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Original Article

The reproducibility of [68Ga]Ga-FAPI-04 PET uptake parameters at 15 min and 60 min post-injection

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Abstract: Gallium-68 labeled fibroblast activation protein inhibitor ([68Ga]Ga-FAPI-04) can be visualized just 15 min post-injection. However, the appearance of imaging at 15 and 60 min remains unclear. This study aimed to explore the relationship between quantitative values in [68Ga]Ga-FAPI-04 PET, specifically at 15 and 60 minutes post-injection, in patients with various tumor. We enrolled 30 patients with cancer who underwent [68Ga]Ga-FAPI-04 PET/CT scan between January 2021 and February 2025 at our institute. Image acquisition was performed using a PET/CT scanner at 15 min and 60 min after [68Ga]Ga-FAPI-04 injection. The maximum, mean and peak standardized uptake value (SUV_{max}, SUV_{mean} and SUV_{peak}), tumor-to-liver ratio (TLR), and uptake tumor volume (UTV) were measured in the region of interest of the target lesion, liver SUV_{mean} (SUV_{liver}) was also measured. Correlation coefficients of the between-image variables were evaluated by Spearman's rank correlation test. Agreement between the variables was evaluated by Bland-Altman plots with 95% limits of agreement. The SUV_{max}, SUV_{mean}, SUV_{peak} and UTV in tumors of all examinations were decreased from 15 min to 60 min. The SUV_{max}, SUV_{mean}, SUV_{peak}, TLR, and UTV at 15 min and 60 min were highly correlated (r_s = 0.945, 0.949, 0.959, 0.943, and 0.958; $P < 0.001$). The 95% limits of agreement ranged from -27.8 to 29.1 with a mean of 0.7 and -24.1 to 29.5 with a mean of 2.7 for SUV_{max} and SUV_{mean}, respectively. Other PET metrics demonstrated that all limits are above ± 30% between 15 min and 60 min. We observed a high correlation between the quantitative values at 15 min and 60 min. Meanwhile, 15 min and 60 min [68Ga]Ga-FAPI-04 PET SUV_{max} and SUV_{mean} have clinically acceptable reproducibility, and 15 min scan is feasible for all patients, but SUV_{peak}, TLR and UTV should not be used interchangeably.

Keywords: FAPI, PET/CT, SUV, TLR, UTV, reproducibility

Introduction

The tumor microenvironment (TME) is a complex milieu of cancer, stromal, and immune cells, which plays a crucial role in tumor proliferation, angiogenesis, invasion, metastasis, and drug resistance through pro-tumorigenic signaling pathways [1, 2]. Cancer-associated fibroblasts (CAFs) as a major TME cellular component, has emerged as attractive TME targets. CAFs is a highly heterogeneous cell population, and several factors, such as the tissue type in which the cancer grows, the local paracrine cues, and the cell type of origin of CAFs, contribute to CAFs heterogeneity [3-5]. Fibroblast activation protein (FAP), a transmembrane serine protease, is highly expressed in CAFs in over 90% of human epithelial neoplasms and is considered a pan-tumor antigen, which is a promising target for CAFs depletion [6].

Gallium-68 labeled fibroblast activation protein inhibitor ([68Ga]Ga-FAPI-04) has recently been introduced as a promising tumor imaging agent targeting CAFs [7]. Numerous studies have reported that [68Ga]Ga-FAPI-04 PET/CT have distinct advantages and clinical value in staging, restaging and radiotherapy planning of a variety of tumors [7-9]. It is reported that tumor imaging can be performed in about 10 min after the injection of [68Ga]Ga-FAPI-04, but most of the images collected in most studies are 15 to 60 min post-injection [10]. In the reports by Giesel et al., Wang et al., and Ballal et al., early [68Ga]Ga-FAPI-04 PET/CT imaging was performed in patients with tumors with satisfactory imaging results [11-13]. By observing the pharmacokinetic profiles of [68Ga]Ga-FAPI-04 in vivo and tumor distribution at different time points, it was found that [68Ga]Ga-FAPI-04 could rapidly achieve stable physiological and biological distribution in vivo, and it changed little in time from 10 min to 60 min [11, 12].

To the best of our knowledge, there is no study focused on the value of [68Ga]Ga-FAPI-04 PET/CT at early imaging. The total examination time can be shortened if the quantitative values of [68Ga]Ga-FAPI-04 PET at 15 min and 60 min post-injection are equivalent.

The purpose of this observational prospective study is to determine the reproducibility of PET parameters obtained at 15 min and 60 min after [68Ga]Ga-FAPI-04 injection.

Materials and methods

Patients

We enrolled 30 patients with various tumor who underwent [68Ga]Ga-FAPI-04 PET/CT scanning between January 2021 and February 2025 at our institute. This study was approved by the Ethics Committee of Changhai Hospital (CHEC2021-071). All patients provided signed informed consents before undergoing the [68Ga]Ga-FAPI-04 PET/CT examination. Patients who had undergone anti-tumor treatment within 3 months prior to the [68Ga]Ga-FAPI-04 PET/CT scans were excluded.

Radiopharmaceuticals

Synthesis and labeling of [68Ga]Ga-FAPI-04 was performed according to the method described in the literature [14]. ^{68}Ga was obtained by eluting a ^{68}Ge-to-^{68}Ga generator (ITG, Germany). It was chelated after the pH adjustment with sodium acetate. Then, the reaction mixture was heated to 100°C for 10 min, and the integrity of the reaction was checked by radio-liquid chromatography. Solid-phase extraction of ^{68}Ga compounds was performed before injection. The final product was sterile and pyrogen-free, and the radiochemical purity was > 95%.

[68Ga]Ga-FAPI-04 PET/CT imaging

Image acquisition was performed at 15 min and 60 min after [68Ga]Ga-FAPI-04 administration. All acquisitions were performed on a Biograph 64 PET/CT scanner (Siemens Healthcare, Germany). The intravenous injection of [68Ga]Ga-FAPI-04 was 1.85-3.70 MBq/kg. The whole-body CT scanning parameters were as follows: voltage, 120 kV; current, 170 mA; and thickness, 3 mm. The PET scan was performed after CT scan acquisition. The whole-body PET scan was 5-6 beds including the entire field of view from the upper thigh to the head and the local scan was 1-2 bed including the lesion site, PET data were acquired for 3 min per bed position. All acquired data were reconstructed using a dedicated post-processing workstation with TrueD software, and CT images were used for attenuation correction.

Image analysis

All images were registered in the Syngo.Via workstation (Siemens Healthcare, Erlangen, Germany) and displayed in coronal, axial, and sagittal planes and with rotating 3D images. Two nuclear medicine physicians (C.C. and Z.C.) with more than 10 years of experience in PET interpretation independently measured the PET parameters with Syngo.Via workstation, and interobserver reliability was evaluated. A spherical VOI was placed in the lesion, with a maximum of 3 different lesions drawn per patient. For each lesion, the maximum standardized uptake value (SUV_{max}), peak standardized uptake value (SUV_{peak}), and mean standardized uptake value (SUV_{mean}) were calculated. SUV_{peak} was the SUV_{mean} of a 1-cm^3 sphere in the target lesion. Additionally, the SUV_{mean} of the liver (SUV_{liver}) were measured as a reference. In order to capture the entire liver as much as possible, three different regions of interest (ROI) without vascular area including two in the right liver lobe anteroposteriorly and one in the left liver lobe were selected. The SUV_{mean} of these ROI were averaged to estimate the liver SUV_{mean} value, and the ratios of tumor uptake to liver uptake ratios (TLR) were calculated. In the present study, relative threshold of 40% SUV_{max} was adopted as the threshold to measure metabolic tumor volume (UTV) based on a previous study [15, 16].

Statistical analysis

Statistical analysis was performed using SPSS software (version 26.0; IBM, Armonk, NY, USA). Interobserver agreement were calculated using the intraclass correlation coefficient (ICC). A *Wilcoxon* signed rank test was used to compare differences between early and late time points. Correlation analysis was also performed using Spearman correlation, and agreement was evaluated based on the Bland-Altman method using 95% limits of agreement (LOA). A correlation coefficient (r_s) greater than ± 0.7 represented a strong correlation, ± 0.5 to ± 0.7 moderate, and less than ± 0.5 weak. The maximal clinically acceptable limits range was defined as ± 30%, based on the PET response evaluation criteria in solid tumors (PERCIST) definition for partial response and progressive disease [17]. Two-tailed *P* values of less than 0.05 were considered statistically significant.

Results

A total of 30 patients with 49 lesions were included for evaluation in this study. The median age of the patients was 61 years (range: 38-86 years); there were 16 men and 14 women. The median time interval between injection and scan start was 15 min (range, 14-17 min) for 15 min post-injection and 60 min (range, 58-65 min) for 60 min post-injection groups (**Table 1**). A typical case was depicted in **Figure 1**.

All the ICCs pertaining to interobserver reliability demonstrated outstanding reliability for all the measurements, as presented in **Table 2**. The ICCs, along with their 95% confidence intervals, for interobserver reliability in the measurement of the diverse values surpassed 0.9 for all the variables. The reason behind this is that [68Ga]Ga-FAPI-04 uptake is higher in tumor tissues and lower in normal tissues, resulting in a higher tumor-to-background ratio and better image contrast. As a result, the average of their observations was employed for the statistical computations.

The SUV_{max}, SUV_{mean}, SUV_{peak} and UTV in tumors of all examinations were decreased from 15 min to 60 min and only the difference in SUV_{peak} and UTV between two-time points was statistically significant ($P < 0.05$; *Wilcoxon*

Table 1. Patient characteristic

		Patients with visible lesions (*N* = 30)
Age (years)		59.5 ± 10.1 (38-86)
Gender	Female	N = 14
	Male	N = 16
Time to first scan (min)		14-17
Time to second scan (min)		58-65
Diseases	Brain	1
	Lung	2
	Heart	1
	Liver	8
	Gallbladder	3
	Bile duct	3
	Pancreas	7
	Stomach	1
	Intestines	2
	Kidney	1
	Bone	1
Number of lesions	1	22
	2	3
	3	7

signed rank test) (**Table 3**). Changes in SUV_{max} and SUV_{mean} in tumor between the 2 PET/CT scans were not significantly different ($P > 0.05$). And the early SUV_{liver} was significantly higher than which on late images ($P < 0.001$; *Wilcoxon* signed rank test). These effects resulted in significantly rising TLR from early images to late images. The differently defined contrasts revealed significantly higher values for examinations 60 min post-injection by applying the *Wilcoxon* signed rank test ($P < 0.001$).

The uptake parameters at 15 min and 60 min were highly positively correlated (**Figure 2**, $P < 0.001$). The 95% LOA and mean difference expressed as percentages for SUV_{max} and SUV_{mean} were below the clinically acceptable range of ± 30%, but was larger for SUV_{peak}, UTV and TLR (**Table 4**). Representative Bland-Altman plots for SUV_{max} and SUV_{mean} with y-axis values expressed as percentages showed 95% LOA ranging from -27.8 to 29.1 with a mean of 0.7 and -24.1 to 29.5 with a mean of 2.7, respectively (**Figure 3**).

Discussion

Among all FAPI tracers, [68Ga]Ga-FAPI-04 was the most studied PET molecular imaging probe. Compared with [18F]FDG, [68Ga]Ga-FAPI-04 imaging is not influenced by movement and blood glucose levels [11]. No fasting or resting preparation is necessary before examination. Because of its high tumor uptake, low accumulation in normal tissues, and ability to rapidly clear from the blood circulation, adequate images can be obtained 10 min post-injection, which makes quick imaging feasible [11, 14].

In previous studies, multiple acquisition protocols were used in [68Ga]Ga-FAPI-04 PET/CT imaging, and most images were collected from 15 min to 60 min post-injection [10]. In recent years, many scholars tried to explore early imaging with a variety of tracers and have obtained abundant results [18-20]. A study by Chondrogiannis et al. [18] found that early (4 min post-injection) ^{18}F-choline images improve clarity of pelvic prostate cancer lesion and the detection rate of pelvic lesions was similar to that of late (60 min post-injection) images. Similarly, Dadgar et al. [19] found that early static (3-6 min post-injection) ^{68}Ga-PSMA-11 PET/CT imaging might discriminate metastases from urinary bladder and early static imaging in combination with 60 min post-injection imaging can improve the detection of local involvement of pelvic disease. Broos et al. [20] studied 64 patients with hyperparathyroidism and found 89% hyperfunctioning parathyroid glands were adequately visualized on 5 min after ^{18}F-fluorocholine injection imaging. The feasibility of early [68Ga]Ga-FAPI-04 PET imaging was also mentioned, but the repeatability of the parameters was not analyzed [11-13].

In the present study, differences between epigastric tumor imaging with [68Ga]Ga-FAPI-04 PET/CT at 15 min and 60 min after injection were analyzed. Overall, tumor foci showed high [68Ga]Ga-FAPI-04 uptake on early images, which is consistent with previously published reports [11, 12]. In the study by Giesel et al. [11], a patient with metastasized breast cancer underwent 10 min, 60 min, and 180 min [68Ga]Ga-FAPI-04 PET imaging, which showed little change in radionuclides in normal tissue from 10 min to 180 min after [68Ga]Ga-FAPI-04 injection. This feature has also been validated in Asian subjects by Wang et al. [12]. From the illustration showed by Giesel et al. [11], there was a small change in SUV_{max} from 10 min to 60 min for the metastases, a slight decrease in SUV_{max} for the lumbar and sternal metastases between the two time points, a slight increase in the femoral and iliac metastases, and the greatest change was seen in the femur (change values less than 2). In a case of [68Ga]Ga-FAPI-04 imaging of pancreatic cancer shown by Röhrich et al. [21], the mass had a slightly elevated SUV_{max} at 60 min relative to 10 min (12.66 *vs.* 11.48). In their study, due to the limited number of subjects no further statistical analyses were performed.

The results of this study show that the [68Ga]Ga-FAPI-04 image has a TLR higher at the 60 min point than at 15 min. Regarding the absolute value, SUV was non-significant, while TLR had significant differences mainly due to decreased background activity resulting from decay and washout. In a study by Wang et al. [12], the SUV_{mean} in most organs decreases with time after injection of [68Ga]Ga-FAPI-04 tracer in all organs of the body and the tumor-to-non-tumor SUV ratio in three lung cancer patients at 44 min was higher than that at 12 min (20.5 *vs.* 14.3, 8.8

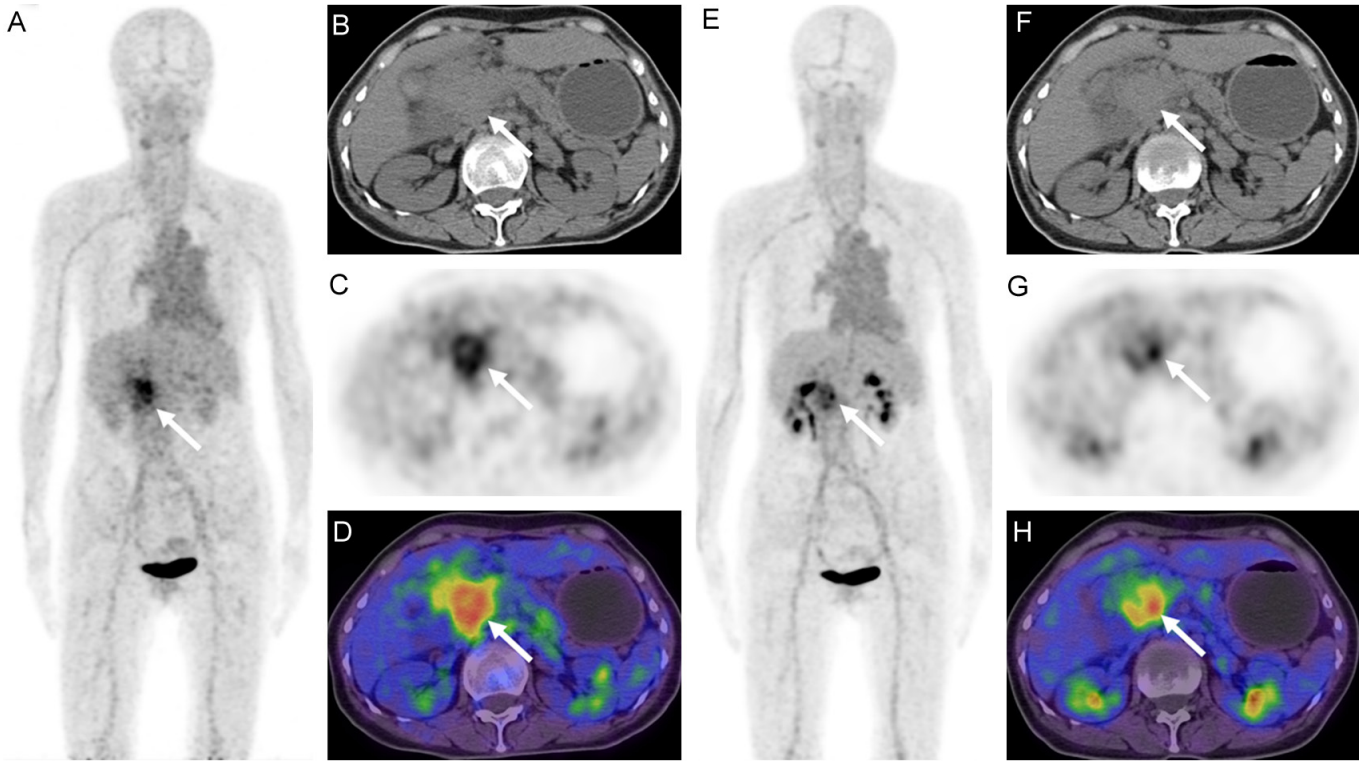

Figure 1. A 65-year-old woman with pancreatic head cancer. 15 min MIP imaging (A) shows a concentrated radioactive image in the upper abdomen. Axial CT (B) reveals an isodense mass in the pancreatic head with indistinct boundaries. Corresponding axial PET (C) and fusion (D) images at the same level indicate increased radioactive uptake in the mass, with SUV_{max} of 12.4, SUV_{mean} of 6.5, SUV_{peak} of 8.8, SUV_{liver} of 2.3, and UTV of 20.1. The 60min MIP (E), CT (F), PET (G), and fusion (H) images are similar to those at 15 min, with SUV_{max} of 11.3, SUV_{mean} of 6.3, SUV_{peak} of 8.5, SUV_{liver} of 2.0, and UTV of 17.5.

Table 2. Interobserver ICC and 95% confidence interval

	15 min		60 min	
	ICC	95% CI	ICC	95% CI
SUV_{max}	1.000	1.000-1.000	1.000	1.000-1.000
SUV_{mean}	0.999	0.998-0.999	0.999	0.998-0.999
SUV_{peak}	1.000	1.000-1.000	1.000	1.000-1.000
SUV_{liver}	0.989	0.981-0.994	0.967	0.943-0.981
TLR	0.963	0.935-0.979	0.915	0.850-0.952
UTV	0.989	0.981-0.994	0.996	0.992-0.997

vs. 6.7 and 5.9 *vs.* 3.8, respectively). This is consistent with our study.

We observed a high correlation between the quantitative values of all [68Ga]Ga-FAPI-04 PET metrics at 15 min and 60 min post-injection with clinically acceptable agreement only for SUV_{max} and SUV_{mean} of lesions. SUV_{peak} is the average value within a small, fixed-size ROI in the hottest part of the tumor. PERCIST recommends using SUV_{peak} from the tumor when comparing two studies for treatment response assessment [17, 22]. According to the latest literature, in a variety of tumors, [68Ga]Ga-FAPI-04 PET also showed promise for monitoring response to treatment in patients [23-25]. We found good correlation of SUV_{peak} at 15 min and 60 min post-injection but a wide range of limits was demonstrated on Bland-Altman plots which is considered to be clinically unacceptable. Therefore, attention should be paid to the consistency of scanning time before and after treatment when using [68Ga]Ga-FAPI-04 PET parameter SUV_{peak} to evaluate curative effect. So far, many studies have shown that the uptake was significantly lower for [68Ga]Ga-FAPI-04 than [18F]FDG in background tissues. Therefore, [68Ga]Ga-FAPI-04 PET has higher tumor-to-background ratios in multiple tumors and metastatic tumors [26, 27]. We found a strong linear correlation of lesional TLR at 15 min and 60 min post-injection. However, the range of 95% LOA was far beyond the clinically acceptable range. The volume parameters (MTV) measured by [18F]FDG PET can better reflect the metabolic load of tumors. Many studies have shown that MTV has high prognostic value [28, 29]. Qin et al. [30] suggested that [68Ga]Ga-FAPI-04 PET may play an important role in the tumor volume delineation of nasopharyngeal carcinoma patients, especially for those with locally advanced diseases. A study of head and neck cancers by Syed et al. [31] found that [68Ga]Ga-FAPI-04 PET has the potential to be ideal for precisely delineating tumor borders and protecting healthy tissue. The results of this study show a strong linear correlation (r = 0.958) between UTV measured at 15 and 60 min post-injection. However, the range of 95% LOA was far beyond the clinically acceptable range. This indicates that attention should be paid to the effect of scanning time when using [68Ga]Ga-FAPI-04

Table 3. Concordance of relevant parameters between 15 and 60 min

	SUV_{max}	SUV_{mean}	SUV_{peak}	SUV_{liver}	TLR	UTV
15 min	7.13 ± 3.24	3.99 ± 1.77	5.39 ± 2.66	2.20 ± 0.91	3.87 ± 2.78	28.19 ± 37.22
60 min	6.99 ± 2.96	3.86 ± 1.66	4.98 ± 2.49	1.90 ± 0.84	4.77 ± 4.30	24.83 ± 32.32
Z	-0.605	-1.508	-3.467	-5.909	-5.158	-2.472
P value	0.545	0.132	0.001	0.000	0.000	0.013
r_s	0.945	0.949	0.959	0.912	0.943	0.958
P value	0.000	0.000	0.000	0.000	0.000	0.000

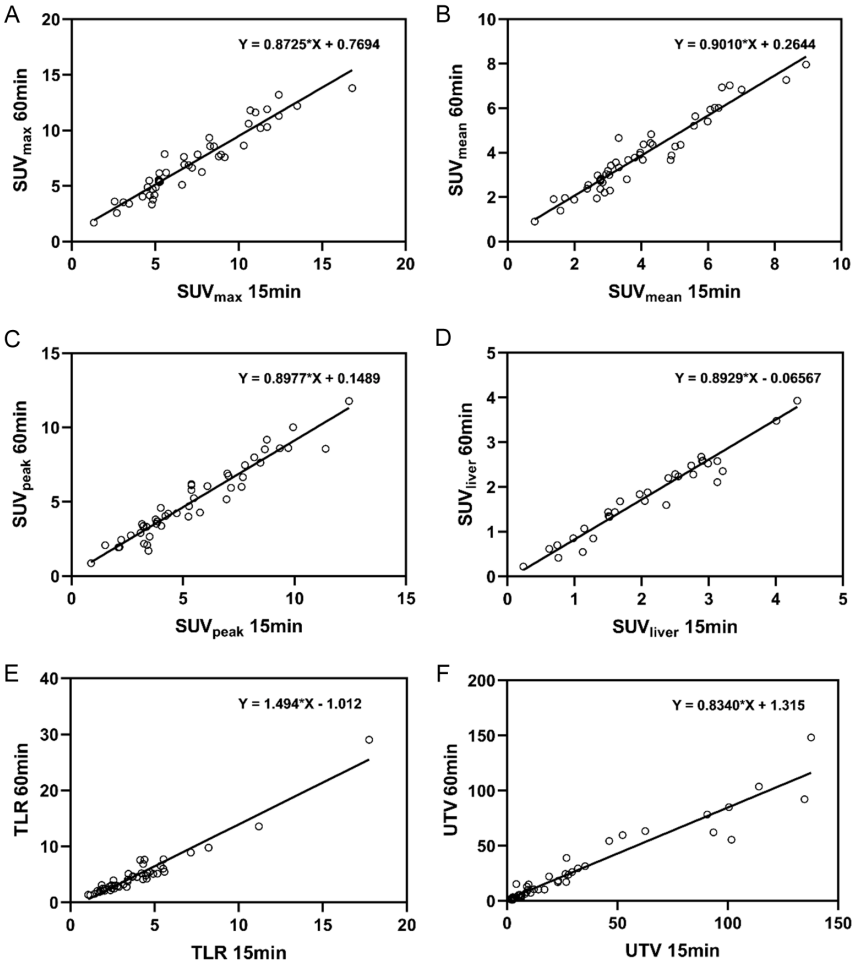

Figure 2. Scatterplots of [68Ga]Ga-FAPI-04 PET 15 min *vs.* 60 min parameters. (A) SUV_{max}, (B) SUV_{mean}, (C) SUV_{peak}, (D) SUV_{liver}, (E) TLR, (F) UTV. The lines show the modelled linear fit of these parameters.

Table 4. Lower and upper 95% LOA and mean difference

	Mean difference (%)	LOA (%)	
		Lower	Upper
SUV_{max}	0.7	-27.8	29.1
SUV_{mean}	2.7	-24.1	29.5
SUV_{peak}	7.9	-25.2	40.9
SUV_{liver}	16.9	-16.9	50.7
TLR	-16.3	-49.4	16.8
UTV	13.4	-56.5	83.2

UTV to evaluate tumor volume. This should be studied in more detail in the future. The significant decline in SUVpeak and UTV between 15 and 60 min scans, despite high correlation, stems from methodological sensitivities in their quantification. SUV_{peak}, reflecting mean uptake in a 1-cm^3 ROI, is affected by spatial tracer redistributions, tumor heterogeneity, and partial volume effects, leading to variability [22, 27]. Physiological clearance of [68Ga]Ga-FAPI-04 may also shift the "hottest" region, lowering SUV_{peak}. For UTV, the 40% SUV_{max} threshold method is sensitive to absolute threshold drift and tracer washout, which can reduce apparent volume while biological tumor burden remains stable, especially for tracers with rapid clearance [14, 28].

Despite very good correlation between 15 min and 60 min measured [68Ga]Ga-FAPI-04 PET parameters, the Bland-Altman 95% LOA in SUV_{peak}, TLR and UTV are far beyond the clinically acceptable range. This highlights the challenge of clinical interchangeability of these parameters between 15 min and 60 min scans. In staging, inconsistent TLR values at different time points may confuse the assessment of tumor and background contrast [21]. For therapy monitoring, the instability of UTV may weaken its correlation with metabolic tumor burden, thereby limiting its role in risk stratification [15]. Therefore, in [68Ga]Ga-FAPI-04 PET, the SUV_{max} and SUV_{mean} measured by 15 min can be used interchangeably with 60min, while SUV_{peak}, TLR and UTV should not be used interchangeably. Standardized scan timing is imperative if SUV_{peak}, TLR, or UTV are clinically adopted, as temporal variability undermines longitudinal comparability. Protocol harmonization ensures consistent biomarker interpretation for staging or therapy monitoring [17, 28].

Our study has several limitations. First, the relatively low number of the patients in a single center. Second, the

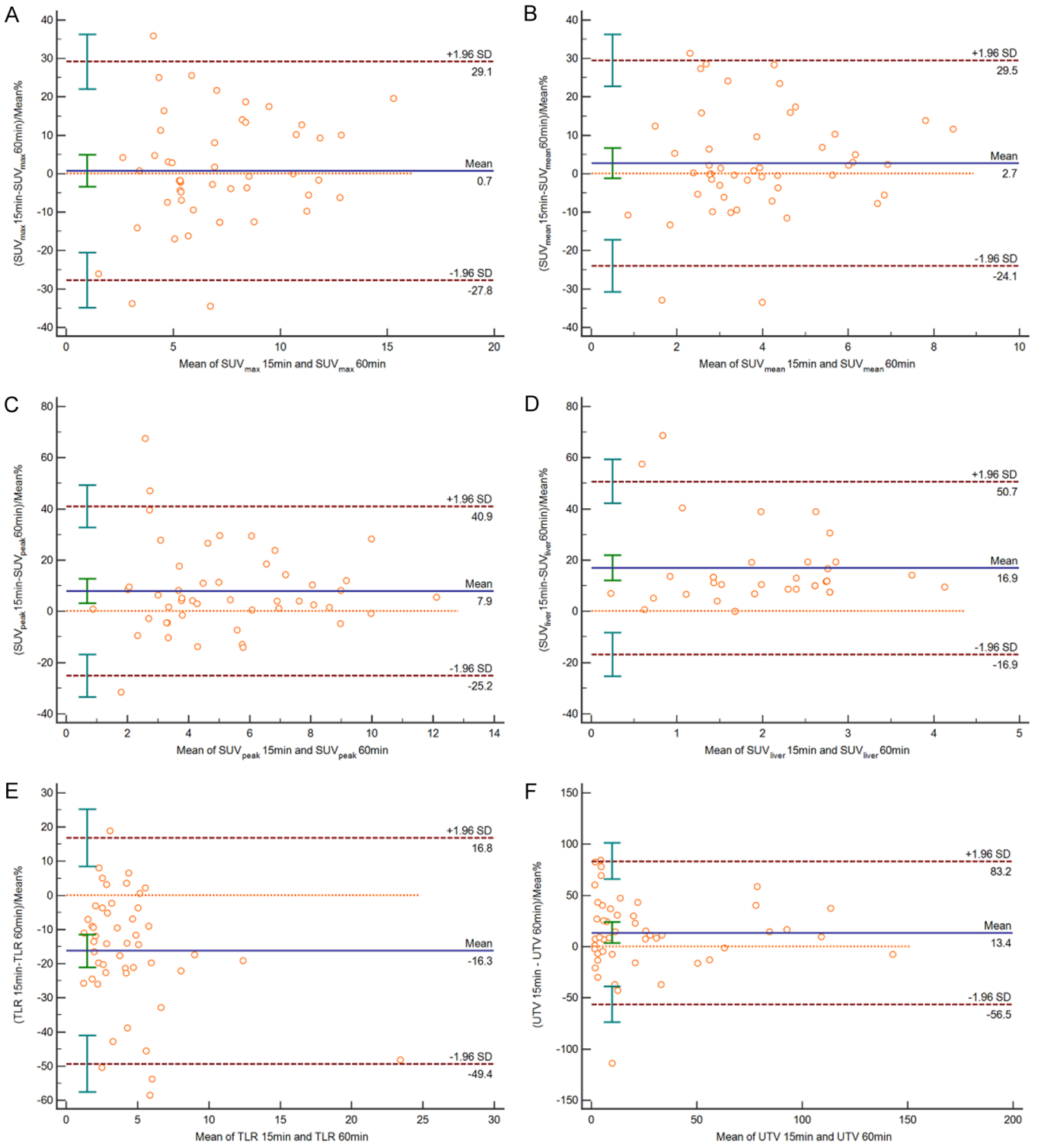

Figure 3. Bland-Altman plots. (A) SUV_{max}, (B) SUV_{mean}, (C) SUV_{peak}, (D) SUV_{liver}, (E) TLR, (F) UTV. Solid lines represent mean regression lines, and dotted lines represent the 95% CIs for total cohort.

variety of diseases included in the study was limited. Third, not all lesions were confirmed by histopathology. Another limitation is that the number of cases with accompanying metastatic tumors in this study was limited, so no grouping analysis was conducted on metastatic lesions.

Conclusion

Our study demonstrated a high correlation between quantitative values obtained at 15 min and 60 min post-injection of [68Ga]Ga-FAPI-04. Our data indicates that imaging

15 min after injection can be used clinically, and reducing scanning time to 15 min can improve workflow efficiency, especially in high-capacity centers, by increasing scanner throughput, reducing operational costs (such as staff time, radiopharmaceutical logistics), and optimizing resource allocation. However, the LOA for SUV_{peak}, TLR, and UTV significantly exceed clinically acceptable ranges. As a result, these indicators cannot be used interchangeably at 15 and 60 minutes. It is crucial to maintain consistent scanning times during clinical applications to ensure reliable results.

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All subjects provided written informed consent.

Disclosure of conflict of interest

None.

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