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Abstract

Objective ^{18}F-FDG PET/CT is a hybrid imaging method widely used as a useful, noninvasive imaging modality for evaluating various neoplastic diseases. When assessing the tumor uptake, the liver and the mediastinal blood pool are often used as a reference region. In daily clinical practice, the ^{18}F-FDG uptake in the liver sometimes appears to decrease on PET images of patients with malnutrition. The purpose of this study was to investigate whether or not the liver ^{18}F-FDG uptake is decreased in patients with malnutrition.

Methods We retrospectively analyzed 246 patients who underwent ^{18}F-FDG PET/CT from January 2018 to June 2018 and whose blood serum albumin was measured within 1 month of PET/CT. We compared the liver uptake and mediastinal blood uptake of patients with low serum albumin level (< 4.0 g/dl) and hypoalbuminemia (< 3.5 g/dl) with those with a normal serum albumin level (≥ 4.0 g/dl). Correlations between the liver and mediastinal blood uptake and the serum albumin level were also calculated.

Results The maximum standardized uptake value (SUV$_{max}$) and mean standardized uptake value (SUV$_{mean}$) of the liver in 117 patients with low serum albumin were 3.1 ±

0.5 and 2.3 ± 0.3, respectively, while they were 2.9 ± 0.4, 2.0 ± 0.3 in 29 patients with hypoalbuminemia; these values were all significantly lower than the respective ones (3.4 ± 0.5, 2.5 ± 0.4) in 129 patients with normal serum albumin (all $p < 0.001$). The SUV_{mean} of the mediastinal blood uptake in patients with hypoalbuminemia and normal serum albumin were 1.6 ± 0.2 and 1.7 ± 0.3, respectively ($p = 0.053$). The serum albumin level demonstrated a significantly positive, moderate correlation with the liver SUV_{mean}, showing a regression line of $y = 0.31x + 1.1$ ($r = 0.41$, $p < 0.001$).

Conclusion The liver ^{18}F-FDG uptake tended to decrease in patients with hypoalbuminemia. In the patients with malnutrition, the mediastinal blood pool may be more stable reference than the liver for evaluating the tumor activity because hypoalbuminemia is considered to less strongly influence the mediastinal blood pool than that in the liver.

Keywords: malnutrition; hypoalbuminemia; albumin; liver; FDG

Introduction

[^{18}F] fluoro-2-deoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) has been widely accepted as a useful, noninvasive diagnostic tool for evaluating a variety of neoplastic diseases [1-3]. To date, the most extensive use of PET/CT has been for the diagnosis, staging and monitoring of malignant tumors. In the field of oncology, in addition to the visual assessment of the ^{18}F-FDG uptake in tumors, the semi-quantitative assessment of the ^{18}F-FDG uptake in tumor lesions using the standardized uptake value (SUV) has also been practiced [4, 5]. Specifically, for malignant lymphoma, the liver and blood pool of the mediastinum are used as reference sites when assessing the tumor uptake [6-8]. In daily clinical practice, the ^{18}F-FDG uptake in the liver sometimes appears to decrease on PET images of patients with a poor nutritional status, such as those with hypoalbuminemia.

The purpose of this study was to determine whether or not the uptake in the liver and blood pool of the mediastinum in patients with a poor nutritional status is decreased compared to patients with a normal nutritional status (as a control). Given that the ^{18}F-FDG uptake in the liver and blood pool in the mediastinum is often used as a reference region for evaluating the tumor activity, it is important to understand the factors that influence this uptake.

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Materials and methods

We retrospectively analyzed 246 patients who underwent ^{18}F-FDG PET/CT from January 2018 to June 2018 and whose blood serum albumin was measured within 1 month of ^{18}F-FDG PET/CT. Low serum albumin was defined as less than 4.0 g/dl and hypoalbuminemia as less than 3.5 g/dl [9-12]. We compared the liver ^{18}F-FDG uptake of patients with low serum albumin (< 4.0 g/dl) with that of patients with normal serum albumin (≥ 4.0 g/dl). We also compared the liver ^{18}F-FDG uptake of hypoalbuminemia patients (< 3.5 g/dl) with that of patients with normal serum albumin (≥ 4.0 g/dl). Liver function test values (glutamic oxaloacetic transaminase [GOT], glutamic pyruvic transaminase [GPT], gamma-glutamyl transferase [γ-GTP] and total bilirubin [T-Bil]) and renal function test values (estimated glomerular filtration rate [eGFR]) measured within 1 month of ^{18}F-FDG PET/CT were compared among these groups. Correlation between the liver ^{18}F-FDG uptake and serum albumin was also calculated.

This retrospective study was approved by the institutional review board, which waived the need for written informed consent from the patients.

Patients

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Two hundred and forty-six patients (male, n=139; female, n=107; mean age 67.4 years) who underwent ^{18}F-FDG PET/CT from January 2018 to June 2018 and whose blood serum albumin had been measured within 1 month were included in this study. Patients who had liver invasion or liver tumors were excluded. Cases of fatty liver (< 40 Hounsfield units on CT) were also excluded. Patients who had diabetes mellitus were excluded, as were those whose blood sugar was $\geq$ 140 mg/dl before ^{18}F-FDG administration were excluded. We excluded patients with liver mass on PET/CT and those with deformity of the liver suspected of being liver cirrhosis. In addition, patients who underwent PET/CT within three months of chemotherapy, surgery or radiotherapy were excluded.

^{18}F-FDG PET/CT scanning and data acquisition

^{18}F-FDG was synthesized with the nucleophilic substitution method using an ^{18}F-FDG-synthesizing instrument (F100, Sumitomo Heavy Industries, Ltd., Tokyo, Japan) and a cyclotron (CYPRIS; Sumitomo Heavy Industries, Ltd., Tokyo, Japan) at our institution. Patients fasted for at least 6 h, after which the blood glucose levels were determined to ensure a level of < 140 mg/dl. Patients then received an intravenous injection of 3.0 MBq/kg of body weight of ^{18}F-FDG. The patients were asked to remain

resting on a bed in order to minimize ^{18}F-FDG consumption by the muscles before the

scans. ^{18}F-FDG PET/CT image acquisition started at 1 hour after the ^{18}F-FDG injection

with the patient in a relaxed supine position using an integrated PET/CT scanner

(Discovery PET/CT 710; GE Healthcare, Milwaukee, WI, USA). First, a total-body

low-dose CT scan to calculate the attenuation correction was performed. CT images

were obtained using a standardized protocol involving 120 kV, a tube-rotation time of

0.6 s per rotation, a section thickness of 3.75 mm, and a scan field from the head down

to the mid-thigh level. Subsequently, PET images consisting of 8 bed positions with 2

minutes per table position over the same region were obtained using a 3-dimensional

high-sensitivity mode. The PET images were reconstructed into a 192×192 matrix,

using an ordered-subset expectation maximization (OSEM) iterative reconstruction

algorithm called VUE Point FX with TOF and sharp IR (16 subsets, 2 iterations) as well

as CT-based attenuation correction. Noise was reduced by smoothing the resultant

images with a Gaussian filter of 4.0 mm full width at half maximum.

The evaluation of the ^{18}F-FDG uptake in the liver and blood pool in the mediastinum of

the study group

Physicians specializing in nuclear medicine evaluated the ^{18}F-FDG PET/CT images.

The SUV_{max} and SUV_{mean} of the liver and SUV_{mean} of the blood pool in the mediastinum were calculated on the viewer (AW server 2.0; GE Healthcare, Milwaukee, WI, USA). The SUV_{max} and SUV_{mean} of liver were calculated by automatically setting a 3-cm-diameter spherical volume of interest (VOI) in the liver of the study group using AW server 2.0 (Fig. 1) [4]. For the mediastinal blood pool SUV_{mean}, a 1-cm-diameter spherical VOI was set in the descending aorta so as not to overlap with the blood vessel wall (Fig. 2) [13].

Statistical analyses

The parameters were expressed in terms of the mean ± standard deviation. The normality of the distribution of the variables was tested by Levene's test. Student's *t*-test (normal distribution) or Welch's t-test (non-normal distribution) was applied to evaluate differences in the variables of the parameters. The SUV_{max} and SUV_{mean} of the liver and SUV_{mean} of the blood pool in the patients of two groups were compared using an independent *t*-test. Before an independent *t*-test and correlation analysis were performed, the normality of the distribution of the variables was tested by the Kolmogolov-Smirnov test. The relationships between the liver and blood pool uptake and the serum albumin level were quantified using Spearman's correlation analysis. The

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SPSS Statistics software program (version 24; IBM, Chicago, IL, USA) was used to perform the statistical analyses. A p value of < 0.05 was considered statistically significant.

Results

A comparison of the clinical characteristics related to PET/CT and the liver and renal function test data of the patients with low serum albumin and those with normal serum albumin is shown in Table 1. However only the mean γ- GTP level of patients with low serum albumin group was slightly over the normal range; the mean serum GOT, GPT and T-Bil levels and the eGFR of each group were within the normal ranges. A comparison of the clinical characteristics of the patients with hypoalbuminemia and those with normal serum albumin is shown in Table 2. The mean serum GOT, GPT, γ-GTP and T-Bil levels and the eGFR of each group were all within the normal ranges.

A comparison of the liver and mediastinal blood uptake of the patients with low serum albumin and those with normal serum albumin is shown in Table 3. The SUV_{max} and SUV_{mean} of the liver in the 117 patients with low serum albumin were 3.1 ± 0.5 and 2.3 ± 0.3, respectively, while those values in the 129 patients with normal serum albumin were 3.4 ± 0.5, 2.5 ± 0.4, respectively. The SUV_{max} and SUV_{mean} of the liver of

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patients with low serum albumin were significantly lower than in those with normal

serum albumin ($p < 0.001$, $p < 0.001$, respectively). The SUV_{mean} of the mediastinal

blood uptake in patients with low and normal serum albumin levels was 1.7 ± 0.3 and

1.7 ± 0.3, respectively ($p = 0.512$).

A comparison of the liver and mediastinal blood uptake of the patients with

hypoalbuminemia and those with normal serum albumin is shown in Table 4. The

SUV_{max} and SUV_{mean} of the liver in the 29 patients with hypoalbuminemia were $2.9 \pm$

0.4 and 2.0 ± 0.3, respectively; these values in the patients with hypoalbuminemia were

significantly lower than in those with normal serum albumin ($p < 0.001$, $p < 0.001$,

respectively). The SUV_{mean} of the mediastinal blood uptake in patients with

hypoalbuminemia and normal serum albumin was 1.6 ± 0.2 and 1.7 ± 0.3, respectively

($p = 0.053$).

Serum albumin demonstrated a significantly positive but weak correlation with

the liver SUV_{max}, showing a regression line of $y = 0.37x + 1.8$ ($r = 0.35$, $p < 0.001$) (Fig.

3). Furthermore, serum albumin demonstrated a significantly positive and moderate

correlation with the liver SUV_{mean}, showing a regression line of $y = 0.31x + 1.1$ ($r =$

0.41, $p < 0.001$) (Fig. 4). Serum albumin demonstrated a significantly positive but very

weak correlation with the mediastinal blood uptake, showing a regression line of $y =$

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$0.09x + 1.4$ ($r = 0.13$, $p = 0.035$) for the mediastinal blood SUV_{mean} (Fig. 5).

Fig. 6 shows the PET/CT images of a malnutrition patient with hypoalbuminemia showing a decreased liver uptake. Fig. 7 shows the PET/CT images of a patient with a normal serum albumin level.

Discussion

The liver SUV_{max} and SUV_{mean} of patients with low serum albumin were significantly lower than in those with normal serum albumin levels. Those variables of patients with hypoalbuminemia were also significantly lower than in those with normal serum albumin levels.

Serum albumin is synthesized in the liver [14]. The direct proof that the liver is the site of albumin synthesis was established by the tissue slice work of Peters and Anfinsen in 1950 [15] and the pioneering work of Miller et al. with isolated perfused rat liver in 1951 [16]. Hypoalbuminemia is frequently observed in patients and can be associated with several different diseases, including cirrhosis, malnutrition and nephrotic syndrome [17, 18]. In the present study, cases of liver cirrhosis apparent on CT were excluded, and the average liver and renal function was in the normal range. Therefore, the inclusion of cases of low albumin caused by liver cirrhosis and a decreased renal function was

minimized, and patients with low albumin levels caused by malnutrition were the primary subjects.

Most of the liver's synthetic machinery is devoted to albumin at rest [19]. The rate of albumin synthesis—more so than other hepatic proteins—depends on the nutritional intake [19]. The synthesis requires energy, ribosomal machinery for assembly, and an adequate supply of amino acids [19]. In an experimental report in rats, a reduction in albumin synthesis was observed in starved rats [20]. Omitting protein from the diet causes a greater reduction in synthesis [20]. Regarding the cause of the decline in the liver FDG uptake in patients with low albumin levels, since the amino acids from the diet in a state of malnutrition are not sufficient for albumin synthesis, the synthesis of albumin decreases; thus, the requirement of glucose for synthetic energy will be reduced. It is hypothesized that this is one factor that reduces FDG uptake in the liver.

The serum albumin was found to be significantly positively correlated with the liver SUV_{max} and SUV_{mean}. Furthermore, the serum albumin was moderately correlated with the liver SUV_{mean}. In contrast, regarding the mediastinal blood uptake, no significant difference was seen between patients with low and normal serum albumin levels nor between patients with hypoalbuminemia and normal serum albumin levels. The target tumor lesion is usually compared with the normal ^{18}F-FDG uptake in the

surrounding background or by referencing the ^{18}F-FDG uptake in the mediastinal blood pool or the liver [21, 22]. Our results suggest that it may be more stable to use the mediastinal blood pool as a reference region than the liver if the patients' serum albumin level is decreasing because hypoalbuminemia is considered to influence the mediastinal blood pool less strongly in comparison to the liver.

The Response Evaluation Criteria in Solid Tumors (RECIST), a method of determining whether tumor measurement data can allow the conclusion that a patient's disease has improved, stayed about the same, or worsened, was developed and published in 2000, based on the original World Health Organization guidelines, which were first published in 1981. In 2009, revisions were made (RECIST 1.1) [23]. However, anatomical imaging modalities may have limited applicability in distinguishing viable residual tumors from reactive changes, such as edema and scar tissue, as well as killed cells and tumor shrinkage. In 2009, researchers in the United States developed Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST), which can assess the metabolic tumor response with ^{18}F-FDG PET [24]. If a patient's nutritional status considerably differs between pre-therapy and post-therapy, the liver FDG uptake may differ before and after therapy, which may affect the results of PERCIST. The mediastinal blood pool uptake is more stable. Thus, to more accurately assess the effects

of treatment in patients with nutritional instability, the mediastinal blood pool may be used as a reference region in follow-up with PERCIST.

Several factors that may influence the liver uptake have been reported. A previous study found no association between the liver attenuation and liver SUV_{mean} [25]. In contrast, it was reported that the liver uptake was increased in cases of hepatic steatosis (CT density of liver <40 HU) [26]. The authors suggested that this likely results from the uptake in inflammatory cells being superimposed on the hepatocyte uptake. In another report, a mild and moderate degree of fatty liver had a positive effect on the liver ^{18}F-FDG uptake, whereas a severe degree of fatty liver negatively affected the ^{18}F-FDG uptake [27]. Patients with hepatic steatosis were excluded from our study.

The present study has several limitations. First, there was selection bias due to the retrospective nature of the study. Second, this study might have included hidden liver lesions within the VOI. Patients with locally identifiable abnormalities in the liver were excluded from the analysis, but those with hemangiomas, small cysts, vascular abnormalities or undetectable liver metastasis with a low ^{18}F-FDG uptake may still have been included. Possible problems, including potential hidden liver lesions, were alleviated by applying a relatively large VOI. Third, some clinical features were not consistent in our comparison among the study subject groups. There were significant

differences in the age, gender, blood glucose, GPT and T-Bil between patients with low

serum albumin and those with normal serum albumin, as well as in the body weight,

GOT, GPT and T-Bil between patients with hypoalbuminemia and those with normal

serum albumin. Although these factors may affect the liver uptake, the average value of

GOT, GPT and T-Bil was within the normal range in every groups. Lin et al. reported

that age has a significant and positive impact on both the SUV_{max} and SUV_{mean} of the

liver on ^{18}F-FDG PET [28]. In our study, patients with low serum albumin group in

which liver uptake was lower were higher age than patients with normal serum albumin

group. Lin et al. also reported there was no statistically significant relationship between

genders. Finally, it was reported that body mass index (BMI) influences the hepatic

uptake [27], but we were unable to calculate the BMI in this retrospective study because

data on the patients' height were not recorded. Therefore, there may have been a

significant difference in the BMI between the two groups despite there being no

significant difference in the body weight in this study.

However, despite these limitations, this is the first report to note that a decrease

in the physiological liver uptake could be attributed to a low serum albumin level

derived from malnutrition. Low serum albumin seems to affect the uptake in the

mediastinal blood pool less markedly than that in the liver.

Conclusion

A reduction in the liver uptake on ^{18}F-FDG PET/CT is associated with hypoalbuminemia derived from malnutrition, which seems to be a factor associated with a reduced liver uptake. Serum albumin was found to be significantly positively correlated with the liver ^{18}F-FDG uptake. In contrast, a low serum albumin level seems to affect the uptake in the mediastinal blood pool less markedly.

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Compliance with ethical standards

Conflict of interest No potential conflicts of interest were disclosed.

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Figure legend

Fig. 1 The SUV_{max} and SUV_{mean} of liver were calculated by automatically setting a

spherical volume of interest (VOI) of 3 cm in diameter on the right lobe of the liver of

the study group using AW server 2.0 (GE Healthcare, Milwaukee, WI, USA).

Fig. 2 To determine the mediastinal blood pool SUV_{mean}, a spherical VOI of 1 cm in

diameter was set in the descending aorta, so as not to overlap with the blood vessel wall.

Fig. 3 Serum albumin demonstrated a significantly positive but weak correlation with

the liver SUV_{max}, showing a regression line of y = 0.37x + 1.8 (r = 0.35, $p < 0.001$).

Fig. 4 Serum albumin demonstrated a significantly positive and moderate correlation

with the liver SUV_{mean}, showing a regression line of y = 0.31x + 1.1 (r = 0.41, $p <$ 0.001).

Fig. 5 Serum albumin demonstrated a significantly positive but very weak correlation with the mediastinal blood SUV_{mean}, showing a regression line of y = 0.09x + 1.4 (r = 0.13, p = 0.035).

Fig. 6 PET/CT image of a representative malnutrition case with hypoalbuminemia showing a decreased liver uptake. Maximum intensity projection of ^{18}F-FDG PET (a), PET/CT fusion image of mediastinal blood pool (b), PET/CT fusion image of liver (c) of an 80-year-old male with hypoalbuminemia (serum albumin: 3.3 g/dl). Parameters of interest were as follows: SUV_{max} of 2.7, SUV_{mean} of 1.9 in liver, SUV_{mean} of 1.6 in mediastinal blood.

Fig. 7 PET/CT image of a representative case with normal serum albumin. Maximum intensity projection of ^{18}F-FDG PET (a), PET/CT fusion image of mediastinal blood pool (b), PET/CT fusion image of liver (c) of a 70-year-old female with normal serum albumin (serum albumin: 4.3 g/dl). Parameters of interest were as follows: SUV_{max} of

3.8, SUV$_{mean}$ of 2.9 in liver, SUV$_{mean}$ of 1.6 in mediastinal blood.

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Table 1 The clinical characteristics of the study groups

	Patients with low serum albumin (< 4.0 g/dl; n=117)	Patients with normal serum albumin (≥ 4.0 g/dl; n=129)	*p* value
Age (years)	70.0 ± 11.1	65.2 ± 13.3	0.003*
Gender			0.028*
Female	42	65	
Male	75	64	
Weight (kg)	54.8 ± 11.7	56.7 ± 10.7	0.174
Blood glucose (mg/dl)	106.2 ± 14.5	101.7 ± 11.8	0.009*
^{18}F-FDG (MBq)	169.3 ± 39.3	176.3 ± 38.3	0.156
GOT (IU/l) [13-30]	21.2 ± 7.6	21.5 ± 6.1	0.703
GPT (IU/l) [7-23]	14.6 ± 7.5	17.2 ± 8.6	0.013*
γ-GTP (IU/l) [9-32]	34.2 ± 47.1	30.7 ± 30.1	0.492
T-Bil (mg/dl) [0.4-1.5]	0.6 ± 0.2	0.8 ± 0.3	< 0.001*
eGFR (ml/min/1.73 m^2)	67.6 ± 20.8	70.0 ± 19.4	0.347

Data are represented as the mean ± standard deviation. A *p* value < 0.05 was considered statistically significant. Normal ranges are shown in brackets.

^{18}F-FDG, fluorodeoxyglucose; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; γ-GTP, gamma-glutamyl transferase; T-Bil, total bilirubin; eGFR, estimated glomerular filtration rate

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Table 2 The clinical characteristics of the study groups

	Patients with hypoalbuminemia (< 3.5 g/dl; n=29)	Patients with normal serum albumin (≥ 4.0 g/dl; n=129)	*p* value
Age (years)	69.8 ± 11.1	65.2 ± 13.3	0.082
Gender			0.304
Female	11	65	
Male	18	64	
Weight (kg)	51.5 ± 9.7	56.7 ± 10.7	0.016*
Blood glucose (mg/dl)	103.8 ± 13.9	101.7 ± 11.8	0.406
^{18}F-FDG (MBq)	162.3 ± 36.9	176.3 ± 38.3	0.075
GOT (IU/l) [13-30]	18.4 ± 6.2	21.5 ± 6.1	0.013*
GPT (IU/l) [7-23]	13.2 ± 6.6	17.2 ± 8.6	0.020*
γ-GTP (IU/l) [9-32]	24.5 ± 12.9	30.7 ± 30.1	0.279
T-Bil (mg/dl) [0.4-1.5]	0.5 ± 0.2	0.8 ± 0.3	< 0.001*
eGFR (ml/min/1.73 m^2)	70.2 ± 21.7	70.0 ± 19.4	0.947

Data are represented as the mean ± standard deviation. A *p* value < 0.05 was considered statistically significant. Normal ranges are shown in brackets.

^{18}F-FDG, fluorodeoxyglucose; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; γ-GTP, gamma-glutamyl transferase; T-Bil, total bilirubin; eGFR, estimated glomerular filtration rate

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Table 3 The comparison of the liver and mediastinal blood uptake between patients with low and normal serum albumin levels

Parameter	Patients with low serum albumin (< 4.0 g/dl; n=117)	Patients with normal serum albumin (≥ 4.0 g/dl; n=129)	p value
Liver			
$\quad$ SUV$_{max}$	3.1 ± 0.5	3.4 ± 0.5	$< 0.001^*$
$\quad$ SUV$_{mean}$	2.3 ± 0.3	2.5 ± 0.4	$< 0.001^*$
Blood pool			
$\quad$ SUV$_{mean}$	1.7 ± 0.3	1.7 ± 0.3	0.512

Data are represented as the mean ± standard deviation.

SUV$_{max}$, maximum standardized uptake value; SUV$_{mean}$, mean standardized uptake value

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Table 4 A comparison of the liver and mediastinal blood uptake between patients with hypoalbuminemia and normal serum albumin levels

Parameter	Patients with hypoalbuminemia (< 3.5 g/dl; n=29)	Patients with normal serum albumin ($\geq$ 4.0 g/dl; n=129)	p value
Liver			
SUVmax	2.9 ± 0.4	3.4 ± 0.5	< 0.001*
SUVmean	2.0 ± 0.3	2.5 ± 0.4	< 0.001*
Blood pool			
SUVmean	1.6 ± 0.2	1.7 ± 0.3	0.053

Data are represented as the mean ± standard deviation.

SUVmax, maximum standardized uptake value; SUVmean, mean standardized uptake value

Fig. 1

Fig. 2

Fig. 3

$y = 0.37x + 1.8$ ($r = 0.35$, $p < 0.001$)

Liver SUVmax

Serum albumin (g/dl)
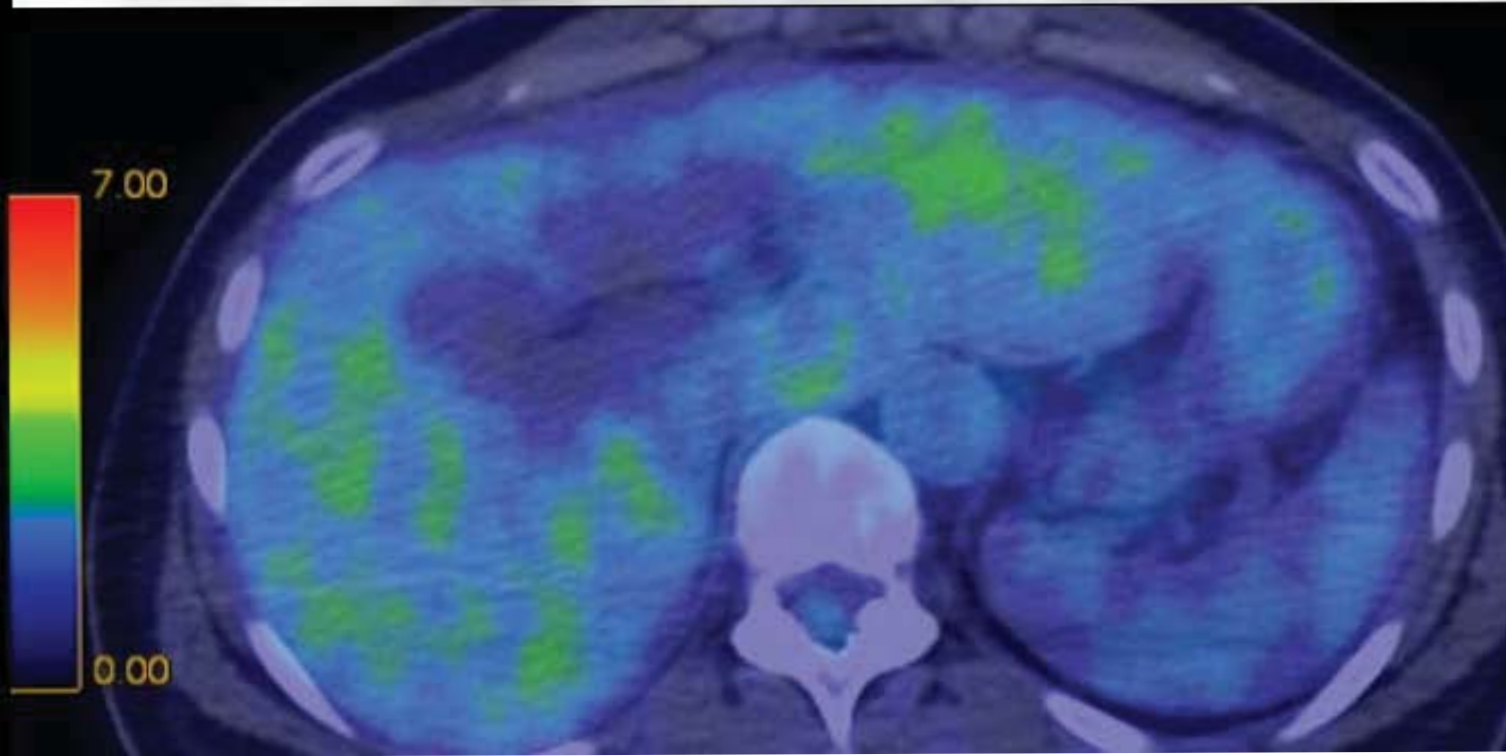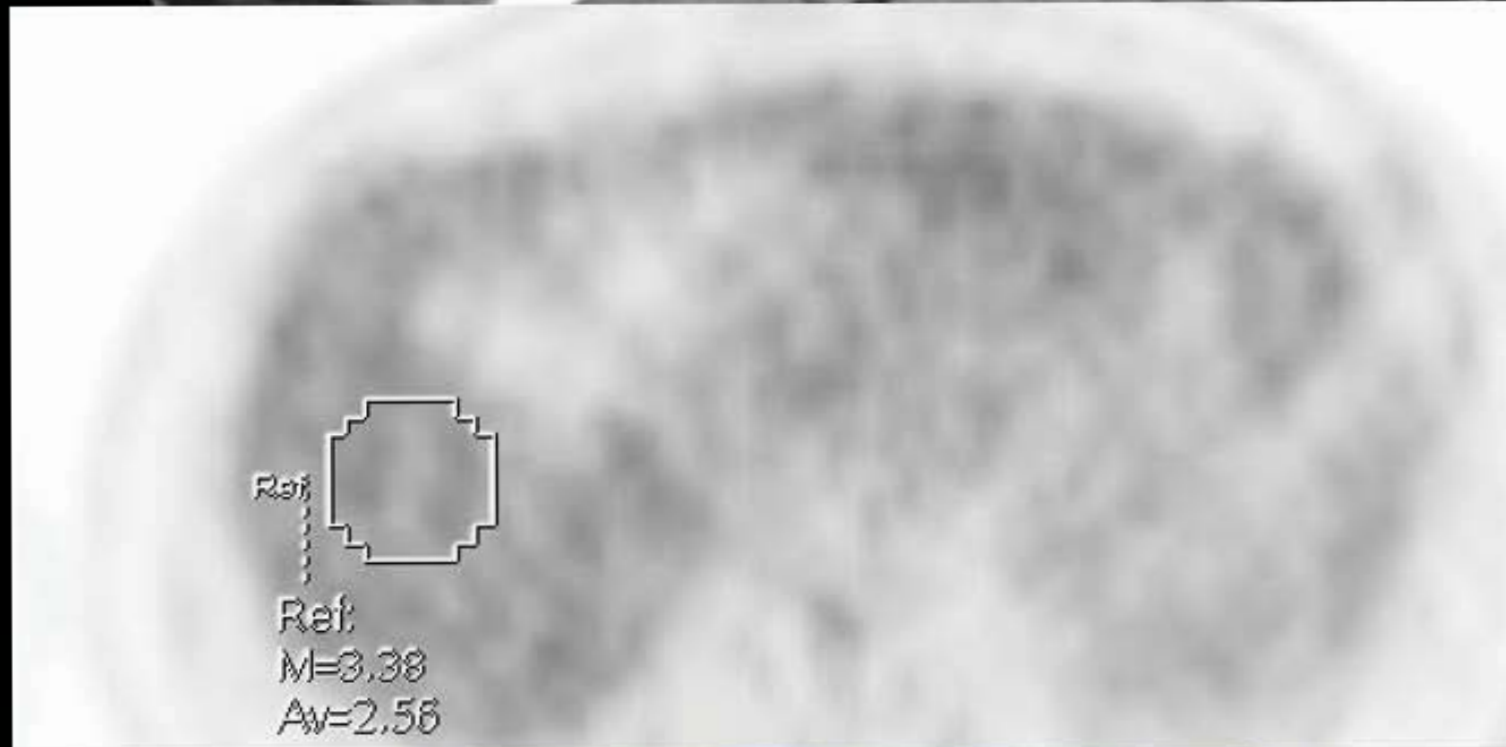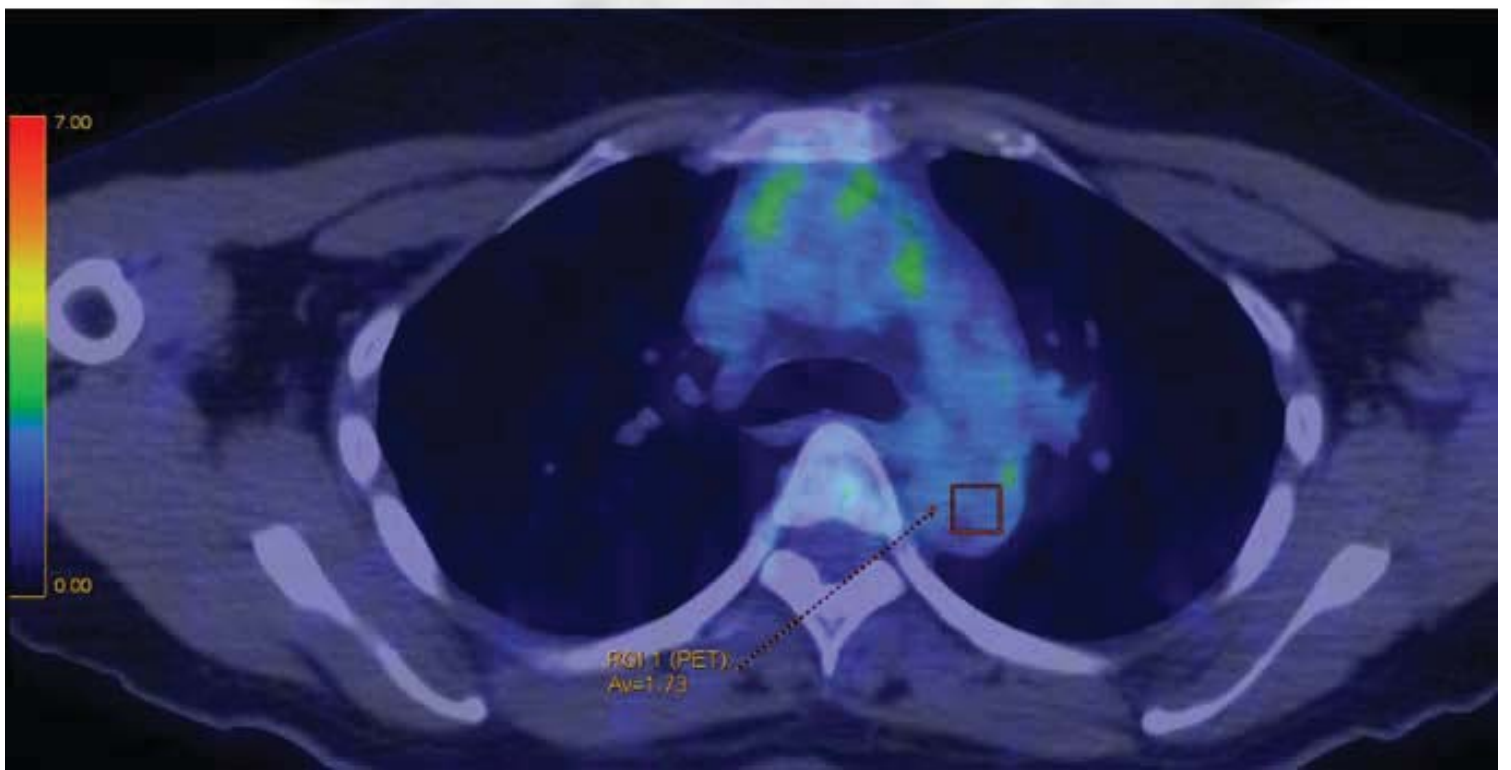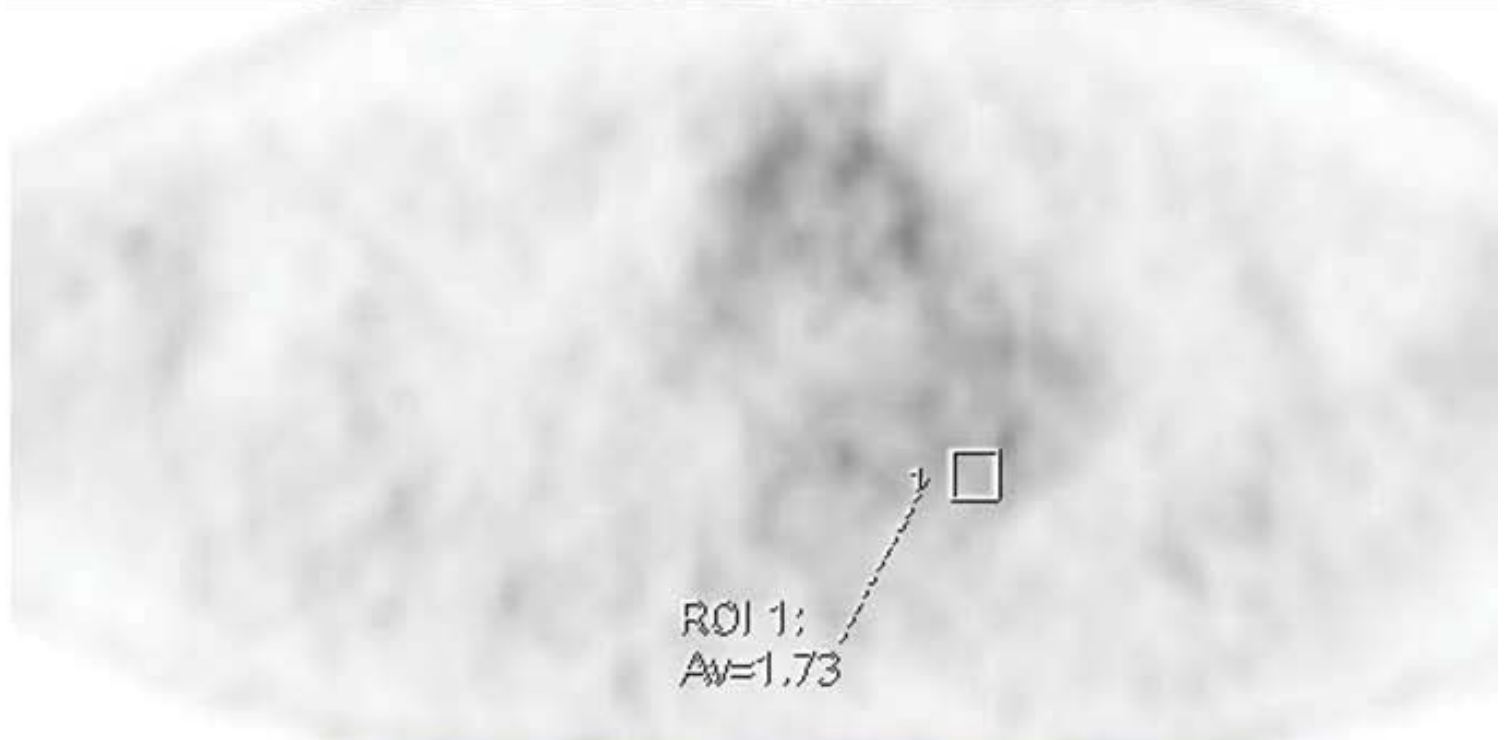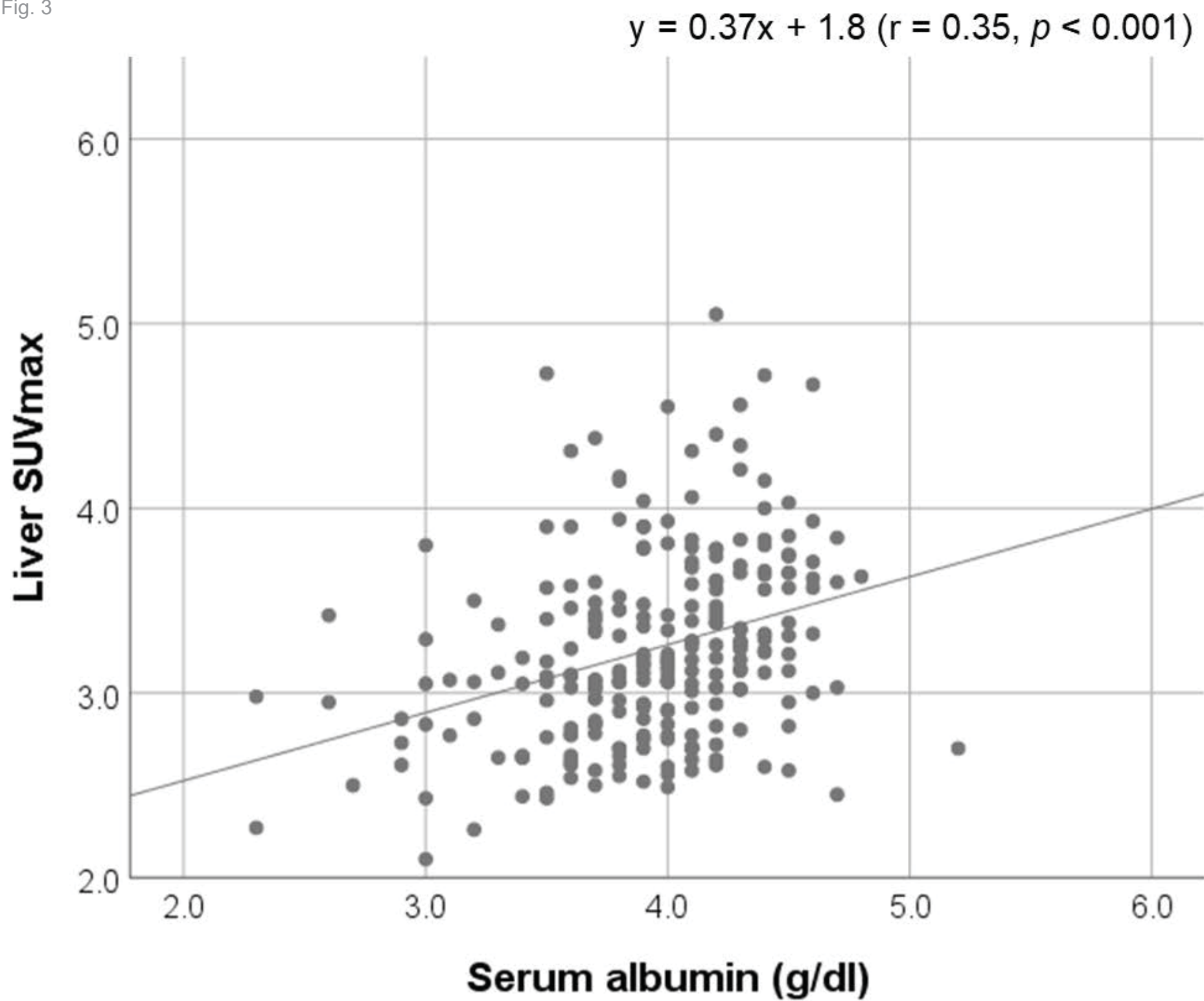
Fig. 4

$y = 0.31x + 1.1$ ($r = 0.41$, $p < 0.001$)
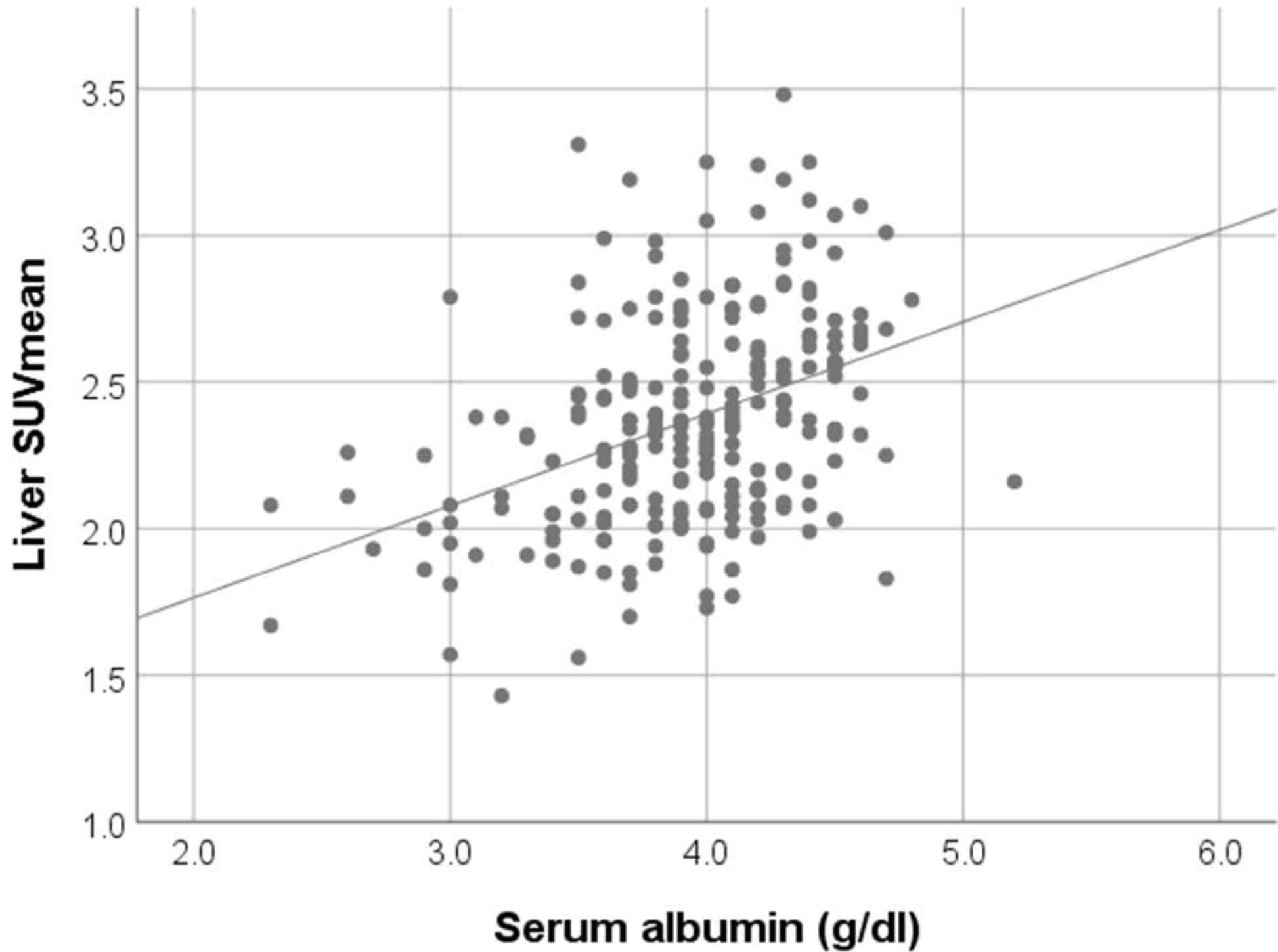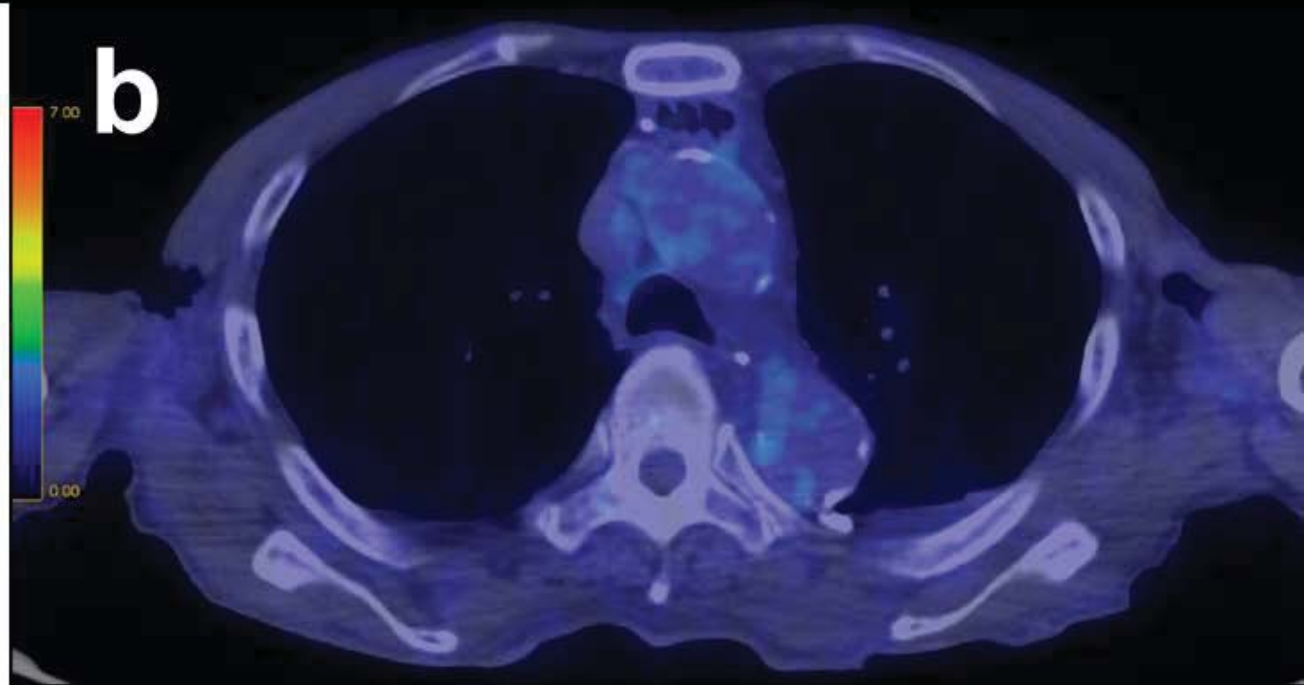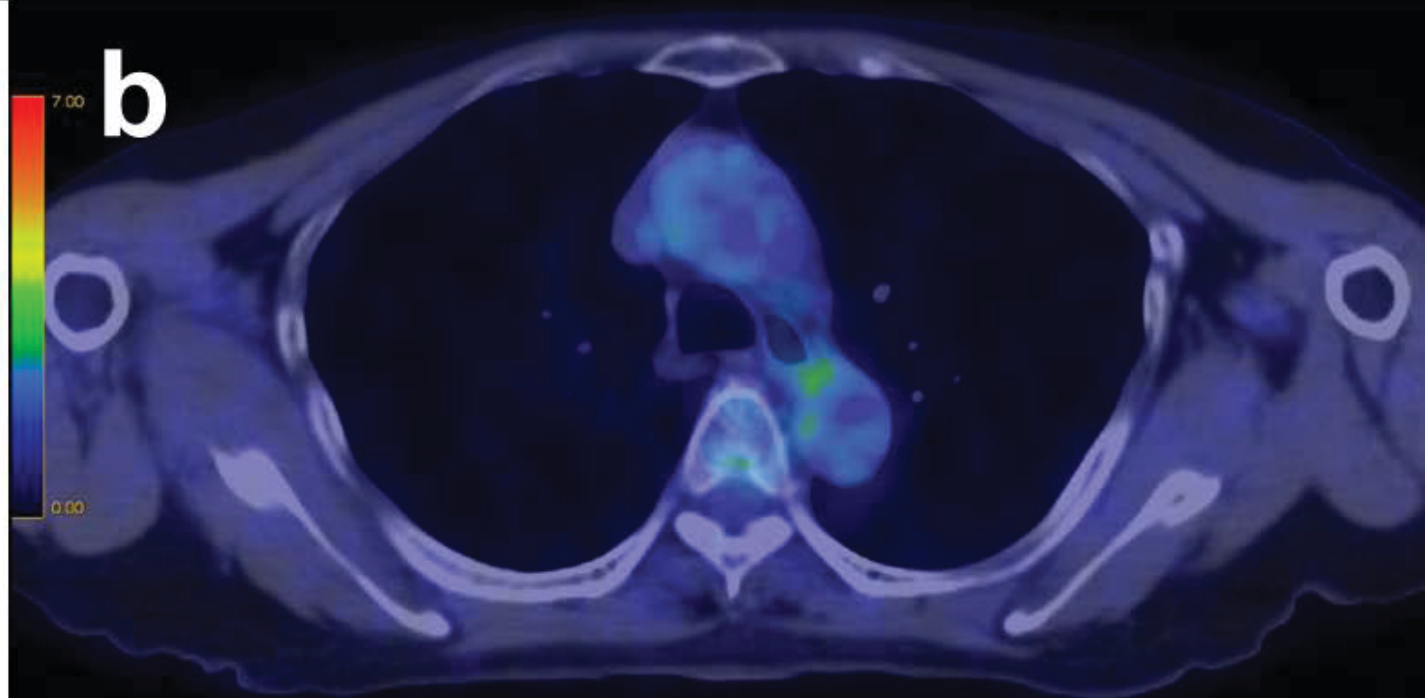
Fig. 5

$y = 0.09x + 1.4$ ($r = 0.13$, $p = 0.035$)

Fig. 6

Fig. 7