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REVIEW ARTICLE

Current research topics in FAPI theranostics: a bibliometric analysis

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Abstract

Purpose The study aimed to provide a comprehensive bibliometric overview of the current scientific publications on fibroblast activation protein inhibitor (FAPI) positron emission tomography imaging and radionuclide therapy.

Methods A PubMed search was performed to identify all MEDLINE-indexed publications on FAPI imaging and radionuclide therapy. The last update was performed on 31 May 2022. An online database of this literature was created, and hierarchical topic-related tags were subsequently assigned to all relevant studies. Frequency analysis was used to evaluate the distribution of the following characteristics: first author's country of origin, journal of publication, study design, imaging techniques and radiopharmaceutical used, histopathological correlation, the type of cancer, and benign disease/uptake types evaluated.

Results A total of 294 relevant publications on original studies were identified, consisting of 209 (71%) case reports/series and 85 cohort studies (29%). The majority of studies focused on imaging topics, predominantly comparing uptake on FAPI-PET/CT with 2-[^{18}F]FDG-PET/CT, anatomical imaging, and/or histopathology results. 68% of studies focused on malignancies, with gastro-intestinal cancer, hepato-pancreato-biliary cancer, mixed cancers/metastases, lung cancer, sarcoma, head and neck cancer, and breast cancer being the most frequently reported. 42% of studies focused on benign disease categories, with cardiovascular, musculoskeletal, HPB, head and neck, and IgG4-related disease as most common categories. 16/294 (5%) studies focused on radionuclide therapy, with preliminary reports of acceptable toxicity profiles, tumour activity retention, and suggestion of disease control.

Conclusion FAPI research is rapidly expanding from diagnostic studies in malignancies and benign diseases to the first reports of salvage radionuclide therapy. The research activity needs to shift now from low-level-of-evidence case reports and series to prospectively designed studies in homogenous patient groups to provide evidence on how and in which clinical situations FAPI theranostics can be of added value to clinical care. We have provided an overview of current research topics to build upon.

Keywords FAPI theranostics · Bibliometric analysis · Positron emission tomography imaging

This article is part of the Topical Collection on Theragnostic.

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Introduction

In the past decades, positron emission tomography/computed tomography (PET/CT) has evolved as a mainstay imaging modality with added clinical value in the diagnosis, staging, and follow-up of various malignant, infectious, and inflammatory diseases. This is mainly attributable to the use of 2-[^{18}F]fluoro-2-deoxy-D-glucose (2-[^{18}F]FDG) as tracer of increased glucose metabolism in a broad range of pathologies.

Since then, a range of indication- and disease-specific tracers have extended the repertoire of PET imaging in daily clinical practice. Examples are the use of myocardial perfusion PET for the study of ischemic heart disease, somatostatin receptor PET for neuro-endocrine tumours, and prostate-specific membrane antigen PET for prostate cancer.

With the recent development and successful first scientific evaluations of fibroblast activation protein inhibitor-α (FAPI)-based PET tracers, nuclear medicine once again witnesses a novel tracer that holds great promise for the evaluation of a broad range of pathologies. Low physiological accumulation in normal tissues that have a high metabolic demand and rapid clearance from the blood pool are important advantages of this tracer compared to 2-[^{18}F]FDG [1].

Scientists at the Heidelberg University developed the first quinolone-based FAP-specific inhibitors coupled to chelators that are suited for PET imaging after labelling with a positron emitter like gallium-68 [2], eventually resulting in the tracers [^{68}Ga]Ga-DOTA-FAPI-02/04/46. These FAPI-tracers were initially developed for the imaging of malignancies, since it was found that FAP is overexpressed by cancer-associated fibroblasts in the tumour-stroma of various malignancies [3]. Indeed, favourable tumour targeting properties were demonstrated for FAPI-PET/CT in the first clinical cohort studies of various cancer types [3, 4]. In a logical extension of the FAP target, which is also overexpressed in activated stromal fibroblasts during fibrotic tissue remodelling, it was subsequently shown that FAPI-PET/CT may also bring a unique value to non-malignant diseases by displaying the fibrotic disease activity in inflammatofibrotic diseases, such as IgG4-related disease [5].

In the past 2 years, an abundance of scientific publications on FAPI-based imaging and radionuclide therapy has emerged, including a large number of case reports demonstrating the added value in a diverse range of common to rare pathologies. Although this will certainly contribute to our understanding of this novel tracer, it may give the impression that there is already a strong scientific foundation that would justify rapid clinical translation.

Here, we provide a comprehensive overview of the characteristics of existing scientific literature on FAPI-based PET imaging and radionuclide therapy based on a bibliometric analysis.

Methods

Bibliometric analysis

The goal of this study was to map the current FAPI theranostics literature.

A bibliometric analysis is best suited to this goal, since it "focuses on quantitatively summarizing bibliometric characteristics of research topics and detailing research constituents, authorship features, and intellectual structure of a research area" [6]. This is different from a systematic review and meta-analysis, which focus on answering a specific research question. Instead of using a typical citation network, which is more suited to already established research fields with a large number of publications and citations, we used a descriptive approach to bibliometric analysis based on frequency analysis of publication characteristics (including country of origin, journal and citations) and research topics.

We used the web-based software platform "Nested Knowledge" [7]. This platform enables users to perform a literature search, screen results on title/abstract, apply custom hierarchical tags for categorization, extract data, and review the results of this process.

Literature search

A PubMed search was performed to identify all relevant original clinical studies on FAPI-PET imaging and radionuclide therapy with a MEDLINE index. The following syntax was performed and last updated on 31 May 2022: FAPI or "fibroblast activation protein inhibitor."

Publications with one of the following characteristics were excluded: no fibroblast activation protein inhibitor, no imaging (diagnostic or post-therapy), no original research (reviews and editorials), ex vivo or preclinical studies, and no full-text available.

Publication characteristics

The country of origin of the first author and journal of publication were extracted from the included publications. The PubMed IDs of all included studies were also entered in the Web of Science platform [8], and the citation analysis function was used to determine the top 10 cited publications.

Categorization

The included publications were screened on full-text, and relevant tags were assigned to facilitate categorization of research constituents. These tags have a hierarchical structure. This means that only the applicable lowest level

(child) tag was assigned, but higher-level (parent) tags can be included in the analysis. A detailed explanation of the methodology used for categorizing research topics with hierarchical tags and a spreadsheet containing the bibliometric data can be found in the supplementary materials.

Analysis

Only descriptive frequency analyses of all tags were performed to provide an overview of the literature topics/characteristics. No hypothesis testing was performed, because this has no clear purpose in this context. It should be noted that studies could be assigned multiple tags, for example "cancer" and "benign" so that the sum of frequencies does not match the number of total studies, and percentages can exceed 100%.

Results

Search results and study selection

The literature search resulted in a total of 409 hits. Of these, 115 (28%) studies had to be excluded (Fig. 1). A total of 294 relevant studies were selected for analysis.

Study type

The majority (209/294; 71%) of studies were case reports or small case series. A little under one-third (85/294; 29%) of studies were cohort studies. No randomized controlled trial was found.

Country of origin, publication journal, and 10 most cited articles

Table 1 displays the country of origin of the first author and journal of publication.

The top 5 countries with FAPI publications are China (67%), Germany (17%), Turkey (8%), India (2%), and the USA (2%). Only German authors published more cohort studies than case reports/series ($n=27$ versus $n=23$ respectively). Authors from the other countries published more case reports/series than cohort studies. Almost three-quarter of case reports/series originate from China (155/209, 74%).

The top 5 journals with FAPI publications are Clin Nucl Med (44%), Eur J Nucl Med Mol Imag (25%), J Nucl Med (8%), J Nucl Cardiol (3%), and Radiology (3%). Only J Nucl Med ($n=16$ vs. $n=8$) and Radiology ($n=5$ vs. $n=3$) published more cohort studies than case reports/series. The

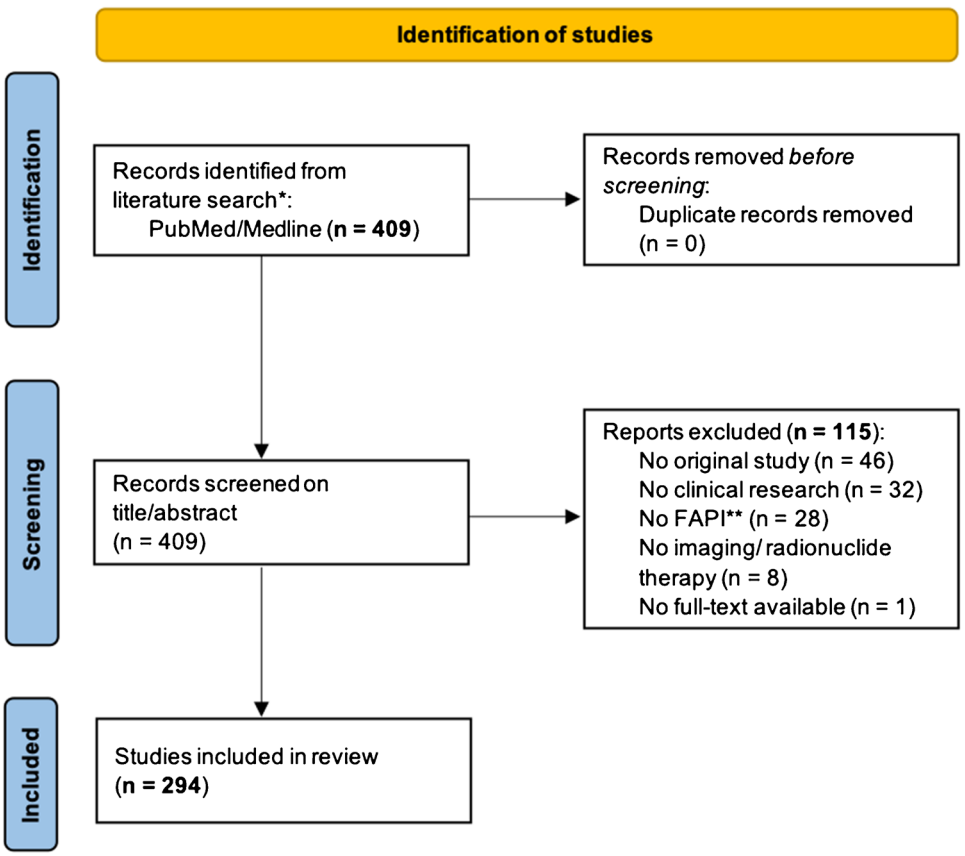

Fig. 1 Flow chart displaying the process of study identification. This flow chart is adapted from the PRISMA statement

* PubMed search syntax: FAPI OR "Fibroblast Activation Protein". Updated on may 31st 2022.

** Fibroblast activation protein inhibitor.

Table 1 Country of first author and journal of publication

	Total ($n=294$)	Case-reports/series ($n=209$)	Cohort studies ($n=85$)
Country			
China	197 (67.0%)	155 (74.2%)	42 (49.4%)
Germany	50 (17.0%)	23 (11.0%)	27 (31.8%)
Turkey	23 (7.8%)	14 (6.7%)	9 (10.6%)
India	6 (2.0%)	4 (1.9%)	2 (2.4%)
USA	5 (1.7%)	4 (1.9%)	1 (1.2%)
Thailand	4 (1.4%)	2 (1.0%)	2 (2.4%)
Iran	3 (1.0%)	2 (1.0%)	1 (1.2%)
The Netherlands	2 (0.7%)	2 (1.0%)	-
Other countries	4 (1.4%)	3 (1.4%)	1 (1.2%)
Journal			
Clin Nucl Med	128 (43.5%)	122 (58.4%)	6 (7.1%)
Eur J Nucl Med Mol Imag	72 (24.5%)	40 (19.1%)	32 (37.6%)
J Nucl Med	24 (8.2%)	8 (3.8%)	16 (18.8%)
J Nucl Cardiol	10 (3.4%)	8 (3.8%)	2 (2.4%)
Radiology	8 (2.7%)	3 (1.4%)	5 (5.9%)
Endocrine	5 (1.7%)	5 (2.4%)	-
Front Oncol	5 (1.7%)	2 (1.0%)	3 (3.5%)
Mol Imaging Biol	5 (1.7%)	2 (1.0%)	3 (3.5%)
Other journals	37 (12.6%)	19 (9.1%)	18 (21.2%)

other journals published much more case reports/series than cohort studies. Clin Nucl Med, for example, published 122 case reports/series and only 6 cohort studies. The majority of case reports/series have been published in Clin Nucl Med (58%), while the majority of cohort studies have been published in Eur J Nucl Med Mol Imag (38%).

Table 2 displays the top 10 most cited FAPI theranostics articles.

Imaging, radionuclide therapy and other

The distribution of relevant imaging, radionuclide therapy, and other study topics is given in Table 3. In summary, the majority of studies (241/249; 82%) focused on imaging. Most studies used a comparison with other imaging modalities, mostly of cases compared to 2-[^{18}F]FDG-PET/CT (60%) and less frequently compared to anatomical imaging with MRI (20%) or contrast enhanced CT (9%). Only 16/294 (5%) studies focused on radionuclide therapy. Approximately half of the studies (49%) mentioned a histopathological correlation.

Radiopharmaceuticals used

An overview of the radiopharmaceuticals used for diagnostic and therapeutic purposes is given in Table 4. The majority of studies reported the use of ^{68}Ga-tracers, mostly [^{68}Ga]Ga-FAPI-04 (48%) and to a lesser degree [^{68}Ga]Ga-FAPI-46 (12%). The specific type of [^{68}Ga]Ga-FAPI compound was not specified ([^{68}Ga]Ga-FAPI-46-NOS) in 31% of publications. Approximately 5% of studies reported the use of ^{18}F-tracers, of which [^{18}F]AlF-NOTA-FAPI was most frequently reported. One study reported the use of the ^{99m}Tc-tracer [^{99m}Tc]Tc-FAPI-34 for gamma camera imaging.

The majority of radionuclide therapy studies (11/16; 69%) reported the use of a ^{177}Lu-radionuclide, mostly the radiopharmaceuticals [^{177}Lu]Lu-FAPI-46 (46%) and [^{177}Lu]Lu-DOTA-SA-FAPi (36%). 5% of studies reported the use of a ^{90}Y-radionuclide ([^{90}Y]Y-FAPI-46 and [^{90}Y]Y-FAPI-04) and 1 study reported the use of [^{153}Sm]Sm-FAPI-04.

Malignant versus benign study topics

The majority of studies reported FAPI-PET/CT findings in malignant diseases (201/294; 68%); this proportion was slightly lower in case reports/series (131/209; 63%) and higher in cohort studies (70/85; 82%) (Fig. 2).

Table 5 provides a comprehensive overview of all malignant disease topics. The five most frequently reported malignant disease categories are gastro-intestinal cancer (11%; gastric cancer 7%; colorectal cancer 3%), HPB cancer (8%; pancreatic cancer 3%; primary liver tumours 3%; liver metastases 2%), various cancers/metastases (8%), lung cancer (5%), soft tissue cancer/sarcoma — head and neck cancer — breast cancer (all 5%).

Table 2 Top 10 most cited FAPI theranostics articles

	First author	Title	Journal	Year
#1	Kratochwil C	Ga-68-FAPI PET/CT: tracer uptake in 28 different kinds of cancer	J Nucl Med	2019
#2	Lidner T	Development of quinoline-based theranostic ligands for the targeting of fibroblast activation protein	J Nucl Med	2018
#3	Giesel FL	Ga-68-FAPI PET/CT: biodistribution and preliminary dosimetry estimate of 2 DOTA-containing FAP-targeting agents in patients with various cancers	J Nucl Med	2019
#4	Loktev A	A tumor-imaging method targeting cancer-associated fibroblasts	J Nucl Med	2018
#5	Chen HJ	Comparison of [Ga-68]Ga-DOTA-FAPI-04 and [F-18]FDG PET/CT for the diagnosis of primary and metastatic lesions in patients with various types of cancer	Eur J Nucl Med Mol Imag	2020
#6	Chen HJ	Usefulness of [Ga-68]Ga-DOTA-FAPI-04 PET/CT in patients presenting with inconclusive [F-18]FDG PET/CT findings	Eur J Nucl Med Mol Imag	2021
#7	Giesel FL	FAPI-74 PET/CT using either F-18-AlF or Cold-Kit Ga-68 labeling: biodistribution, radiation dosimetry, and tumor delineation in lung cancer patients	J Nucl Med	2021
#8	Pang YZ	Comparison of (68)Ga-FAPI and F-18-FDG uptake in gastric, duodenal, and colorectal cancers	Radiology	2021
#9	Syed M	Fibroblast activation protein inhibitor (FAPI) PET for diagnostics and advanced targeted radiotherapy in head and neck cancers	Eur J Nucl Med Mol Imag	2020
#10	Luo YP	Intense FAPI uptake in inflammation may mask the tumor activity of pancreatic cancer in Ga-68-FAPI PET/CT	Clin Nucl Med	2020

Top 10 most cited FAPI theranostics articles based on the Web of Science citation analysis. Ordered by decreasing number of citations. From the included 294 studies, 3 articles published ahead of print in 2022 [9–11] were not yet available in the Web of Science database

Table 3 Imaging, radionuclide therapy and other

	Total ($n = 294$)
Imaging	241 (82.0%)
Biodistribution/dosimetry study	17 (5.8%)
Comparison other imaging modalities	226 (76.9%)
2-[^{18}F]FDG-PET/CT	176 (59.9%)
MRI	60 (20.4%)
Contrast enhanced CT	26 (8.8%)
Somatostatin receptor PET/CT	8 (2.7%)
^{131}I scintigraphy	5 (1.7%)
Ultrasound	5 (1.7%)
Bone scintigraphy	4 (1.4%)
PSMA PET/CT	4 (1.4%)
Parathyroid scintigraphy	2 (0.7%)
Myocardial perfusion scintigraphy	2 (0.7%)
MIBG scintigraphy	1 (0.3%)
[^{11}C]Acetate PET/CT	1 (0.3%)
PET timing	7 (2.4%)
Radiation therapy planning	5 (1.7%)
Reproducibility assessment	1 (0.3%)
PET/MRI	27 (9.2%)
Dynamic PET	5 (1.7%)
Other	150 (51.0%)
Tracer development	6 (2.0%)
Histopathology correlation	144 (49.0%)
Radionuclide therapy	16 (5.4%)

Slightly less than half of studies reported FAPI-PET/CT findings in benign diseases (122/294; 42%); this proportion was higher in case reports/series (101/209; 48%) and lower in cohort studies (21/85; 25%).

Table 6 provides a comprehensive overview of all non-malignant disease topics. The five most frequently reported non-malignant disease categories are cardiovascular (8%; myocardial infarction 3%; atherosclerosis 1%), musculoskeletal (8%; degenerative disease 2%; arthritis 2%), HPB (4%; focal nodular hyperplasia, benign pancreatic lesions, pancreatitis and cholecystitis all 1%), head and neck (3%; thyroid 2%; Graves ophthalmopathy 1%), and IgG4-related disease (3%).

Suggestions for future FAPI research

Based on the results of the bibliometric analysis, we have synthesized recommendations for future FAPI research. These are displayed in Table 7.

Discussion

The number of publications on FAPI-based radiopharmaceuticals for imaging, and to a lesser degree also therapy, has drastically increased since their development and first clinical validation in 2019. This clearly mirrors the nuclear medicine's community interest in this novel radiopharmaceutical,

Table 4 Radiopharmaceuticals used

All studies	Total (n = 294)
^{68}Ga-tracers	269 (92%)
[^{68}Ga]Ga-FAPI-04	140 (47.6%)
[^{68}Ga]Ga-FAPI NOS*	91 (31.0%)
[^{68}Ga]Ga-FAPI-46	36 (12.2%)
[^{68}Ga]Ga-FAPI-02	6 (2.0%)
[^{68}Ga]Ga-FAPI-74	6 (2.0%)
[^{68}Ga]Ga-DOTA-SA-FAPi	5 (1.7%)
[^{68}Ga]Ga-DATA5m-SA-FAPi	2 (0.7%)
[^{68}Ga]Ga-OncoFAP-DOTAGA	1 (0.3%)
[^{68}Ga]Ga-FAP-2286	1 (0.3%)
^{18}F-tracers	15 (5.1%)
[^{18}F]AlF-NOTA-FAPI	9 (3.1%)
[^{18}F]F-FAPI-42	3 (1.0%)
[^{18}F]F-FAPI-74	2 (0.7%)
[^{18}F]AlF-P-FAPI	1 (0.3%)
[^{18}F]F-FAPI-NOS	1 (0.3%)
^{99m}Tc-tracers	1 (0.3%)
[^{99m}Tc]Tc-FAPI-34	1 (0.3%)
Radionuclide therapy studies	Total (n = 16)
^{177}Lu-radionuclides	11 (68.8%)
[^{177}Lu]Lu-FAPI-46	5 (45.5%)
[^{177}Lu]Lu-DOTA-SA-FAPi	4 (36.4%)
[^{177}Lu]Lu-FAPI-04	1 (9.1%)
[^{177}Lu]Lu-FAPI-2286	1 (9.1%)
^{90}Y-radionuclides	5 (5.1%)
[^{90}Y]Y-FAPI-46	4 (36.4%)
[^{90}Y]Y-FAPI-04	1 (9.1%)
^{153}Sm-radionuclides	1 (0.3%)
[^{153}Sm]Sm-FAPI-04	1 (9.1%)

which is rooted in its unique properties such as a lack of physiological uptake combined with markedly increased uptake in various diseased tissues, both for oncological and inflammatory indications.

Despite accumulating evidence in favour of using FAPI, its future role in clinical practice has not yet been established. The purpose of this bibliometric analysis was to create an overview of FAPI publication characteristics and detect emerging patterns of study type, country of origin, publication journal, purpose of study, comparisons with other imaging modalities, histopathological correlation, and diseases under study. This is complementary to a systematic review/diagnostic meta-analysis published by Sollini et al. in 2021 [12], with a focus on critical appraisal and substantive discussion of study results in published cohort studies only, as well as a comprehensive topic review published by Li et al. in 2022 [13].

The first study to emerge on FAPI imaging originated from Germany and was a well-designed explorative cohort study, comparing the uptake of [^{68}Ga]Ga-FAPI-04 with that of 2-[^{18}F]FDG-PET/CT in patients with various types of histopathologically proven malignancies [4]. Since no approved and commercially available FAPI-radiopharmaceutical exists to date, research and limited clinical care on compassionate use basis has in most Western countries been limited to centres who obtained the radiopharmaceutical with permission from iTheranostics, Inc. (affiliate of SOFIE, Inc.). Chinese and Turkish publications, however, reported to have purchased a GMP-grade DOTA-FAPI-04 precursor (from for example MedChemExpress LLC; Jiangsu Huayi Technology Co Ltd, CSBio Ltd) and produced the radiotracer in-house. This may explain the difference in the nature of publications in these

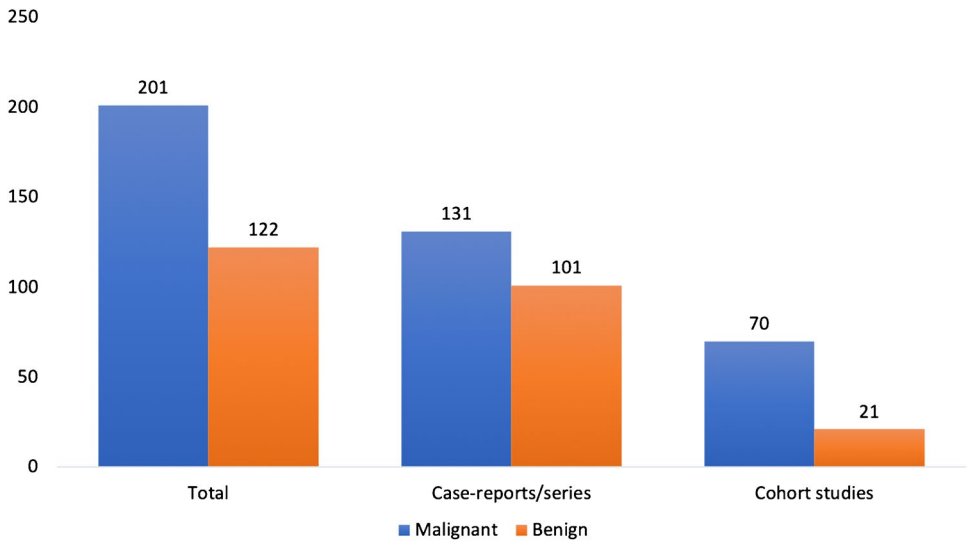

Fig. 2 Bar chart showing the frequency of malignant versus benign study topics in the current FAPI literature and distribution in the total selected studies (n = 294), case-reports/series (n = 209), and cohort studies (n = 85). Notice that the sum of the malignant and benign categories is greater than the number of studies, because some studies focused on malignant and benign diseases

Table 5 Malignant disease research topics

	Total ($n=294$)	Case-reports/ series ($n=209$)	Cohort studies ($n=85$)
Cancer	201 (68.4%)	131 (62.7%)	70 (82.4%)
Gastro-intestinal cancer	32 (10.9%)	21 (10.0%)	11 (12.9%)
Gastric cancer	21 (7.1%)	14 (6.7%)	7 (8.2%)
Colorectal cancer	10 (3.4%)	6 (2.9%)	4 (4.7%)
Small bowel cancer	1 (0.3%)	-	
Peutz-Jeghers syndrome	1 (0.3%)	1 (0.5%)	-
HPB cancer	24 (8.2%)	12 (5.7%)	12 (14.1%)
Pancreatic cancer	9 (3.1%)	5 (2.4%)	4 (4.7%)
Primary liver tumours	8 (2.7%)	3 (1.4%)	5 (5.9%)
Liver metastases	7 (2.4%)	3 (1.4%)	4 (4.7%)
Cholangiocarcinoma	2 (0.7%)	1 (0.5%)	1 (1.2%)
Various cancers/metastases	22 (7.5%)	7 (3.3%)	15 (17.6%)
Lung cancer	16 (5.4%)	10 (4.8%)	6 (7.1%)
Soft tissue cancer/sarcoma	16 (5.4%)	13 (6.2%)	3 (3.5%)
Angiosarcoma	3 (1.0%)	3 (1.4%)	-
Leiomyosarcoma	1 (0.3%)	1 (0.5%)	-
Intimal sarcoma	1 (0.3%)	1 (0.5%)	-
Dermatofibrosarcoma protuberans	2 (0.7%)	2 (1.0%)	-
Epithelioid haemangioendothelioma	1 (0.3%)	1 (0.5%)	-
Head and neck cancer	16 (5.4%)	10 (4.8%)	6 (7.1%)
Adenoid cystic carcinoma	1 (0.3%)	-	1 (1.2%)
Nasopharyngeal carcinoma	6 (2.0%)	6 (2.9%)	-
Oral squamous cell carcinoma	2 (0.7%)	-	2 (2.4%)
Tracheal mucoepidermoid carcinoma	1 (0.3%)	1 (0.5%)	-
Breast cancer	14 (4.8%)	11 (5.3%)	3 (3.5%)
Thyroid cancer	11 (3.7%)	8 (3.8%)	3 (3.5%)
Lymphoma	9 (3.1%)	8 (3.8%)	1 (1.2%)
Peritoneal carcinomatosis	9 (3.1%)	5 (2.4%)	4 (4.7%)
Bone cancer/metastases	9 (3.1%)	7 (3.3%)	2 (2.4%)
NET	8 (2.7%)	7 (3.3%)	1 (1.2%)
Urological	8 (2.7%)	6 (2.9%)	2 (2.4%)
Renal cell carcinoma	2 (0.7%)	2 (1.0%)	-
Prostate cancer	4 (1.4%)	3 (1.4%)	1 (1.2%)
Bladder cancer	2 (2.4%)	1 (0.5%)	1 (1.2%)
Oesophageal cancer	8 (2.7%)	7 (3.3%)	1 (1.2%)
Gynaecological cancer	5 (1.7%)	3 (1.4%)	2 (2.4%)
Ovarian cancer	2 (0.7%)	2 (1.0%)	-
Cervical cancer	1 (0.3%)	1 (0.5%)	-
Lymph node metastases	5 (1.7%)	3 (1.4%)	2 (2.4%)
Unknown primary	3 (1.0%)	1 (0.5%)	2 (2.4%)
Brain tumours	3 (1.0%)	3 (1.4%)	-
Primary brain tumours	1 (0.3%)	1 (0.5%)	-
Brain metastases	2 (0.7%)	2 (1.0%)	-
Melanoma	2 (0.7%)	2 (1.0%)	-
Plasmacytoma/Multiple myeloma	2 (0.7%)	1 (0.5%)	1 (1.2%)
Skin cancer	2 (0.7%)	2 (1.0%)	-
Extramammary Paget disease	1 (0.3%)	1 (0.5%)	-
Cutaneous plasmacytosis	1 (0.3%)	1 (0.5%)	-
Pleural carcinomatosis	2 (0.7%)	2 (1.0%)	-
Leptomeningeal metastases	1 (0.3%)	1 (0.5%)	-

Table 5 (continued)

	Total ($n=294$)	Case-reports/ series ($n=209$)	Cohort studies ($n=85$)
Thymus carcinoma	1 (0.3%)	1 (0.5%)	-
Malignant peritoneal mesothelioma	1 (0.3%)	1 (0.5%)	-
Cardiac metastases	1 (0.3%)	1 (0.5%)	-
Erdheim Chester	1 (0.3%)	1 (0.5%)	-
Germ cell tumours	1 (0.3%)	1 (0.5%)	-
Perivascular epithelioid cell tumour	1 (0.3%)	1 (0.5%)	-

regions. While German scientists have published more cohort studies than case reports/series — predominantly in high-impact journals such as the European Journal of Nuclear Medicine and Molecular Imaging, Journal of Nuclear Medicine and Radiology –, authors from other countries have published remarkably more case reports/series than cohort studies. At this moment, 71% of original research articles on FAPI-imaging and therapy are case reports/series (with < 10 patients). Furthermore, more than half of these have been published in the same journal, Clinical Nuclear Medicine. Most case reports/series publications describe the degree of FAPI-uptake in various malignant lesions, and increasingly also benign causes of FAPI-uptake. Although interesting, and potentially hypothesis generating, these case reports contribute little evidence for the added clinical value of FAPI imaging.

The reports of unexpected benign causes of FAPI-uptake, however, are collectively contributing to a growing awareness of pitfalls one can expect when reading FAPI-PET/CT scans in the future. FAPI-uptake was initially expected in malignancies (CAF activity) and purely fibrotic diseases (myofibroblast activity), but turns out to be present also in some physiological processes and in a variety of benign diseases with an inflammatory component (Table 6). Some of these are unlikely to cause diagnostic challenges, due to very faint FAPI-uptake or characteristic appearance on CT, whereas others might be hard to distinguish from malignant diseases without histopathological assessment. This distinction should ideally be emphasized in future publications.

A novel area of interest is that of diseases with an inflammatory and fibrotic disease component, where phenotypical dominance of one over the other could guide therapeutic decisions, such as in IgG4-related disease, rheumatic arthritis, fibrotic interstitial lung disease and renal fibrosis [5, 14–18]. This would provide a valuable tool for clinical care, since currently no such biomarker exists. A dual tracer strategy with [^{18}F]-FDG has been described to distinguish inflammation from primarily fibrotic disease. Inflammation is markedly FDG avid due to hypermetabolic activity of lymphocytes, granulocytes and macrophages, and variably FAPI-avid due to fibroblast activation in wound-healing. Primarily fibrotic disease activity is non-FDG avid, but markedly FAPI-avid [16].

Another emerging area of scientific interest is that of FAPI-PET imaging in cardiovascular disease, which has grown out to the single largest category of benign disease topics studied in the FAPI literature so far. Several reports and cohort studies compared FAPI uptake with cardiac MRI findings after myocardial infarction [19–23]. The results of these first studies suggest that myocardial FAPI imaging may open an avenue towards improved understanding of cardiac remodelling mechanisms and evaluation of antifibrotic therapy after myocardial infarction.

Cancer remains the dominant study area in FAPI-imaging research. Studies have consistently reported a favourable target-to-background ratio in a range of carcinomas and sarcomas [4, 24–27]. Specifically, tumour-to-background ratios (TBR) compared favourably to 2-[^{18}F]FDG uptake in organ systems with a high or variable physiological glucose metabolism such as the brain [28, 29], head and neck [30–33], heart [34, 35], breast [36, 37], gastrointestinal tract [38–46], hepato-pancreatico-biliary system [47–53], urological system [54, 55], and gynaecological system [56]. FAPI-PET/CT appears especially promising for the detection of primary tumours and metastases that are notoriously challenging to detect on 2-[^{18}F]FDG-PET/CT and standard anatomical imaging such as (adeno)carcinoma of unknown primary [31, 57], differentiated thyroid cancer [58], signet-ring cell type gastric cancer [59, 60], small liver metastases [61], diffuse peritoneal metastases [62, 63], and intramedullary bone metastases [64, 65]. Although lung cancer does not appear to fall in the latter category, improved accuracy of staging with FAPI-PET/CT has been reported in the first cohort studies compared to 2-[^{18}F]FDG-PET/CT[66–68]. In some tumour types, such as soft-tissue-sarcoma, the diagnostic accuracy of FAPI-PET/CT may be dependent on the specific subtype [69, 70]. Therefore, it remains unclear whether FAPI-PET/CT will have additional clinical value over established imaging modalities for the evaluation of these cancers. Other tumour types, such as neuro-endocrine tumours, prostate cancer, lymphoma, and multiple myeloma are less to benefit from FAPI imaging due to the availability of disease-specific tracers or worse diagnostic accuracy of FAPI-PET/CT compared to 2-[^{18}F]FDG-PET/CT.

Table 6 Benign disease/uptake research topics

	Total ($n=294$)	Case-reports/ series ($n=209$)	Cohort studies ($n=85$)
Benign	122 (41.5%)	101 (48.3%)	21 (24.7%)
Cardiovascular	24 (8.2%)	16 (7.7%)	8 (9.4%)
Myocardial infarction	8 (2.7%)	4 (1.9%)	4 (4.7%)
Atherosclerosis	3 (1.0%)	2 (1.0%)	1 (1.2%)
Myocarditis	2 (0.7%)	2 (1.0%)	-
CTEPH	2 (0.7%)	1 (0.5%)	1 (1.2%)
Cardiac sarcoidosis	1 (0.3%)	1 (0.5%)	-
Cardiac amyloidosis	1 (0.3%)	1 (0.5%)	-
PVI damage	1 (0.3%)	1 (0.5%)	-
Vasculitis	1 (0.3%)	1 (0.5%)	-
Venous thrombosis	1 (0.3%)	1 (0.5%)	-
Pulmonary arterial hypertension	2 (0.7%)	1 (0.5%)	1 (1.2%)
Musculoskeletal	23 (7.8%)	22 (10.5%)	1 (1.2%)
Degenerative disease	7 (2.4%)	7 (3.3%)	-
Arthritis	3 (1.0%)	3 (1.4%)	-
Fracture	2 (0.7%)	2 (1.0%)	-
Fibrous dysplasia	2 (0.7%)	2 (1.0%)	-
Elastofibroma dorsi	1 (0.3%)	1 (0.5%)	-
Bone cyst	1 (0.3%)	1 (0.5%)	-
Hyperparathyroidism	1 (0.3%)	1 (0.5%)	-
Brown tumour	1 (0.3%)	1 (0.5%)	-
Polymyositis	1 (0.3%)	1 (0.5%)	-
Avascular necrosis	1 (0.3%)	1 (0.5%)	-
Ankylosing spondylitis	1 (0.3%)	1 (0.5%)	-
Intramuscular hematoma	1 (0.3%)	1 (0.5%)	-
HPB	11 (3.7%)	10 (4.8%)	1 (1.2%)
Focal nodular hyperplasia	2 (0.7%)	2 (1.0%)	-
Benign pancreatic lesions	2 (0.7%)	1 (0.5%)	1 (1.2%)
Pancreatitis	2 (0.7%)	2 (1.0%)	-
Cholecystitis	2 (0.7%)	2 (1.0%)	-
Cholangitis	1 (0.3%)	1 (0.5%)	-
Liver cirrhosis and nodules	1 (0.3%)	1 (0.5%)	-
Portal biliopathy	1 (0.3%)	1 (0.5%)	-
Head and neck	9 (3.1%)	9 (4.3%)	-
Thyroid	5 (1.7%)	5 (2.4%)	-
Thyroiditis	4 (1.4%)	4 (1.9%)	-
Thyroid adenoma	1 (0.3%)	1 (0.5%)	-
Graves ophthalmopathy	2 (0.7%)	2 (1.0%)	-
Orbital granulomatous inflammation	1 (0.3%)	1 (0.5%)	-
Inverted papilloma	1 (0.3%)	1 (0.5%)	-
IgG4-related disease	8 (2.7%)	6 (2.9%)	2 (2.4%)
Tuberculosis	7 (2.4%)	7 (3.3%)	-
Various benign	6 (2.0%)	1 (0.5%)	5 (5.9%)
Benign breast uptake	6 (2.0%)	5 (2.4%)	1 (1.2%)
Lung	6 (2.0%)	5 (2.4%)	1 (1.2%)
Pulmonary infection	3 (1.0%)	3 (1.4%)	-
Lung fibrosis	1 (0.3%)	-	1 (1.2%)
Pulmonary necrotizing granuloma	1 (0.3%)	1 (0.5%)	-
Organizing pneumonia	1 (0.3%)	1 (0.5%)	-
Solitary fibrous tumour	5 (1.7%)	4 (1.9%)	1 (1.2%)

Table 6 (continued)

	Total ($n=294$)	Case-reports/ series ($n=209$)	Cohort studies ($n=85$)
Benign uterus uptake	4 (1.4%)	2 (1.0%)	2 (2.4%)
Angiomyolipoma	3 (1.0%)	3 (1.4%)	-
Benign lymph nodes	2 (0.7%)	2 (1.0%)	-
Inflammatory bowel disease	2 (0.7%)	2 (1.0%)	-
Renal fibrosis	2 (0.7%)	1 (0.5%)	1 (1.2%)
Central nervous system	2 (0.7%)	2 (1.0%)	-
Progressive multifocal leukoencephalopathy	1 (0.3%)	1 (0.5%)	-
Myxopapillary ependymoma	1 (0.3%)	1 (0.5%)	-
Subcutaneous lipoma	1 (0.3%)	1 (0.5%)	-
Esophagitis	1 (0.3%)	1 (0.5%)	-
Omental nodular hyperplasia	1 (0.3%)	1 (0.5%)	-
Splenic haemangioma	1 (0.3%)	1 (0.5%)	-
Idiopathic retroperitoneal fibrosis	1 (0.3%)	1 (0.5%)	-
Teratoma	1 (0.3%)	1 (0.5%)	-
SAPHO	1 (0.3%)	1 (0.5%)	-
Inflammatory myofibrolastic tumour	1 (0.3%)	1 (0.5%)	-
Peripheral nerve tumour	1 (0.3%)	1 (0.5%)	-
Cutaneous neurofibromatosis	1 (0.3%)	1 (0.5%)	-
Dermatomyositis	1 (0.3%)	1 (0.5%)	-

Table 7 Recommendations for future FAPI research

Reporting
- Describe the exact type of radiopharmaceutical used
- Qualitative and semi-quantitative measures of FAPI uptake should be reported
- Diagnostic research studies should describe the reference standard used to compare the FAPI uptake with, distinguishing between patient- and lesion-based comparisons
- Case-reports should explicitly explain why that particular case warrants publication and what the reader can learn from it

Study design
- Research activity needs to shift from low-level-of-evidence case reports and series to prospectively designed studies in homogenous patient groups to provide evidence on how and in which clinical situations FAPI theranostics can be of added value to clinical care
- Randomized controlled trials (RCTs) of test-plus-treatment strategies would offer ideal evidence of the benefits of introducing a new diagnostic test (FAPI-PET/CT) relative to current best practice

Research topics

Optimization of the diagnostic imaging procedure
- Research on the optimization of the imaging procedure should be prioritized. This includes comparisons between different radiopharmaceuticals, dynamic versus static acquisition protocols, and different timing strategies for the scan acquisition. Additional topics of interest include inter-observer reproducibility, definition of positive and negative FAPI-PET/CT test results, and the need for and standardization of semi-quantitative analysis

Diagnostic imaging in diseases with an unsolved clinical dilemma
- Diseases with a current clinical dilemma due to imperfect imaging results may be prioritized. Examples are carcinoma of unknown primary, peritoneal carcinomatosis, invasive lobular breast cancer, incidental pulmonary nodules, nodal staging in various malignancies, and the distinction of inflammatory and purely fibrotic phenotypes in inflammatofibrotic diseases

Tumour response assessment
- It remains unclear whether FAPI-PET/CT can be used reliably for tumour response assessment. This needs to be evaluated, especially if FAPI-PET/CT is to replace other imaging modalities for tumour staging, such as 2-[^{18}F]FDG-PET/CT

Potential benefits for clinical workflow
- It may be of interest to evaluate potential practical benefits of using FAPI-PET/CT in indications where 2-[^{18}F]FDG-PET/CT is routinely used, such as a higher clinical throughput (due to short time between administration and scan acquisition) and the independence from fasting state and metabolism

Radionuclide therapy
- The development of a FAPI-compound with prolonged tumour retention and sound clinical validation of its therapeutic efficacy are of high priority for therapeutic research

So far, relatively little work has been put into the optimization of the imaging procedure such as comparisons between different radiopharmaceuticals, dynamic versus static acquisition protocols, timing of acquisition and evaluation, inter-observer reproducibility, and the need and standardization of semi-quantitative analysis. Of note, Matting et al. recently did perform a study in which they compared the diagnostic value of FAPI-PET/CT for acquisition times (10, 22, 34, 46, and 58 min post-injection) and different tracers ([^{68}Ga]Ga-FAPI-02, -46 and -74) in malignant, inflammatory, and degenerative lesions [9]. The authors conclude that "FAPI tracer variants show significant differences in their time-dependent biodistributional behaviour and should be selected carefully depending on the clinical setting." Yet, more research is needed to define the differential behaviour of the different imaging tracers, especially the most frequently used radiopharmaceuticals [^{68}Ga]Ga-FAPI-04, [^{68}Ga]Ga-FAPI-46, and [^{18}F]AlF-NOTA-FAPI, before we can claim that a given tracer type works best in a certain clinical setting.

So far, 16 reports have been published on the use of a FAPI-based radionuclide for cancer therapy. These mostly include case reports of salvage-setting intravenous therapy using diverse ^{177}Lu-, ^{90}Y-, or ^{153}Sm-based radiopharmaceuticals in patients with various types of metastatic disease. Post-therapy imaging using planar scintigraphy γ- or bremsstrahlung imaging was broadly applied, demonstrating preferential tumour uptake in most patients. Baum et al. [71] and Ferdinandus et al. [72] published the largest studies so far, with 11 and 9 patients treated respectively. Both publications reported an acceptable mean healthy tissue absorbed dose in the kidneys and bone marrow. G3/G4 toxicity was observed in 27–44% of patients, comprising pancytopenia, leukocytopenia, thrombocytopenia, and pain flare-up. Tumour absorbed dose values were roughly comparable to those reported for [^{177}Lu]Lu-PSMA therapy in metastatic castrate-resistant prostate cancer [73]. Stable disease on imaging was achieved in multiple patients and up to 27% of patients reported a pain response. While preliminary, these first results in the experimental salvage setting clearly justify further exploration of FAPI-based radionuclide therapy. The majority of available reports claim "prolonged tumour retention," but longitudinal data are limited to case-reports qualitatively demonstrating tumour-uptake on 44–72 h posttherapy scintigraphy [74, 75]. Better tumour retention needs to be demonstrated in order to parallel the success of other systemic radionuclide therapies such as peptide receptor radionuclide therapy for neuro-endocrine tumours and [^{177}Lu]-PSMA in prostate cancer.

To our knowledge, we have provided the first overview of scientific topics in the field of FAPI theranostics. We used a bibliometric analysis for this purpose. A strength of this method is that we were able to identify several interesting patterns that can be used to inform scientists on the most promising and perhaps also under-studied research topics, thus informing the future agenda. A limitation is that this analysis is not aimed to provide a comprehensive overview on the study results and critical appraisal. For this, we refer to previously published reviews [1, 12, 13, 38, 76–81].

Conclusion

FAPI research is rapidly expanding from diagnostic studies in malignancies and benign diseases to the first reports of salvage radionuclide therapy. The research activity needs to shift now from low-level-of-evidence case reports and series to prospectively designed studies in homogenous patient groups to provide evidence on how and in which clinical situations FAPI theranostics can be of added value to clinical care. We have provided an overview of current research topics to build upon.

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Author contribution Andor van den Hoven performed the literature search, topic categorization, and bibliometric analysis. The first draft of the manuscript was written by Andor van den Hoven, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

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