Head-to-Head Comparison of ^{68}Ga-FAPI-04 and ^{18}F-FDG PET/CT for the Assessment of Crohn's Disease

A Prospective Pilot Study

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Background: Crohn disease is a chronic granulomatous inflammatory disease of gastrointestinal tract. Previous studies showed Crohn disease strictures overexpress fibroblast activation protein and had active ^{68}Ga-FAPI-04 uptake. Our study was to compare the diagnostic performance of ^{68}Ga-FAPI-04 and ^{18}F-FDG PET/CT in Crohn disease.

Patients and Methods: This is a prospective cohort study recruiting patients with newly diagnosed or relapsed Crohn disease. All the patients underwent ^{68}Ga-FAPI-04 and ^{18}F-FDG PET/CT. The diagnostic performance of the 2 PET/CT modalities and their uptake values were compared. The correlation of PET semiquantitative parameters [metabolic intestinal volume (MIV_{FDG} and MIV_{FAPI}), total intestinal uptake (TIU_{FDG} and TIU_{FAPI})] with clinical biomarkers were also analyzed.

Results: Seventeen participants (13 men and 4 women, age 32.3 ± 15.9 y) were recruited. The sensitivity of ^{68}Ga-FAPI-04 and ^{18}F-FDG PET/CT in detecting Crohn lesions were 90.0% and 85.0%, and the specificities were 93.0% and 88.4%, respectively. In receiver operating characteristic curve analysis, ^{68}Ga-FAPI-04 PET/CT [area under the curve = 0.92 (95% CI: 0.83–0.97), $P < 0.001$] showed better diagnostic performance compared with ^{18}F-FDG PET/CT [area under the curve = 0.87 (95% CI: 0.78–0.93), $P < 0.001$; $P = 0.043$]. The SUVmax of ^{68}Ga-FAPI and ^{18}F-FDG in stricture/fistula lesions were significantly higher than those in non-stricture/fistula lesions (^{68}Ga-FAPI, 10.9 ± 6.7 vs 5.0 ± 3.5, $P = 0.0002$; ^{18}F-FDG, 9.5 ± 4.9 vs 5.3 ± 1.8, $P = 0.0016$). TIU_{FAPI} and MIV_{FAPI} of ^{68}Ga-FAPI-04 PET/CT were significantly correlated with high sensitivity C-reactive protein and simple endoscopic score for Crohn disease ($P < 0.05$). TIU_{FDG} and MIV_{FDG} of ^{18}F-FDG PET/CT were also correlated with simple endoscopic scores for Crohn disease ($P < 0.05$).

Conclusions: ^{68}Ga-FAPI-04 PET/CT showed better diagnostic performance than ^{18}F-FDG PET/CT in Crohn disease.

Key Words: Crohn disease, 68Ga-FAPI-04, PET/CT

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Crohn disease is a chronic granulomatous inflammatory disease that may involve any portion of luminal gastrointestinal tract, from the oral cavity to the perianal area, with a tendency of recurrence. The diagnosis of Crohn disease is established on the basis of clinical, radiologic [including computed tomography enterography (CTE), magnetic resonance enterography, and ultrasound of the gastrointestinal tract (GIUS)], endoscopic, and/or histologic findings that demonstrate segmental and transmural inflammation of the luminal gastrointestinal tracts in a patient with compatible clinical presentations (eg, abdominal pain, chronic intermittent diarrhea). ^{18}F-FDG PET/CT has proven to be effective in imaging a wide variety of infectious or inflammatory conditions, including Crohn disease.[1–3] ^{18}F-FDG PET/CT has a high sensitivity (range from 72.9% to 90.0%) in detecting involvements of Crohn disease, while the specificity is suboptimal around 55.3%–86.0%.[4–7] The physiological FDG uptake in the bowel, which is frequently seen in PET scans, poses a practical problem in reading PET images by falsely mimicking pathology or obscuring malignant lesions.[8]

At disease onset of Crohn disease, nearly 90% of patients have an inflammatory pattern, but over time, almost all patients develop intestinal fibrosis and stricture.[9] Currently, treatment of Crohn disease has anti-inflammatory properties, but there is still no available drug to prevent or reverse fibrosis.[10,11] Patients with extended, fibrostenotic patterns have a 13-fold increased risk of disease recurrence, with a relapse rate as high as 50% at 5 years and 70% at 10 years.[12] Thus, direct targeting of bowel fibrosis has a pivotal role in understanding the pathogenesis and investigating new therapeutic approaches to Crohn disease. Previous ex vivo studies showed Crohn disease strictures overexpressed fibroblast activation protein (FAP), an inducible cell surface glycoprotein that was specifically upregulated on intestinal myofibroblasts of Crohn disease strictures.[13,14] Recently ^{68}Ga-FAPI-04 PET/CT, a non-invasive tool that facilitates the quantification and precise localization of FAP expression in vivo, has been applied in clinical studies of Crohn disease. The results revealed that

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^{68}Ga-FAPI-04 activity was associated with histologically assessed fibrosis in the bowel wall[15] and correlated well with endoscopic, CTE, and clinical biomarkers of Crohn disease.[6] But the diagnostic performance of ^{68}Ga-FAPI-04 and ^{18}F-FDG PET/CT has not yet been well investigated. Herein, we performed a prospective head-to-head comparison study to indicate the diagnostic performance of ^{68}Ga-FAPI-04 and ^{18}F-FDG PET/CT in Crohn disease, as well as their correlation with disease activity of Crohn disease.

PATIENTS AND METHODS

Patients and Study Design

This is a prospective cohort study on ^{68}Ga-FAPI-04 PET/CT in the evaluation of Crohn disease (NCT04507932). Seventeen consecutive patients with newly diagnosed (11 patients) or relapsed (6 patients) Crohn disease were included between July 2020 and August 2022. Patients with a history of gastrointestinal malignancy were excluded. Written informed consent was obtained from each patient, and the study was approved by the Institutional Review Board of Peking Union Medical College Hospital (protocol ZS-1810). Within 1 week of the endoscopic procedure, all recruited patients underwent ^{68}Ga-FAPI-04 and ^{18}F-FDG PET/CT (performed in 2 consecutive days), CTE, and GIUS. Demographic data and laboratory results, Montreal classification,[16] Crohn Disease Activity Index (CDAI) score (based on weight/height, hematocrit, stool count factor, using antidiarrheic, abdominal pain, general wellbeing, arthritis/arthralgia, iritis /uveitis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis, anal fissure/fistula/abscess, temperature, abdominal mass, and weight deviation points),[17] and simplified CDAI score (based on general wellbeing, abdominal pain, number of liquid stools in last 24 h, as well as finding of an abdominal mass and complications)[18] were obtained from medical records. Simple endoscopic scores for Crohn disease (SES-CD; based on endoscopic findings including the presence and size of ulcers, amount of the surface affected by ulcers or by any Crohn lesion, and presence/type of narrowing of the bowel lumen)[19] were recorded by endoscopists.

PET/CT Procedure and Imaging Analysis

PET/CT Procedure

The DOTA-FAPI-04 peptide was purchased from CSBio Co. The radiolabeling of ^{68}Ga-FAPI-04 was performed manually before injection according to the procedures previously published.[20] The PET scans were performed on dedicated PET/CT scanners (Biograph 64 Truepoint TrueV, Siemens; Polestar m660, SinoUnion). The PET/CT images (2 min/bed) were acquired with an uptake time of 79.9 ± 26.9 minutes. For ^{68}Ga-FAPI-04 PET/CT, imaging was performed (2 min/bed) with an uptake time of 60.6 ± 25.4 minutes after an injection of 114.7 ± 23.3 MBq ^{68}Ga-FAPI-04.

PET/CT Image Interpretation

Two experienced nuclear medicine physicians (Y.L. and Q.P.) visually assessed PET/CT images and were in consensus for the image interpretation. As to the gastrointestinal lesions, with the help of CT images for precise localization, the bowel was divided into 5 segments: (1) stomach and duodenum, (2) jejunum and proximal ileum, (3) the terminal ileum (10 cm from the ileocecal valve), (4) colorectum, and (5) anus. Uptake in the intestine was assessed visually, and increased radioactivity > hepatic uptake was interpreted as positive. In addition, in ^{18}F-FDG PET/CT, involved lesions and physiological bowel uptake were differentiated with coregistered CT, including wall thickening, perienteric inflammation, stricture, sinus tract/fistula, and lymphadenopathy. Extraintestinal involvement detected in PET/CT was also recorded.

Semiquantitative Analysis

Quantitative parameters of gastrointestinal lesions were measured as metabolic intestinal volume (MIV_{FDG} for ^{18}F-FDG and MIV_{FAPI} for ^{68}Ga-FAPI-04, defined as the sum of the metabolic volumes of intestinal lesions) and total intestinal uptake (TIU_{FDG} for ^{18}F-FDG and TIU_{FAPI} for ^{68}Ga-FAPI-04, defined as the sum of individual MIV multiplied by its mean SUV). PET/CT data were transferred in DICOM format to MIM workstation (version 6.6.11, MIM Software). Then, volumes of interest were drawn, including all intestinal lesions in the PET/CT images. Subsequently, lesion contours were first semiautomatically segmented with a SUV cutoff of 2.5 and were then checked and manually adjusted to exclude the physiological uptakes in urinary tract, etc. Afterward, volumetric parameters of TIU_{FAPI}, MIV_{FAPI}, TIU_{FDG}, MIV_{FDG}, and SUVmax were automatically obtained from the statistics generated with the final volumetric extraction.

Ileocolonoscopy and Conventional Imaging

Ileocolonoscopy

Ileocolonoscopies were performed after macrogol preparation, by senior endoscopists experienced in the field of Crohn disease and unaware of the results of other imaging results. For endoscopic assessment, 5 segments, including terminal ileum, the ascending colon, the transverse colon, the descending colon (including the sigmoid colon), and rectum to the anus, were evaluated, except for one patient in whom endoscopic exploration was terminated in the transverse colon due to strictures. The SES-CD values of each segment were calculated during the endoscopy, including the presence and size of ulcers, amount of the surface affected by ulcers or by any Crohn lesion, and the presence/type of narrowing of the bowel lumen.[21] The features of endoscopic lesions were also documented, including nonulcerated lesions (eg, erythema or pseudopolyp), erosions, or aphthoid ulcers, ulcers, stricture, and sinus tract/fistula.

Computed Tomography Enterography

The patients underwent an enema cleanse and a 12-hour fast before receiving CTE. The CT images were analyzed by 2 radiologists who were blinded to the ileocolonoscopy results and with 10 and 12 years of experience in abdominal CT, respectively. Typical features of Crohn disease included mural hyperenhancement, thickness, stratification, mesenteric fat density, and comb sign. Conclusions were reached by consensus.

Ultrasound of the Gastrointestinal Tract

The GIUS examinations were performed on bowel segments by 2 investigators who were blinded to the results of ileocolonoscopy and with 5 and 11 years of experience, and conclusions were reached by consensus.

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Statistical Analysis

Statistical analyses were done with Medcalc (version 19.6.4). Quantitative parameters between ^{68}Ga-FAPI-04 and ^{18}F-FDG PET/CT were compared using the Student *t* test for data with normal distribution or Wilcoxon test for skewed data (Shapiro-Wilk test for normality). The sensitivity and specificity for the detection of Crohn lesions in intestines by ^{68}Ga-FAPI-04 and ^{18}F-FDG PET/CT were calculated. The gold standard for confirming Crohn lesions was defined as the lesion detected by at least 2 diagnostic imaging examinations (CTE, GIUS, ^{18}F-FDG, and ^{68}Ga-FAPI-04 PET/CT) or ileocolonoscopy. Confirmation of anal involvement also included physical examination. The receiver operating characteristic curve analysis was performed to estimate the diagnostic performance of ^{68}Ga-FAPI-04 and ^{18}F-FDG PET/CT, and areas under the curve were compared. The correlation of PET semiquantitative indexes (TIU_{FAPI}, MIV_{FAPI}, TIU_{FDG}, MIV_{FDG}, and SUVmax) and clinical biomarkers were analyzed with Pearson correlation coefficients (for data with normal distribution) or Spearman rank correlation coefficients (for skewed data). A P value <0.05 was considered statistically significant.

RESULTS

Clinical Characteristics

Seventeen participants were recruited (13 men and 4 women, age 32.3 ± 15.9 y), presenting with abdominal pain (16/17), diarrhea (8/17), gross gastrointestinal bleeding (3/17), and perianal lesions (9/17). Clinical complications related to Crohn disease included intestinal obstruction (9/17), strictures (10/17), fistulas (9/17), and abdominal abscess (1/17). Eight patients presented with fever. Ten patients had extraintestinal manifestations, including aphthous ulcers, arthritis, iritis, renal stones, and skin disorders. Anemia was found in 10/17 patients, and 5/17 patients had hypoalbuminemia. Ten patients showed elevated erythrocyte sedimentation rate, whereas 11 patients had elevated high sensitivity C-reactive protein (hsCRP) levels.

For classification of gastrointestinal disease, ileocolonic type (13/17) was most frequently seen, followed by upper gastrointestinal plus ileocolonic type (2/17), ileal type (1/17), and colonic type (1/17). Summarizes the clinical characteristics of the participants.

PET/CT Diagnostic Performance

Two patients had received right hemicolectomy before enrollment, thus a total of 83 bowel segments were finally analyzed. Among the analyzed bowel segments, 40/83 (48.2%) of the segments were diagnosed as involvement of Crohn disease according to the gold standard as described previously. ^{68}Ga-FAPI-04 PET/CT correctly diagnosed 36 involved segments but detected 3 false-positive segments in anus and 4 false negative segments (3 anal lesions and 1 colon lesion), yielding a sensitivity and specificity of 90.0% and 93.0%, respectively. For ^{18}F-FDG PET/CT, 34 involved segments were correctly diagnosed, but 5 false-positive segments (4 anal lesions and 1 colon lesion) and 6 false-negative segments (4 anal lesions, 1 colon lesion, and 1 small intestinal lesion) were also noted, yielding a sensitivity and specificity of 85.0% and 88.4%, respectively. In receiver operating characteristic curve analysis, the area under the curve for detection of affected segments with ^{68}Ga-FAPI-04 and ^{18}F-FDG PET/CT were 0.92 (95% C: 0.83–0.97, $P <$ 0.001) and 0.87 (95% CI: 0.78–0.93, $P <$ 0.001), respectively. ^{68}Ga-FAPI-04 PET/CT showed better diagnostic performance compared with ^{18}F-FDG PET/CT (P = 0.043). The sensitivity of CTE and GIUS was 62.5% and 75.0%, and the specificity was 86.0% and 83.7%, respectively.

As to the positive segments on PET/CT, the SUVmax of ^{68}Ga-FAPI-04 and ^{18}F-FDG PET/CT was similar (8.7 ± 6.0 vs 8.0 ± 4.1, P = 0.881). However, the uninvolved segments showed significantly lower uptake of ^{68}Ga-FAPI-04 than ^{18}F-FDG (SUVmax: 1.3 ± 0.7 vs 2.2 ± 1.4, P = 0.0001), confirming the fact of lower background uptake of the bowels in ^{68}Ga-FAPI-04 than in ^{18}F-FDG.

Among the 40 affected segments, 22 segments were stricture or fistula lesions, and the remaining 18 segments were non-stricture or fistula lesions. The SUVmax of ^{68}Ga-FAPI-04 and ^{18}F-FDG in stricture/fistula lesions were significantly higher than those in non-stricture/fistula lesions (^{68}Ga-FAPI-04, 10.9 ± 6.7 vs 5.0 ± 3.5, P = 0.0002; ^{18}F-FDG, 9.5 ± 4.9 vs 5.3 ± 1.8, P = 0.0016). To further evaluate the weight of fibrotic activation (shown by ^{68}Ga-FAPI-04) and inflammation (shown by ^{18}F-FDG) in an individual lesion, we further calculated the PET index of each Crohn lesion, which was defined as the ratio of SUVmax of ^{68}Ga-FAPI-04 to SUVmax of ^{18}F-FDG. We found that the PET index of stricture/fistula lesions was significantly higher than the index of non-stricture/fistula lesions (1.23 ± 0.50 vs 0.93 ± 0.44, P = 0.0237). Representative images of PET/CT, CTE, and endoscopy are shown in Figures 1–4.

Eight patients had received medications before PET/CT scan, including mesalazine, infliximab, azathioprine, thalidomide, methotrexate, vedolizumab, and prednisone. There was no significant difference of the SUVmax of Crohn lesions in ^{68}Ga-FAPI-04 between pretreated patients and treatment-naïve patients (12.1 ± 9.7 vs 12.2 ± 4.7, P = 0.541); however, there was a tendency that the SUVmax in ^{18}F-FDG was higher in treatment-naïve patients than those with premedication, although the difference was not statistically significant (11.8 ± 3.9 vs 8.6 ± 6.0, P = 0.075).

Except for gastrointestinal involvement, 10 patients were detected with extraintestinal uptake on ^{68}Ga-FAPI-04 and ^{18}F-FDG PET/CT, including mesenteric lymph nodes (n = 6), skin (n = 3), spleen (n = 1), and vertebral facet joint and sacroiliac joint (n = 1). ^{68}Ga-FAPI-04 PET/CT detected additional extraintestinal involvement in salivary glands (n = 4) and peritoneum (n = 1). Apart from this, 5/17 patients (29.4%) showed increased FDG uptake in bone marrow (uptake higher than liver). Furthermore, patients with increased bone marrow metabolism had significantly higher CDAI scores than those with normal bone marrow uptake in ^{18}F-FDG PET/CT (305.0 ± 66.8 vs 159.2 ± 110.4, P = 0.0158).

Correlations of PET/CT With Clinical Biomarkers

We analyzed the correlations between semiquantitative indexes of PET/CT and biochemical, clinical activity, and endoscopic biomarkers, and the results showed that TIU_{FAPI} and MIV_{FAPI} were significantly correlated with hsCRP (r = 0.49, P = 0.045; r = 0.57, P = 0.016, respectively), meanwhile, MIV_{FAPI} was also significantly correlated with SES-CD (r = 0.53, P = 0.036). As to ^{18}F-FDG, TIU_{FDG} and MIV_{FDG} were significantly correlated with SES-CD (r = 0.52, P = 0.045; r = 0.52, P = 0.016, respectively). Other biomarkers, including

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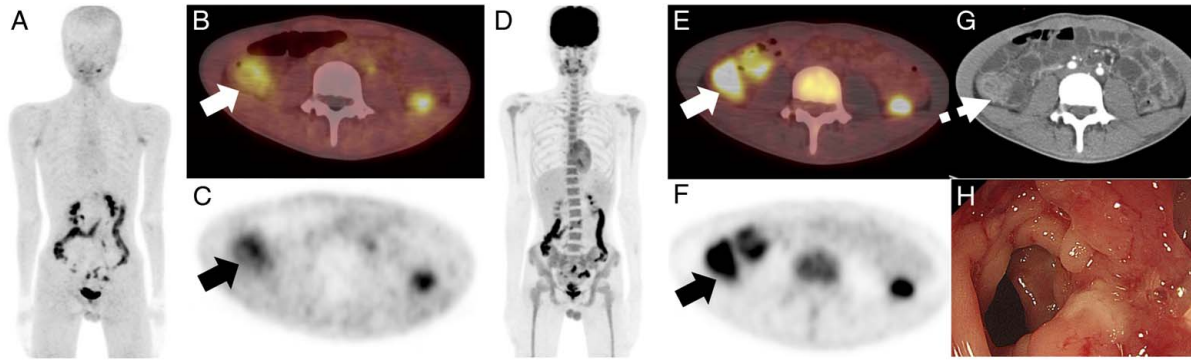

FIGURE 1. A 17-year-old man diagnosed with Crohn disease [Montreal classification A2L3B2P0, Crohn Disease Activity Index (CDAI) 376, simplified CDAI 9, simple endoscopic score for Crohn disease (SES-CD) 13]. The MIP of ^{68}Ga-FAPI-04 PET (**A**) showed intense uptake of radioactivity in the abdomen. Axial fusion image (**B**) and axial PET (**C**) indicated the abnormal uptake was located in the terminal ileum and colon with wall thickening (SUVmax: 9.0, arrows). The MIP of ^{18}F-FDG PET (**D**) showed FDG-avidity in the abdomen and increased uptake in bone marrow. The axial fusion image (**E**) and axial PET (**F**) of ^{18}F-FDG PET/CT exhibited intense uptake in the involved bowels (^{18}F-FDG SUVmax: 10.8, arrows). Consistently, computed tomography enterography (CTE; **G**) showed wall thickening and hyperenhancement in the terminal ileum and colon, with strictures in the iliocecum (dotted arrow). The ileocolonoscopy showed mucosa edema and ulcers in the terminal ileum and colon (**H**).

erythrocyte sedimentation rate, hemoglobin, albumin, interleukin-6, interleukin-8, interleukin-10, tumor necrosis factor-α, CDAI, and simplified CDAI, were not correlated with the semiquantitative indexes yielded in ^{68}Ga-FAPI-04 or ^{18}F-FDG PET/CT ($P > 0.05$).

DISCUSSION

In the current study, we found ^{68}Ga-FAPI-04 PET/CT showed better diagnostic performance compared with ^{18}F-FDG PET/CT in detecting intestinal lesions of Crohn disease. ^{68}Ga-FAPI-04 and ^{18}F-FDG uptake in stricture/fistula lesions were significantly higher than that in non-stricture/fistula lesions. Furthermore, the PET index (ratio of SUVmax of ^{68}Ga-FAPI-04 to SUVmax of ^{18}F-FDG) of stricture/fistula lesions was significantly higher than the index of non-stricture/fistula lesions. Semiquantitative indexes of ^{68}Ga-FAPI-04 PET/CT were significantly correlated with hsCRP level and SES-CD, meanwhile TIU_{FDG} and MIV_{FDG} in ^{18}F-FDG PET/CT was also correlated with SES-CD.

^{68}Ga-FAPI-04 and ^{18}F-FDG PET/CT could detect most of lesions in Crohn disease patients, and both had some false-positive and negative lesions in our study. The majority of false-positive and false-negative lesions in both PET/CT scans were located in anus, indicating the limitation of ^{68}Ga-FAPI-04 and ^{18}F-FDG in diagnosing perianal disease. Consistent with the incidence of perianal Crohn disease reported in the literature (varies from 3.8% to 80%), 52.9% (9/17) of the participants had perianal diseases in our cohort, including perianal fistula, perianal abscess, and anal fissures.[22] Physiological and benign FDG uptake in anus is commonly seen due to smooth muscle uptake, lymphatic tissue uptake, fecal microbes or hemorrhoids.[8] Similarly, moderate focal uptake of ^{68}Ga-FAPI in the anal canal had been incidentally found in 25.8% of cancer patients due to hemorrhoids, according to the literature.[23] These possibilities contribute to the false-positive results of perianal involvement of Crohn disease with ^{68}Ga-FAPI-04 and ^{18}F-FDG PET/CT. The false-negative results in anal diseases may be due to healed and non-active inflammation or small size of the lesions. Therefore, PET/CT could give

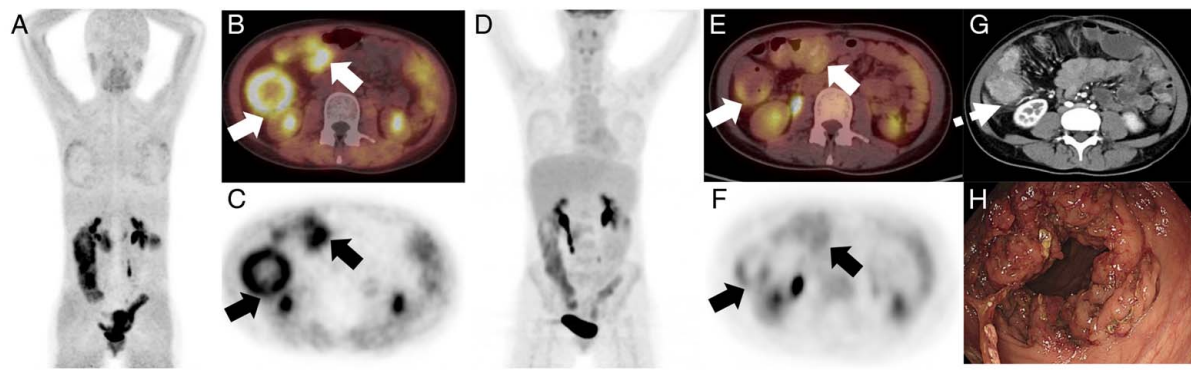

FIGURE 2. A 30-year-old woman diagnosed with Crohn disease (Montreal classification A2L2B2P0, CDAI 80.9, simplified CDAI 5, SES-CD 7). The MIP of ^{68}Ga-FAPI-04 PET (**A**) revealed intense radioactivity uptake in the abdomen, localized in the colon with wall thickening as shown in the axial fusion image (**B**) and axial PET (**C;** SUVmax: 10.4, arrows). The MIP (**D**), axial fusion image (**E**), and axial PET (**F**) of ^{18}F-FDG PET/CT demonstrated moderate avidity in the colon (SUVmax: 5.2, arrows), which was lower than the uptake of ^{68}Ga-FAPI-04. Consistently, CTE (**G**) showed wall thickening and hyperenhancement in the corresponding segments (dotted arrows). The ileocolonoscopy detected strictures and polyps in the ascending colon (**H**).

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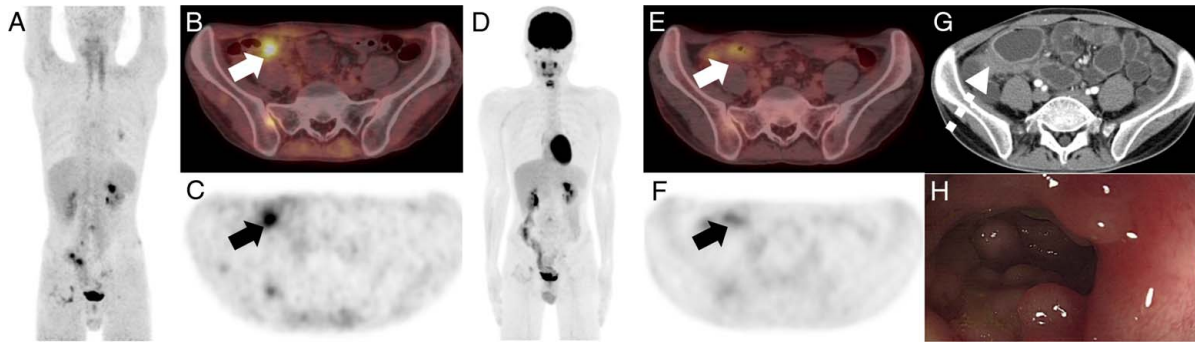

FIGURE 3. A 22-year-old man diagnosed with Crohn disease (Montreal classification A2L3B2+3P1, CDAI 128.7, simplified CDAI 5, SES-CD 4). The MIP of ^{68}Ga-FAPI-04 PET (**A**) exhibited focal uptake in the right lower quadrant, localized to the terminal ileum according to the axial fusion image (**B**) and axial PET (**C**; SUVmax: 9.1, arrows). Furthermore, increased uptake was observed in the right sacroiliac joint. The MIP of ^{18}F-FDG PET (**D**) showed physiological uptake in the ascending colon, while the uptake of ^{18}F-FDG in the terminal ileum lesion was mild (**E**, axial fusion image; **F**, axial PET of 18F-FDG PET/CT, SUVmax: 3.8, arrows). Consistently, CTE (**G**) showed mural hyperenhancement and stricture in the terminal ileum (dotted arrow). The ileocolonoscopy confirmed stricture and ulcers in the terminal ileum (**H**).

higher diagnostic accuracy when excluding the assessment of anus.

Except anal diseases, both ^{68}Ga-FAPI-04 and ^{18}F-FDG missed a nonulcerative lesion in colorectal segment, presenting as scattered pseudopolyps in endoscopy, possibly due to its low-grade activity of inflammation.[6] In addition, ^{18}F-FDG PET/CT missed a stricture disease in small intestine (SUVmax: 2.4), and it also mistaken a focal physiological uptake in the colon as Crohn disease involvement. Physiological FDG uptake in colorectum was seen in 52.9% (9/17) of the patients in our cohort (none of them had diabetes or used metformin), presenting as diffuse segmental uptake. This physiological uptake masked the colorectal lesion in one patient and impaired the diagnostic performance as being a false negative result.

In line with previous studies that showed FAP expression in immunohistochemistry was strongly expressed in the submucosa of Crohn disease strictures rather than non-strictured areas,[13,15,24] we found the SUVmax of stricture/fistula disease in ^{68}Ga-FAPI-04 was significantly higher than ^{68}Ga-FAPI-04 uptake in non-stricture/fistula lesions (10.9 ± 6.7 vs 5.0 ± 3.5, P = 0.0002). Meanwhile, the SUVmax of stricture/fistula lesions in ^{18}F-FDG PET/CT was also significantly higher than non-stricture/fistula lesions (9.5 ± 4.9 vs 5.3 ± 1.8, P = 0.0016). This result suggested that apart from stronger FAP expression, stricture/fistula disease also had higher activity of inflammation. This was consistent with previous studies showing the intensity of FDG uptake was significantly increased according to the severity of endoscopic lesions and was higher in deep ulcers or strictures than aphthoid or superficial ulcers.[4,24] Moreover, we further investigated the weight of activated fibrosis (presented by ^{68}Ga-FAPI-04 uptake) and inflammation (presented by ^{18}F-FDG uptake) in different types of Crohn lesions and found that the PET index (the ratio of SUVmax of ^{68}Ga-FAPI-04 to SUVmax of ^{18}F-FDG) was significantly higher in stricture/fistula lesions than that in non-stricture/fistula lesions (1.23 ± 0.50 vs 0.93 ± 0.44, P = 0.0237). This indicated that despite more activated inflammation in stricture/fistula disease, the

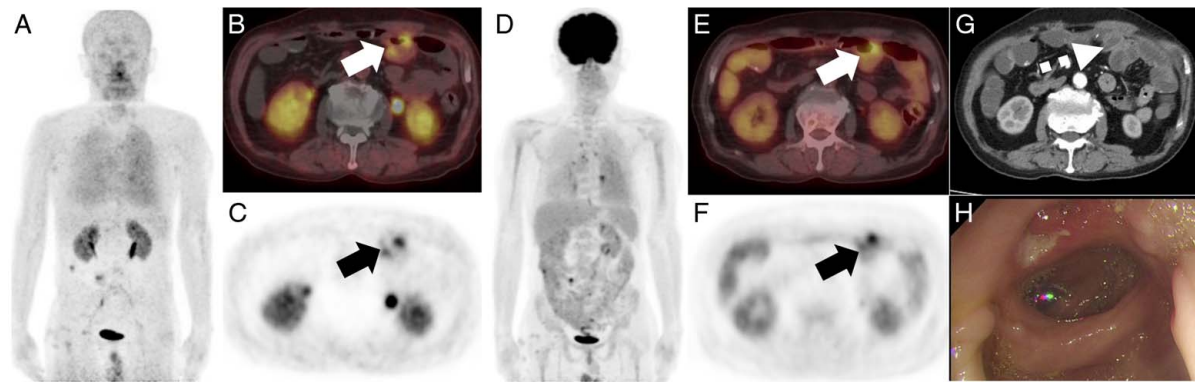

FIGURE 4. A 74-year-old man diagnosed with Crohn disease (Montreal classification A3L3B2+3P0, CDAI 280, simplified CDAI 10, SES-CD 2). He had received right hemicolectomy because of intestinal obstruction before enrollment. The MIP of ^{68}Ga-FAPI-04 (**A**), axial fusion image (**B**), and axial PET (**C**) showed moderate uptake in the anastomotic stoma and small intestines (SUVmax: 5.1, arrows). The MIP of ^{18}F-FDG PET (**D**) showed diffuse physiological uptake in the bowels with several focal areas of increased uptake. The axial fusion image (**E**) and axial PET (**F**) revealed the focal uptake was located in the anastomotic stoma and small intestines (SUVmax: 5.3, arrows). Notably, there was diffuse uptake of both ^{68}Ga-FAPI-04 and ^{18}F-FDG in bilateral lungs, consistent with interstitial pulmonary fibrosis. CTE (**G**) showed mural hyperenhancement but normal intestinal lumen in the anastomotic stoma (dotted arrow), which was confirmed by ileocolonoscopy showing only ulcerations in the anastomotic stoma (**H**).

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fibrogenic process may predominate over inflammation in these lesions than in non-stricture/fistula lesions.

In correlation analysis, we found semiquantitative indexes derived from ^{68}Ga-FAPI-04 PET/CT (TIU_{FAPI} and MIV_{FAPI}) were significantly correlated with hsCRP. Elevated levels of CRP in Crohn disease indicated active disease,[25,26] and increased FAP overexpression in activated fibroblasts was the major pathologic feature of the progression of Crohn disease. However, we did not find a significant correlation between ^{68}Ga-FAPI-04 uptake values and CDAI or simplified CDAI scores in the current study. These scoring systems used a combination of patient-reported symptoms (such as the number of stools per day and abdominal pain), extraintestinal manifestations, physical examination findings, hematocrit, etc. However, bowel inflammation might be asymptomatic and underestimated even during symptom-free intervals, and ongoing subclinical inflammation can often lead to irreversible bowel damage.[27] In addition, they evaluated the disease in a single moment in time and overlooked cumulative bowel damage.[28] By contrast, PET/CT can provide an objective method to evaluate the overall burden of disease, and we found significant correlations between both ^{68}Ga-FAPI-04 and ^{18}F-FDG PET/CT and SES-CD, which was a disease activity score evaluated by endoscopy. We think this may explain the irrelevance of PET/CT parameters and clinical disease activity assessment (CDAI or simplified CDAI) in our study.

In ^{18}F-FDG PET/CT, 29.4% of the patients (5/17) showed increased bone marrow uptake (uptake higher than liver), in whom the CDAI scores were higher than that in patients with normal bone marrow uptake (305.0 ± 66.8 vs 159.2 ± 110.4, $P = 0.0158$). Bettenworth and colleagues had observed intense FDG uptake in the bone marrow induced by hyperplasia of immature neutrophils in mice models of inflammatory bowel disease. It was speculated this activation significantly correlated to the ongoing intestinal inflammation, which was also predominantly mediated by neutrophils and macrophages.[29] Moreover, enhanced metabolic activation of bone marrow can also be caused by anemia, a common extraintestinal complication of Crohn disease.[30] These factors suggested that more activated disease may lead to hypermetabolism of bone marrow, showing higher bone marrow uptake in ^{18}F-FDG PET/CT.

Our study had several limitations. First, as a prospective pilot study, the cohort had a relatively small number of patients. Second, we did not perform FAP immunohistochemistry on intestinal specimens. Third, treatment response and long-term prognosis were not included in the current study, which needed to be further investigated.

CONCLUSIONS

^{68}Ga-FAPI-04 PET/CT showed better diagnostic performance compared with ^{18}F-FDG PET/CT in detecting involved bowels in Crohn disease. The SUVmax of ^{68}Ga-FAPI-04 and ^{18}F-FDG in stricture/fistula lesions were significantly higher than those in non-stricture/fistula lesions, suggesting more activated fibrosis and inflammation in stricture/fistula disease. Semiquantitative indexes of ^{68}Ga-FAPI-04 PET/CT were significantly correlated with hsCRP and SES-CD.

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