sensitivity of FAPI PET/CT over fluorodeoxyglucose (FDG) PET/CT in several types of cancer. However, the cancer specificity of FAPI uptake remains understudied, and several cases of false-positive FAPI PET/CT findings have been reported.

A systematic search of PubMed, Embase, and Web of Science was conducted for studies published prior to April 2022 reporting nonmalignant FAPI PET/CT findings. We included original peer-reviewed articles of studies in humans using FAPI tracers radiolabeled with ^{68}Ga or ^{18}F that were published in English. Papers without original data and studies with insufficient information were excluded. Nonmalignant findings were presented on a per-lesion basis and grouped according to the type of organ or tissue involved. The search identified a total of 1.178 papers, of which 108 studies were eligible. Eighty studies were case reports (74%), and the remaining 28 were cohort studies (26%). A total of 2.372 FAPI-avid nonmalignant findings were reported, with the most frequent being uptake in the arteries, e.g., related to plaques (n = 1178, 49%). FAPI uptake was also frequently related to degenerative and traumatic bone and joint lesions (n = 147, 6%) or arthritis (n = 92, 4%). For organs, diffuse or focal uptake was often seen in cases of inflammation, infection, fibrosis, and IgG4-related disease (n = 157, 7%). FAPI-avid inflammatory/reactive lymph nodes (n = 121, 5%) and tuberculosis lesions (n = 51, 2%) have been reported and could prove to be potential pitfalls in cancer staging. Periodontitis (n = 76, 3%), hemorrhoids (n = 47, 2%), and scarring/wound healing (n = 35, 2%) also presented as focal uptake on FAPI PET/CT. The present review provides an overview of the reported FAPI-avid nonmalignant PET/CT findings to date. A large number of benign clinical entities may show FAPI uptake and should be kept in mind when interpreting FAPI PET/CT findings in patients with cancer.

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Background

Fibroblast activation protein (FAP) is a type-II transmembrane proteinase expressed in cancer-associated fibroblasts (CAFs) which constitutes a part of the tumor stroma and influences the tumor microenvironment.[1] The presence of FAP-expressing cancer-associated fibroblasts in tumors has been known for decades in a variety of solid cancer types, especially epithelial carcinomas, and is associated with dissemination and overall reduced survival.[2] In 2018, the first study on a promising radioactive positron emission tomography/computed tomography (PET/CT) tracer targeting FAP was published and introduced fibroblast activation protein inhibitor (FAPI), originally labeled with gallium-68 (^{68}Ga). The first preclinical studies demonstrated FAPI PET/CT to be highly feasible with low physiological uptake and promising diagnostic features in several different cancer entities.[3,4] Multiple comparative studies

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have been conducted since then in different types of cancers, where FAPI PET/CT has generally been superior to ^{18}F-fluorodeoxyglucose (FDG) PET/CT regarding detection rate, sensitivity, standardized uptake values (SUVs), and tumor-to-background ratio.[5,6]

However, there are several limitations to the majority of these studies, in general: the study populations were relatively small, and few studies compared their imaging results to the gold standard of histopathology. Therefore, although the sensitivity of FAPI PET/CT compared to other imaging modalities is reasonably well studied, the cancer specificity and positive predictive values of FAPI-avid PET/CT findings are currently understudied. In addition, FAP is normally not physiologically expressed in noncancer related cells, but FAP expression has been demonstrated in wound healing, arthritis, atherosclerotic plaques, and fibrosis.[7-10] With the increasing number of FAPI PET/CTs performed worldwide, there are consequently rapidly accumulating cases of false-positive FAPI-avid nonmalignant PET/CT findings, but most findings have been published as case reports.[11]

The objective of this review was to evaluate the nature of FAPI-avid nonmalignant PET/CT findings and their relative prevalence, aiming to provide an up-to-date overview relevant for the interpretation of clinical FAPI PET/CT findings.

Materials and Methods

Study Design

This expedited systematic review was compliant with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting systematic reviews.[12] The term "expedited" indicates that some aspects of the systematic review methodology were kept at a minimum. The search, screening, eligibility assessment, and subsequent inclusion processes were performed by one reviewer (M.B.). Data extraction was conducted by two independent reviewers (M.B. and N.A.), and their results were compared. In cases of conflict/disagreements, a third reviewer was included (H.Z.). Data were grouped, and the risk of bias was assessed by one reviewer (M.B.). A synopsis of the review was reported in PROSPERO while screening was performed and before any data extraction took place (CRD42022310911). The "expedited" methodology was chosen due to the high production of studies on FAPI PET/CT and the development of different tracers. A pilot study (not published) was conducted prior to initiation of the feasibility analysis. A flowchart of the search and exclusion and inclusion criteria applied has been produced.

Search Strategy

A literature search was performed in PubMed, Embase, and Web of Science from inception up to 1 April 2022 using the following search string: ([FAPI] OR [fibroblast activation protein inhibitor]) AND ([PET] OR [positron emission tomography]). This broad search strategy was chosen based on our pilot study that revealed a feasible number of studies and few studies with nonmalignant findings reported in the title or abstract. All references were imported into Endnote 20 (Clarivate, London, United Kingdom), and after removal of the duplicates in Endnote 20, the remaining references were uploaded to Covidence (Covidence, Melbourne, Australia) and screened for potential inclusion. We did not contact any authors of any studies without retrievable data or contained insufficient information. In such cases, the studies were excluded due to the expected delay in the process of including these studies, which enabled our expedited review.

Eligibility Criteria

The following inclusion criteria were used: 1. original peer-reviewed published articles, 2. studies using FAPI tracers derived from the Heidelberg group FAPI precursor (e.g., FAPI-02, FAPI-04, FAPI-46, FAPI-74) labeled with either the radioactive isotope gallium-68 (^{68}Ga) or fluorine-18 (^{18}F), 3. studies on FAPI PET/CT in human study subjects, 4. studies in which the FAPI-avid lesions were confirmed with further diagnostics (pathological examination, biochemistry, imaging modalities, etc.) or were reported as certainly benign by the authors, and 5. studies written in English.

Studies were excluded based on the following exclusion criteria upon screening and full text readthroughs: 1. no report of nonmalignant findings, 2. study design without original data (reviews, conference/congress abstracts, editorials, etc.), 3. papers not immediately retrievable (within a time frame of 30 days from an international medical library), and 4. insufficient information regarding reported nonmalignant findings at the patient level. In most cases, the term "insufficient" was applicable in cases with a lack of follow-up/confirmatory diagnostics for a specific lesion or a lack of information regarding FAPI avidity for specific lesions.

Sorting and Data Extraction

References were searched and sorted for eligibility by one reviewer (M.B.). Upon a full text readthrough of only the abstract, the results, discussion, and conclusion sections were read thoroughly. Automate mapping using the search words 'benign' and/or 'false' was used in these cases. The data were extracted by two independent reviewers (M.B. and N.A.). A consensus decision was made in cases of disagreement between M.B. and N.A.; if not, H.Z. was included. The data sought was found in the full text, figures, tables, their corresponding legends, and supplementary data, if provided.

The following data were extracted from the included studies: first author, year, title, tracer of choice, study design, PET/CT scan indication, number of included study subjects, country of conducted study, type of nonmalignant finding, number of nonmalignant findings on a per-lesion basis (if possible), anatomical location of the finding, FAPI SUV levels in nonmalignant lesions, and FDG uptake and SUV levels (in nonmalignant FAPI PET/CT findings).

Data Synthesis and Presentation

The data were synthesized and grouped, and tables were created using Microsoft Excel 365. Only specific findings with a

total of ≥ 3 cases are presented in the text; other findings are available in the tables.

Due to the inhomogeneity of the included studies and with limited information known from our pilot study, a proper meta-analysis was not feasible due to the low quality of the evidence. The findings were grouped according to anatomical location and type of tissue where the nonmalignant findings were discovered. The proportion of major nonmalignant findings was calculated as a percentage of the total amount of reported nonmalignant findings and the number of nonmalignant findings in the respective anatomical/tissue location. Nonmalignant findings were reported on a per-lesion basis; however, in cases

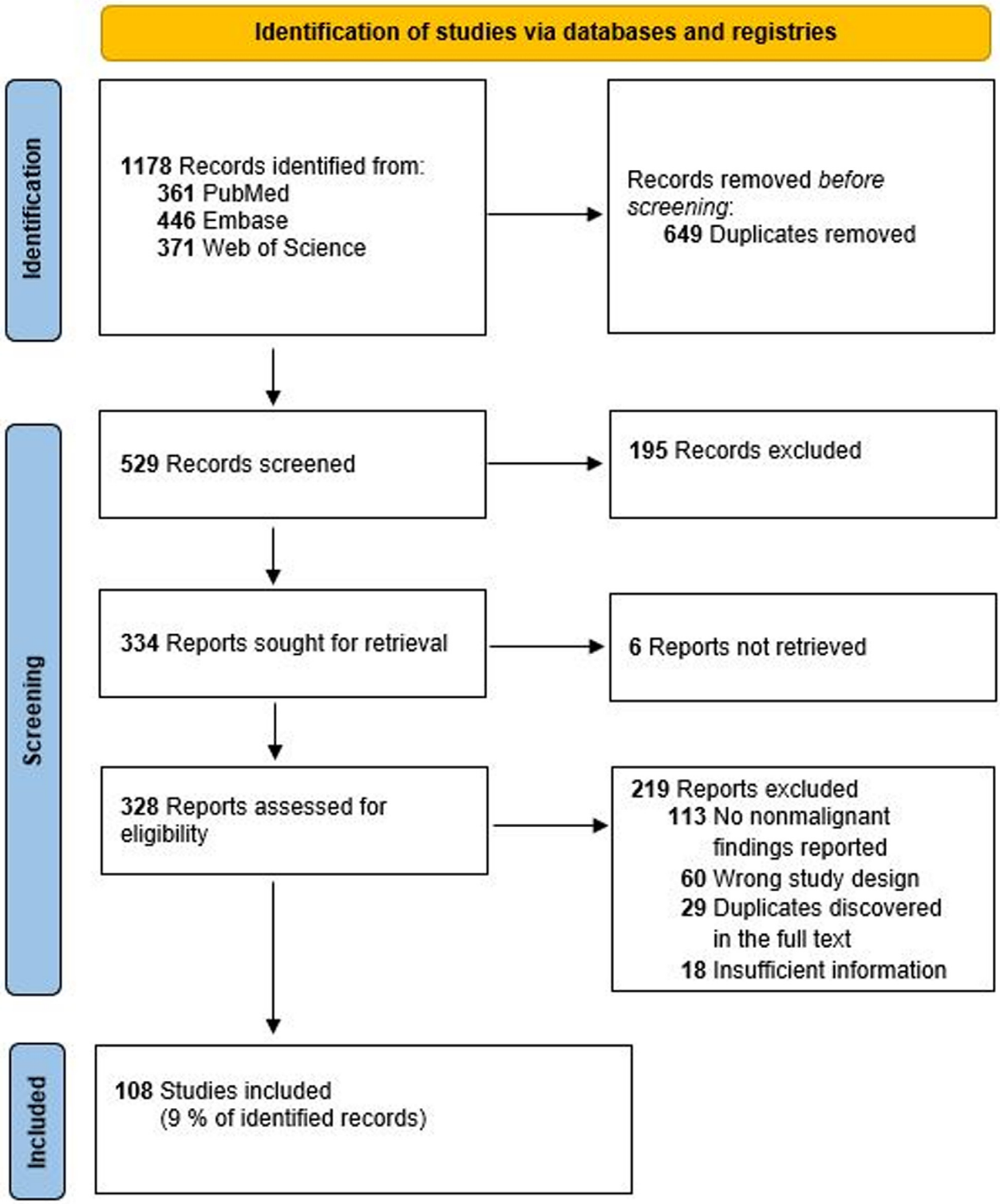

Figure 1 Flowchart of the search strategy and screening process.

Table 1 Study Characteristics

Country	No. Studies	%
China	82	76%
Germany	11	10%
Turkey	6	6%
USA	4	4%
India	1	1%
Thailand	1	1%
The Netherlands	1	1%
Sweden	1	1%
Italy	1	1%
Scan Indication	**No.**	**%**
Cancer	90	83%
Benign condition (trial)/unknown	18	17%
Tracer	**No.**	**%**
^{68}Ga-FAPI-04	50	46%
^{68}Ga-FAPI-46	11	10%
^{68}Ga-FAPI (unspecified)	46	42%
^{18}F-AlF-NOTA-FAPI	1	1%
^{68}Ga-FAPI04 and ^{68}Ga-FAPI46	1	1%

with limited information regarding the specific number of lesions, the lowest number of lesions was reported in our review.

Furthermore, findings consistent with one condition are reported as one finding (e.g., bilateral uptake due to one condition) unless the uptake could theoretically be due to a conflicting condition.

Assessment of Bias

From our pilot study, it was expected that most of the included studies would be case reports or single cases from cohort studies with limited information. Therefore, a thorough risk of bias assessment and quality of evidence assessment were not conducted.

Results

Study Selection

Our search identified a total of 1178 papers. After removing duplicates, irrelevant studies, unretrievable papers, and papers meeting the exclusion criteria, a total of 108 studies were found to be eligible (9%) (flowchart, Fig. 1).

Table 2 Benign Findings Relative to Location in Descending Order

Region of findings	No.
Various/miscellaneous	1432
Bone and joints	458
Head and neck	185
Abdomen and pelvis	150
Thorax	134
Total	*2359*

Study Characteristics and Demographics

Eighty of the included studies were case reports (74%), and the remaining 28 (26%) were cohort studies. A total of 1096 study subjects were included from these studies: 80 from case reports (7%) and 1016 from cohort studies (93%); these patients had a total of 2362 FAP-avid nonmalignant lesions. A complete list of the included studies and their respective findings is provided in the supplementary material.

Most studies were conducted in China (82/108, 76%), Germany (11/82, 11%), and Turkey (6/82, 6%). The majority of the studies included patients with known or highly suspected cancer (90/108, 83%). The remaining studies were conducted as feasibility studies for benign conditions, or the indication for FAPI PET/CT was not mentioned in the paper (18/108, 17%).

^{68}Ga-FAPI-04 was the ligand of choice in almost half of the studies (50/108, 46%). In 45 studies (42%), the FAPI ligand used was not named. In 11 studies (10%), 68Ga-FAPI-46 was utilized (Table 1).

Most studies were published in Clinical Nuclear Medicine (58/108, 54%), followed by the European Journal of Nuclear Medicine and Molecular Imaging (27/108, 25%), Journal of Nuclear Cardiology (5, 5%), and Journal of Nuclear Medicine (4/108, 4%).

Table 3 FAPI-avid Benign PET/CT Findings in the Head and Neck

Head and Neck		
Location	**Pathology**	**No.**
Intracranial	Sinus thrombosis related to neuro-Behcet's disease	6
	Progressive leukoencephalopathy	4
	Intracranial tuberculosis	3
	Pituitary stalk (IgG4 related disease)	1
	All	14
Head and neck	Periodontitis	76
	Dental, salivary glands, nasal mucosa, extraocular muscles	41
	Salivary glands (IgG4 related disease)	5
	Mastoiditis	3
	Graves ophthalmopathy	2
	Granulomatous inflammation of orbital soft tissue	1
	Nasopharynx inflammation (EBV)	1
	Parotitis	1
	Postradiation changes	1
	Postsurgery inflammation	1
	Salivary glands (Sjogren's disease)	1
	Sinonasal inverted papilloma	1
	Tongue amyloidosis	1
	All	*135*
Thyroid	Thyroiditis	34
	Thyroid adenoma	2
	All	*36*
All	*All*	*185*

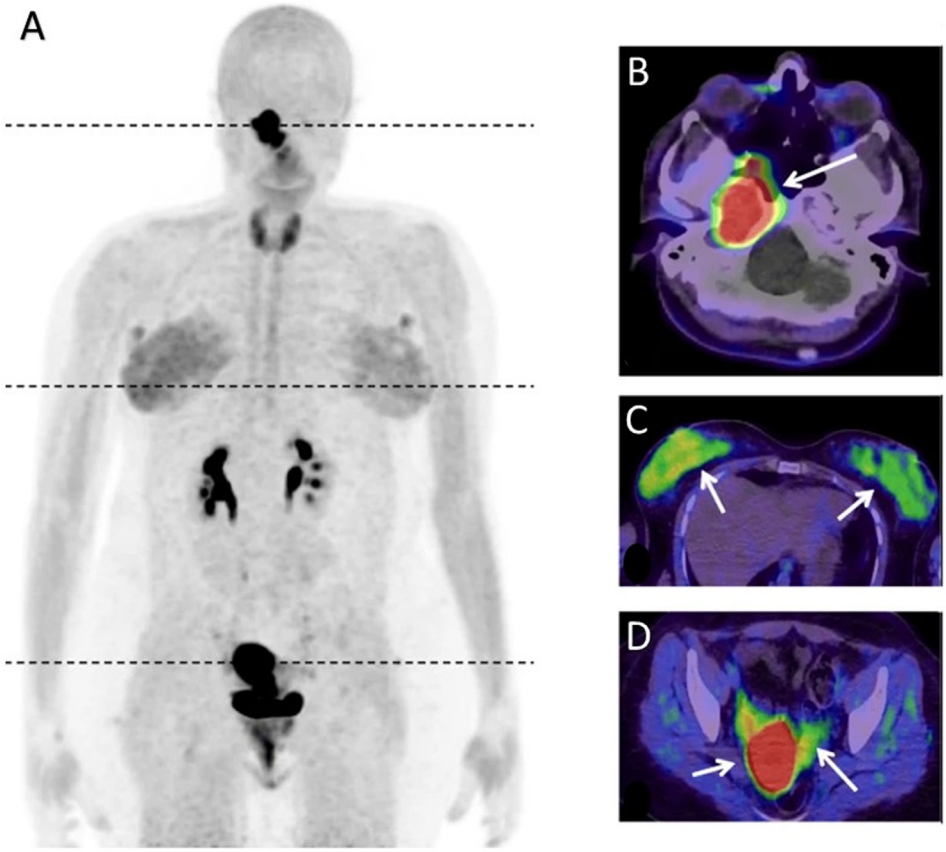

Figure 2 FAPI PET/CT nonmalignant findings in postpartum woman. FAPI PET maximum intensity projection (MIP) (A) of a female patient with known parapharyngeal adenoid cystic carcinoma (SUVmax 17.3) as highlighted in the fused image (B). (C) Increased FAPI uptake is seen in the thyroid gland (SUV 6.3) and in the breast parenchyma (SUVmax of 4.1 in the right and 3.5 in the left). (D) Furthermore, greatly increased FAPI uptake is seen in the endometrium (SUVmax 25.7). The elevated uptake in the thyroid is attributed to postpartum thyroiditis. Uptake in breast parenchyma is hypothesized to be physiological due to lactating breasts or hormone induced, and uptake in the endometrium could be hormone induced or as a result of wound healing. Originally published by Dendl et al.,[28] *Physiological FAP-activation in a postpartum woman observed in oncological FAPI-PET/CT*. Eur J Nucl Med Mol Imaging, 2021. 48(6): p. 2059-2061. https://doi.org/10.1007/s00259-021-05203-8, licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/). Slightly adapted by designating the images differently (from A-D instead of the original A-C for the fused images).

Overview of Benign Lesions

A total of 2.362 FAPI-avid nonmalignant lesions were included in our study, with more than 2000 of the reported lesions being from 5 cohort studies.[13-17] The number of benign findings according to anatomical region is summarized in Table 2. The most common finding was nonspecific uptake in the arteries (n = 1178, 49%), followed by degenerative and/or arthrosis-related lesions (n = 123, 5%), inflammatory lymph nodes (n = 121, 5%), and sites of arthritis (n = 92, 4%), periodontitis (n = 76, 3%), osteoarthritis (58, 2%), and exostosis (n = 54, 2%).

Benign Lesions in the Head and Neck

FAPI has a significantly lower physiological uptake than FDG in the brain, oral mucosa, and parotid glands, but the physiological thyroid FAPI- and FDG-uptake are approximately the same.[18] A total of 185 benign findings were reported in the head and neck region (Table 3).

Benign intracranial lesions with FAPI uptake were reported in the following conditions: sinus thrombosis related to Neuro-Bechet's disease (n = 6),[19] progressive multifocal leukoencephalopathy (n = 4),[20] and intracranial tuberculosis lesions (n = 3).[21]

In the head and neck region, periodontitis was the most frequent finding (n = 76),[14-16,22] followed by thyroiditis (n = 35). The included cases of thyroiditis were mostly seen in relation to Graves' disease and Hashimoto's thyroiditis, but such cases were also seen in patients with postpartum thyroiditis (Fig. 2), follicular thyroid adenomas, and immune checkpoint inhibitor-induced thyroiditis.[17,23-29]

Salivary gland uptake above the physiological level has been described to be related to IgG4-related disease (n = 5),[30-32] but without any well-established definite SUV threshold levels. Increased FAPI uptake was also encountered in mastoiditis (n = 3).[14] Uptake in extraocular muscles could also be seen—with or without coexisting Graves' disease;

however, an analysis of the relative prevalence of orbital FAPI uptake in Graves' disease could not be performed due to insufficient information in the original articles.[16,26,33]

Benign Lesions in the Thoracic Cavity

FAPI exhibits significantly lower physiological uptake in the myocardium and blood pool than FDG.[18]

One hundred thirty-four cases of nonmalignant FAPI uptake have been reported in the thorax (Table 4). A total of 69 lesions were related to the heart, most commonly with diffuse uptake in the right ventricle and right atrium in patients with known pulmonary artery hypertension (n = 34).[34,35] FAPI uptake was also present in patients with post myocardial infarction (n = 15) (Fig. 3) and thermal damage after pulmonary vein isolation (n = 10) and was also observed in patients with myocarditis (n = 3).[36-38] Nonspecific myocardial FAPI uptake also seems to be related to high cardiovascular risk factors and metabolic disease.[39]

Forty-seven FAPI-avid lesions caused by benign conditions were reported in the lung, and most were related to infectious pneumonia (n = 21) and tuberculosis lesions (n = 16).[14,17]

Esophagitis (n = 14) and pleuritis (n = 3) could present with elevated uptake and be potential pitfalls in cancer diagnostics.[14]

Benign Lesions in the Abdomen and Pelvis

In general, the physiologic FAPI uptake level is low in the liver, pancreas, spleen, colon transversum, and kidney cortex and is lower than that observed of FDG.[18]

One hundred fifty benign findings with elevated FAPI uptake on PET were reported in the abdomen and pelvis (Table 5). The most common sites were hemorrhoids (n = 47), followed by intestinal tuberculosis lesions (n = 6).[14,40]

Liver cirrhosis (n = 12) may exhibit diffuse or inhomogeneous FAPI uptake, similar to renal fibrosis (n = 12).[29,41,42] Focal FAPI uptake in liver hemangioma was also reported (n = 3).[17]

However, pancreatitis (n = 15) and IgG4-related disease (n = 6) could be the cause of elevated FAPI uptake in pancreatic tissue (Fig. 4).[14,43]

The uterus has a relatively high level of physiological uptake overlapping with malignancies, especially in premenopausal women, which may be a result of angiogenesis, tissue remodeling, and fibrogenesis of the uterus (Fig. 2).[44] In men, elevated FAPI uptake has been reported in cases of prostatitis (n = 5).[14]

Benign Lesions in Bone and Joints

FAPI uptake has frequently been encountered in degenerative bone and joint lesions (n = 114), exostoses (n = 54), fractures (n = 33), osteofibrous dysplasia (n = 13), degenerative osteophytes (n = 10), Schmorl nodes (n = 8), fibrous dysplasia (n = 6), and tuberculosis lesions (n = 6).[14-17,45-47]

FAPI uptake has also been reported in joints affected by arthritis (n = 92) (Fig. 5), osteoarthritis (n = 59), and inflammatory or trauma-related lesions (n = 51) (Table 6).[14-16,48]

Table 4 FAPI-Avid Nonmalignant PET/CT Findings in the Thorax

Thorax		
Location	**Pathology**	**No.**
Heart	Pulmonary arterial hypertension	34
	Postmyocardial infarction	15
	Thermal damage after pulmonary vein isolation	10
	Myocarditis	3
	Hypertensive heart disease	2
	Cardiac amyloidosis	1
	Pericardium (IgG4-related disease)	1
	Cardiac sarcoidosis	1
	Coronary atherosclerotic plaque	1
	Ischemic myocardium	1
	All	*69*
Lung	Pneumonia	21
	Pulmonary tuberculosis	16
	Silicosis nodules	2
	Inflammatory granuloma	1
	Solitary benign fibrous tumor	1
	Lung uptake (IgG4-related disease)	1
	Benign teratoma	1
	Post COVID-19 sequela	1
	Pneumonitis	1
	Pulmonary fibrosis	1
	Lung dystelectasis	1
	All	*47*
Esophagus	Esophagitis	14
	All	*14*
Pleura	Pleuritis	3
	Pleura (IgG4-related disease)	1
	All	*4*
All	*All*	*134*

Miscellaneous Benign Lesions in Various or Otherwise Unspecified Regions

The physiological uptake of FAPI in fat tissues is lower than that of FDG, and skeletal muscles generally have low FAPI uptake but higher SUVs than FDG PET/CT.[18]

Unspecified arterial wall uptake with a low SUV was the single most frequently encountered benign FAPI PET/CT finding (n = 1178) overall (Table 7).[13] Another cause of arterial FAPI uptake was Takayasu arteritis (n = 6).[49]

Unspecific FAPI uptake in the muscle was the most common finding in patients with muscle-related disorders (n = 26), but FAPI uptake can also be seen in patients with enthesopathy (n = 8), dermatomyositis (n = 5), juvenile polymyositis (n = 5), and tendinopathy (n = 3).[14,16,22,50] Dermatomyositis has also shown elevated FAPI uptake in the skin.[51]

Inflammatory, reactive, or tuberculosis lymph nodes frequently presented with FAPI uptake (n = 126).[14,17] Similarly, scarring and wound healing often led to FAPI uptake (n = 34).[14,16] Physiological, diffuse uptake in the breasts was frequently encountered (n = 15) and seemed to depend on hormonal status (Fig. 2).[16,28]

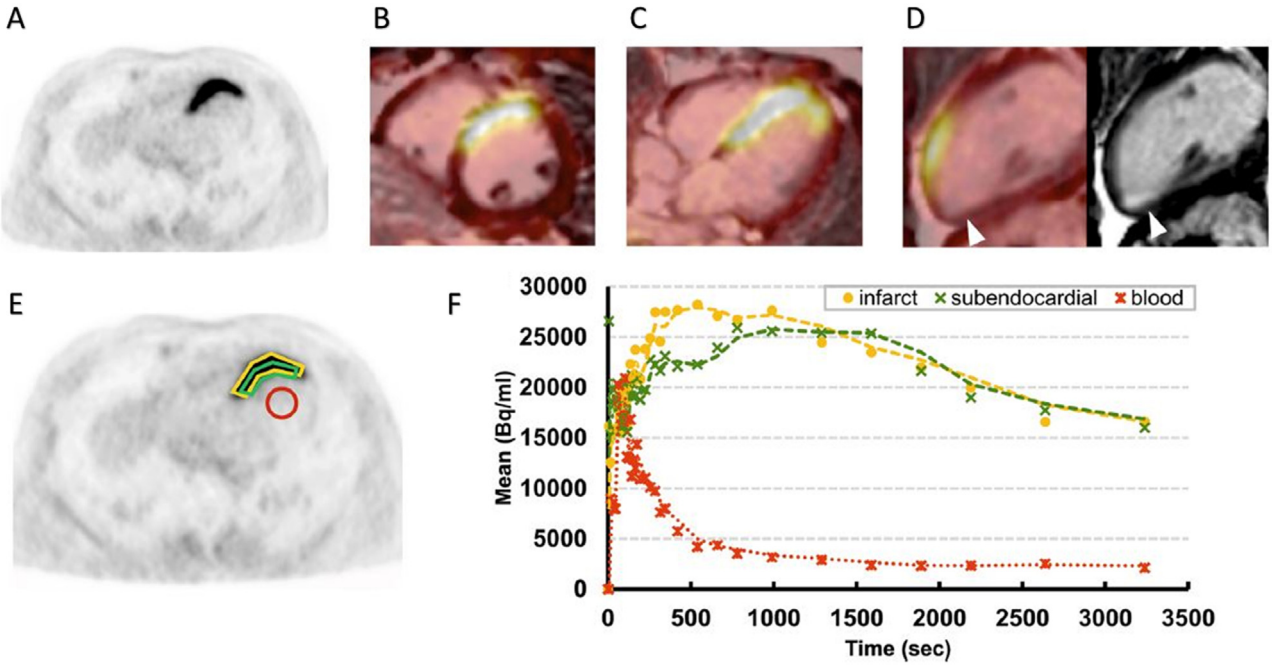

Figure 3 FAPI PET/CT post myocardial infarction. FAPI-04 PET/magnetic resonance imaging (MR) in a patient 6 days after acute ST-elevation (in V1-V4) myocardial infarction (STEMI) in left anterior descending artery (LAD) territory. Intense FAPI-uptake can be seen in the anterior and anterior septal wall: Axial PET (A), short axis PET/MR (B), horizontal long axis PET/MR (C), vertical long axis PET/MR and, MR (D). Examples of ROI placement for dynamic analysis (E) and the corresponding time-activity curve (F). Originally published by Notohamiprodjo, S., et al.[67] *Imaging of cardiac fibroblast activation in a patient after acute myocardial infarction using Ga-68-FAPI-04.* Journal of Nuclear Cardiology, https://doi-org.auh.aub.aau.dk/10.1007/s12350-021-02603-z, licensed under Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Discussion

A full systematic investigation of FAPI-avid nonmalignant lesions is highly relevant, as FAPI PET/CT is rapidly being implemented in both research and clinical settings throughout the world. Knowledge of the pitfalls of FAPI PET/CT, common findings and physiological FAPI uptake is mandatory to properly interpret the imaging findings, but these topics have not been fully investigated. To date, new case reports on benign FAPI PET/CT findings have been published every month along with a few cohort studies reporting benign FAPI PET uptake in specific organs. The present systematic review is the first to systematically present cumulative evidence of FAPI uptake in benign conditions.

Overall, 2362 benign lesions with FAPI uptake in 1096 patients were reported, and focal FAPI uptake in the arterial wall was the most frequent finding. However, it should be noted that all arterial lesions originated from one feasibility study investigating FAP expression in arterial walls with FAPI PET/CT. The SUV levels of the reported findings were low, and no strict cutoff values were presented.[13] The arterial wall findings were included as they presented as focal uptake, and it has been speculated whether FAPI PET/CT could prove to be of value when evaluating if arterial plaques are vulnerable or stable,[52] but these findings do not seem to represent pitfalls in interpreting FAPI PET findings in patients with cancer.

The second most common site of benign FAPI uptake was degenerative bone and joint lesions and fractures. Such findings are important to recognize when evaluating potential bone metastases or sarcomas. Several studies have shown FAPI PET/CT to be superior to FDG PET/CT in the evaluation of bone metastases; however, in many cases, the SUV levels of malignancies overlap with those of benign lesions.[15,53,54]

With the low physiological FAPI uptake in the brain, FAPI PET/CT could be useful in the diagnosis of brain metastases.[55] However, care should be taken in interpreting such findings, as both sinus thrombosis and intracranial tuberculosis may exhibit FAPI avidity.[19,21]

Recent studies in lung cancer seem to indicate that FAPI PET/CT is slightly superior to FDG PET/CT regarding metastases[56,57] However, it was shown that infectious diseases have overlapping SUV levels with malignancies, which could prove to be a pitfall, especially in cases of organizing pneumonia and tuberculosis.[14,58] FAPI shows diffusely elevated uptake correlating with the severity of fibrotic interstitial lung disease and could, in the future, be a potential prognostic and response monitoring marker for interstitial lung disease.[59] Due to its low physiological uptake in normal hearts compared to FDG, FAPI PET/CT could improve the evaluation of possible cardiac metastases in cancer.[60] Interestingly, our search revealed several cases of diffuse FAPI uptake in the strained right myocardium in relation to that in

Table 5 FAPI-Avid Nonmalignant PET/CT Findings in the Abdomen and Pelvis

Abdomen and Pelvis		
Location	**Pathology**	**No.**
Liver	Cirrhosis	12
	Liver hemangioma	3
	Liver fibrosis	3
	Focal nodular hyperplasia in liver	2
	Liver tuberculosis	1
	Liver (IgG4-related disease)	1
	Sclerosing cholangitis (IgG4-related disease)	1
	Benign liver nodules	1
	Bile ducts (IgG4-related disease)	1
	Hepatic angiomyolipoma	1
	Inflammatory nodules in the liver	1
	Liver abscess	1
	Portal biliopathy secondary to cavernous transformation of the portal vein	1
	All	*29*
Pancreas	Pancreatitis	15
	Pancreas (IgG4-related disease)	6
	Pseudopapillary tumor	1
	Pancreatic cystadenoma	1
	Pancreatic tuberculosis	1
	Pancreatic pseudocyst	1
	Localized pancreatic inflammation	1
	All	*26*
Kidney	Renal fibrosis	15
	Renal angiomyolipoma	2
	Kidney tuberculosis	1
	All	*18*
Spleen	Splenic hemangioma	2
	Hypersplenism	1
	Splenic tuberculosis	1
	All	*4*
GI tract	Hemorrhoid	47
	Intestinal tuberculosis	6
	Appendicitis	2
	Post chemotherapy fibrosis and inflammation	1
	Crohn's disease	1
	Chronic colitis	1
	All	*58*
Uterus	Uterus (postpartum)	1
	Uterine myoma	1
	Uterine fibroma	1
	All	*3*
Prostate	Prostatitis	5
	Prostate (IgG4-related disease)	1
	All	*6*
Abdomen	Mesenteric myofibroblastic tumor	1
	Idiopathic retroperitoneal fibrosis (mass)	1
	Renal angiomyolipoma	1
	Peritoneal tuberculosis	1
	All	*4*
Pelvis	Myxopapillary ependymoma	1
	Schwannoma	1
	All	*2*
All	*All*	*150*

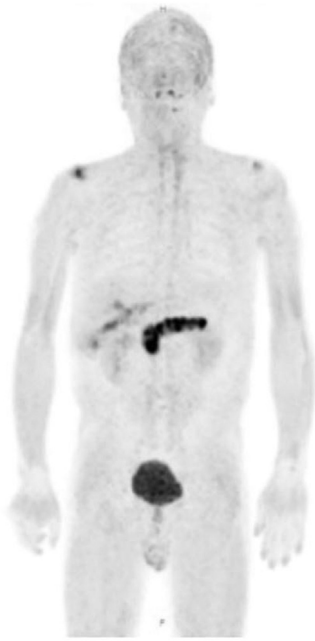

Figure 4 FAPI PET/CT in patient with IgG4 disease related pancreatitis. FAPI PET MIP with intense FAPI-04 tracer accumulation in the pancreas and bile ducts in patient with IgG4 disease related pancreatitis. Originally published by Shou, Y., et al.,[68] *Ga-68-FAPI-04 PET/MR is helpful in differential diagnosis of pancreatitis from pancreatic malignancy compared to F-18-FDG PET/CT: a case report.* European Journal of Hybrid Imaging, 2021. 5(1). https://doi.org/10.1186/s41824-021-00106-1, licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/). Adapted where only the original sub-image D in has been reused.

pulmonary hypertension, as well as uptake in the left injured ventricular myocardium postinfarction and in the left atria after therapeutic thermal damage.[37,38]

FAPI PET/CT has several advantages over FDG PET/CT regarding patient preparation and interpretation, e.g., no fasting or insulin pause is needed. FAPI PET/CT imaging seems to be especially well suited for epithelial cancer originating from the gastrointestinal tract and related organs, as several studies have shown FAPI PET/CT to outperform FDG PET/CT in diagnosing gastric cancer, pancreatic cancer, and colorectal cancer, especially in regard to identifying distant metastases, e.g., lymph nodes and peritoneal metastases.[29,61-64] Our search revealed pancreatitis as a potential challenge, as both focal and diffuse FAPI uptake have been seen in pancreatitis. Moreover, several studies on pancreatic cancer have shown tumor-induced pancreatitis, which could be challenging, especially if FAPI PET/CT is used for tumor delineation or radiotherapy evaluation. Cases of tumor-induced pancreatitis were not included as nonmalignant findings in our review, as there were no pathological analyses to differentiate between cancerous and inflammatory tissue.[14] It is hypothesized that delayed imaging could render better tumor delineation, as pancreatitis has faster FAPI washout.[48] FAPI uptake in the kidneys has been shown to

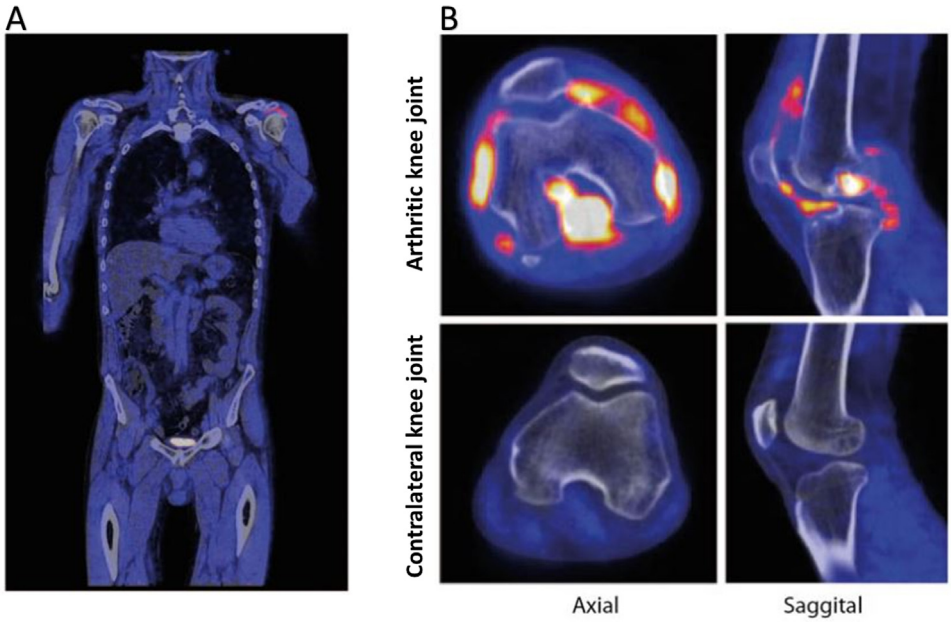

Figure 5 FAPI PET/CT findings in a patient with rheumatoid arthritis. FAPI PET/CT with FAPI-04 tracer accumulation in left arthritic shoulder (A) and synovium of arthritic knee (B) in patient with rheumatoid arthritis. Originally published by Dorst, D.N., et al.,[69] *Targeting of fibroblast activation protein in rheumatoid arthritis patients: imaging and ex vivo photodynamic therapy*. Rheumatology (Oxford), 2021 https://doi.org/10.1093/rheumatology/keab664 licensed under Creative Commons Attribution-NonCommercial (https://creativecommons.org/licenses/by-nc/4.0/).

Table 6 FAPI-Avid Benign PET/CT Findings in the Bone and Joints

	Bone and Joints	
Location	**Pathology**	**No.**
Bone	Exostosis	54
	Fractures	33
	Osteofibrous dysplasia	13
	Degenerative osteophytes	10
	Schmorl node	8
	Bone tuberculosis	6
	Fibrous dysplasia	6
	Femoral head necrosis	2
	Brown tumor	2
	Myelofibrosis	2
	Bone cyst	1
	Whole body scan due to hyperparathyroidism	1
	Osteitis	1
	Enostosis	1
	All	*141*
Bone and joints	Degenerative bone and joint lesions	114
	Osteoarthritis	59
	Inflammatory or trauma related lesions	52
	All	*225*
Joints	Arthritis	92
	Synovitis	1
	All	*93*
All	*All*	*458*

correlate with the severity of renal fibrosis and reduced GFR. Likewise, diffuse FAPI uptake with elevated SUV levels was also seen in cirrhosis. FAPI imaging could therefore potentially be applied for noninvasive evaluations of chronic kidney and liver disease.[65,66] FAPI-avid hemorrhoids were frequently encountered, but all these findings were from one study.[14]

A previous study by Hotta et al.[11] described the physiological distribution of FAPI uptake and mentioned potential FAPI uptake in benign conditions. A number of the benign conditions seen with FAPI uptake in our study overlapped with those in the study by Hotta et al., as expected. However, the present study has the advantage of systematically assessing the cumulative incidence of benign FAPI uptake published in the literature. Some choices in the methodology of the present study should be discussed: this review was expedited as the screening and data handling were performed by one reviewer, and papers not retrievable within 30 days were excluded. This study design was chosen due to the rapidly evolving field of FAPI PET/CT. In the included studies, it is highly expected that many of the included cases have been reported in duplicate, as cases could be presented in a case report and then included in a retrospective cohort study. Consequently, the encountered obvious double reports were excluded on a percase level. Additionally, the majority of the included studies were case reports, which will most likely skew the results of our review toward rare pathologies. Furthermore, the findings were counted on a per-lesion basis. Therefore, multiple FAPI-avid lesions in one patient with a rare condition would boost the number of FAPI-avid

Table 7 FAPI-Avid Benign PET/CT Findings in Miscellaneous Regions

Miscellaneous		
Location	**Pathology**	**No.**
Arteria	Arterial uptake related to plaques or an unspecified cause	1178
	Takayasu arteritis	6
	Carotid body	1
	All	*1185*
Muscle	Unspecific muscle uptake	26
	Enthesopathy	8
	Dermatomyositis	5
	Juvenile polymyositis	5
	Tendinopathy	3
	Strain-related muscle uptake	2
	Gluteal hematoma	1
	All	*50*
Breast	Physiological breast uptake	15
	Mastitis	1
	Accessory breast	1
	All	*17*
Soft tissue	Elastofibroma dorsi	2
	Lipoma	1
	Cutaneous fibroma	1
	All	*4*
Lymph nodes	Tuberculosis lymph nodes	5
	Inflammatory/reactive lymph nodes	121
	All	*126*
Various/unspecified	Tuberculosis	10
	Post-surgery/wound healing	35
	Post-surgery inflammation	4
	Nail implant	1
	All	*50*
All	*All*	*1432*

nonmalignant findings for that specific pathology. Furthermore, the number of lesions could vary depending on the data extractor, e.g., selection bias. Moreover, some studies reporting interesting results could not be included due to quantitively insufficient information, e.g., cardiac uptake in cardiovascular risk patients, uptake in the kidneys due to chronic kidney disease, uptake in the lung parenchyma due to interstitial lunge disease, and varying degrees of FAPI uptake in the uterus relative to the patients' menstrual cycle.[39,44,59,65] Our study does not include bias or quality assessments of the included studies as the majority were case reports and most of the included findings came from studies with limited information, e.g., lack of histopathology as reference standard. Due to several limitations and lack of high-quality data, the findings in our review are presented as descriptive, as no proper meta-analysis was feasible.

Conclusion

In conclusion, the present systematic review found many cases of FAPI uptake related to inflammation or fibrotic disease in specific locations or organs, such as the dental mucosa, thyroid gland, heart, lung, GI tract, liver, pancreas, kidneys, bone, joints, and muscles. In many cases, tuberculosis—the great imitator—has proven to be challenging to diagnose with oncological PET/CT, as the findings mimic those of primary tumors and metastases. To date, no official guidelines on FAPI PET/CT interpretation have been published, and the present review can serve as a temporary overview of benign findings.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1053/j.semnuclmed.2023.02.001.

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