Hong Kong J Radiol. 2023;26:240-7. Epub 11 Dec 2023 | https://doi.org/10.12809/hkjr2217526

ORIGINAL ARTICLE **CME**

Effects of Different Liver Diseases on Metabolic Reference in ^{18}F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography

KS Ng, KK Ng, KS Chu, BT Kung, TK Au Yong

Nuclear Medicine Unit, Queen Elizabeth Hospital, Hong Kong SAR, China

ABSTRACT

Introduction: *In addition to visual assessment, measuring standardised uptake values (SUVs) in ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) for extrahepatic lesion characterisation often uses comparisons with normal liver and blood pool uptake as metabolic references. However, the effects of liver diseases on these metabolic references are not well understood. This study therefore aimed to investigate how different liver diseases affect ^{18}F-FDG uptake in the liver and the blood pool.*

Methods: *A total of 168 patients who underwent ^{18}F-FDG PET/CT in our institution were retrospectively evaluated. The mean SUVs in the liver and blood pool were measured. Based on their clinical history and investigation results, patients were categorised into the following five groups: normal liver, hyperbilirubinaemia, cirrhosis, steatosis, and polycystic liver disease. The mean liver-to–blood pool SUV ratios of the different groups were statistically analysed using t tests and linear regression.*

Results: *Compared with the control group, patients with hyperbilirubinaemia were associated with a higher mean lesion SUV, while those with cirrhosis, steatosis, and polycystic liver disease had lower ratios. Increasing severity of steatosis correlated with decreasing SUV. All results were statistically significant.*

Conclusion: *This study demonstrates that liver diseases can affect lesion SUV in proportion to their severity. Radiologists should review the underlying hepatic conditions of patients before using liver and blood pool as references for ^{18}F-FDG measurements.*

Key Words: *Fluorodeoxyglucose F18; Liver; Positron-emission tomography*

Correspondence: *Dr KS Ng, Nuclear Medicine Unit, Queen Elizabeth Hospital, Hong Kong SAR, China*
Email: nks176@ha.org.hk

Submitted: 13 Jan 2022; Accepted: 10 May 2022.

Contributors: KSN designed the study, acquired the data, analysed the data and drafted the manuscript. KKN, KSC, BTK and TKAY critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of Interest: As editors of the journal, KSN and TKAY were not involved in the peer review process. Other authors have disclosed no conflicts of interest.

Funding/Support: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data Availability: All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics Approval: The study was approved by the Queen Elizabeth Hospital Research Ethics Committee of Hospital Authority, Hong Kong (Ref No.: KC/KE-19-0048-ER-4). Informed patient consent was waived by the Committee due to the retrospective nature of the study.

中文摘要

不同肝臟疾病對^{18}F-氟脫氧葡萄糖正子斷層掃描／電腦斷層掃描代謝參考的影響

吳國勝、吳官橋、朱競新、龔本霆、歐陽定勤

簡介：除了視覺評估之外，測量^{18}F-氟脫氧葡萄糖正子斷層掃描／電腦斷層掃描（^{18}F-FDG PET/CT）中的標準化攝取值（SUV）來表徵肝外病變特徵通常使用與正常肝臟和血池攝取的比較作為代謝參考。然而，肝臟疾病對這些代謝參考的影響尚不清楚。因此，本研究旨在調查不同的肝臟疾病如何影響肝臟和血池中^{18}F-FDG的攝取。

方法：本研究對在本院接受^{18}F-FDG PET/CT檢查的168位患者進行回顧性分析，並測量其肝臟和血池中的平均SUV。根據患者的臨床病史和檢查結果，我們將患者分為以下五組：正常肝臟、高膽紅素血症、肝硬化、脂肪變性和多囊性肝病。我們使用t檢定和線性迴歸對不同組別的平均肝臟與血池SUV比率進行統計分析。

結果：與對照組相比，高膽紅素血症患者的平均病變SUV值較高，而肝硬化、脂肪變性和多囊性肝患者的平均病變SUV值較低。脂肪變性嚴重程度的增加與 SUV的減少有關。所有結果均具有統計意義。

結論：本研究表明，肝臟疾病對病變SUV的影響與其嚴重程度成正比。在使用肝臟和血池作為^{18}F-FDG測量的參考之前，放射科醫生應檢查患者的潛在肝臟狀況。

INTRODUCTION

Both semiquantitative assessment and qualitative visual interpretation are applied in ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) for lesion characterisation.[1] In the semiquantitative approach, the maximum standardised uptake value (SUV_{max}) is calculated, but this depends on multiple factors, including injection time, uptake period, and blood glucose level.[2] Thus, it is difficult to compare the absolute SUV_{max} between different PET/CT systems.[2] For qualitative visual interpretation, the ^{18}F-FDG uptake of a lesion is typically graded with respect to mean blood pool and liver uptake of a patient (e.g., score 1: no uptake; 2: less than or equal to blood pool; 3: between blood pool and liver; 4: moderately more than liver; and 5: markedly more than liver[3]). This approach is useful in lesion delineation: a lesion is generally regarded as genuine (i.e., the lesion is true instead of false positive) if its uptake is higher than that of liver and not genuine if its uptake is less than or equal to that of blood pool. This is also useful in treatment response assessment (e.g., a disease is likely deteriorating if the score increases in interval scan). Visual interpretation is the recommended method in different guidelines, including the Deauville criteria for high-grade lymphoma,[3] PERCIST (Positron Emission Tomography Response Criteria in Solid Tumors) 1.0 for solid tumours proposed by the Society of Nuclear Medicine and Molecular Imaging,[4,5] as well as for vasculitis assessment developed by the European Association of Nuclear Medicine and the Society of Nuclear Medicine and Molecular Imaging.[6] Ideally, blood pool and liver uptake should have minimal variability such that they can be utilised as reliable metabolic references. There are existing procedural protocols standardising patient preparation and acquisition techniques.[7] The aim of this study was to evaluate the liver and blood pool uptake in different liver diseases (hyperbilirubinaemia, cirrhosis, steatosis, and polycystic liver disease) and their potential effect on lesion assessment. Focal liver diseases (e.g., hepatocellular carcinoma and liver metastasis) were not included here as their effects have already been covered in the literature,[8] and we believe that general hepatic metabolism is likely more dependent on systemic liver diseases than focal liver pathologies. Throughout this research, the ratio between the mean SUV of the liver and that of the blood pool (SUV_{liver}/$SUV_{blood\ pool}$ ratio) instead of absolute SUV was evaluated because the ratio was more relevant to the grading. Mean SUV (SUV_{mean}), instead of SUV_{max}, of liver and blood pool was investigated as an analogue of visual interpretation.

METHODS

Patient Recruitment

Cases of patients who underwent whole-body ^{18}F-FDG PET/CT in our centre from 1 January 2011 to 31 December 2015 were retrospectively reviewed. The clinical background and investigation results were reviewed, including drinking history, blood test results, radiological images, and endoscopic findings. Continuous data were reported as mean ± standard deviation. Subjects were excluded if: (1) liver malignancy had been diagnosed histologically; or (2) liver malignancy was suspected radiologically (e.g., by ^{18}F-FDG PET/CT, ultrasound, CT or magnetic resonance imaging) within 12 weeks of ^{18}F-FDG PET/CT imaging; or (3) no liver function tests were available within 2 weeks of ^{18}F-FDG PET/CT imaging; or (4) blood glucose level was > 11 mmol/L before ^{18}F-FDG PET/CT acquisition.

A total of 168 adult patients (56.5% male, 43.5% female) with a mean age of 62.3 ± 13.4 years were included. The majority had undergone ^{18}F-FDG PET/CT for oncological indications: lung (23.2%), lymphoma (14.8%), breast (12.5%), biliary (9.5%), colon (8.3%), renal (6.0%), and other (12.6%) cancers. Some of the subjects (13.1%) showed no evidence of malignancy after thorough workup. Each case was then assigned to one of the following five groups (Table 1):

(1) The control group (n = 50): liver function (i.e., serum bilirubin, alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase levels) was normal, and there was no evidence of cirrhosis, steatosis or polycystic liver disease;
(2) the hyperbilirubinaemia group (n = 29): the serum bilirubin level was greater than or equal to the upper limit of the normal level (21 μmol/L) within 2 weeks of ^{18}F-FDG PET/CT acquisition, and there was no evidence of cirrhosis, steatosis or polycystic liver disease;
(3) the cirrhosis group (n = 27): features of cirrhosis had been documented by means of imaging (e.g., ultrasound, CT or magnetic resonance imaging) or oesophagogastroduodenoscopy. Liver function was normal, and there was no evidence of steatosis or polycystic liver disease;
(4) the steatosis group (n = 52): the mean liver density in Hounsfield units (HU_{liver}) on CT was lower than that of the spleen (HU_{spleen}). As SUV measurement is potentially dependent on the distribution of steatosis (e.g., diffuse, focal, multinodular, etc.), this study focused on the patients with diffuse steatosis. Liver function was normal, and there was no evidence of cirrhosis or polycystic liver disease; and
(5) the polycystic liver disease group (n = 10): the liver contained > 20 cysts as defined in the literature.[9] Liver function was normal, and there was no evidence of cirrhosis or steatosis.

Technical Aspects

All ^{18}F-FDG FDG PET-CT examinations were performed with the same PET/CT scanner (Discovery 710; General Electric, Milwaukee [WI], United States). The mean ^{18}F-FDG activity administered was 407.0 ± 45.5 MBq. After a mean uptake time of 59.8 ± 6.21 minutes, PET data were acquired from skull vertex to mid thighs in seven to eight bed positions (3 minutes per bed position) with mean axial bed coverage of 15.2 cm per bed and 9-slice bed overlap in two-dimensional acquisition mode. Reconstruction using Optimization of Ordered Subset Expectation Maximization was performed with 4.2-mm section thickness in a 128 × 128 matrix and processed through a standard filter. Non-contrast CT data were acquired for anatomical correlation and attenuation correction.

Measurements and Statistical Analyses

The SUV is defined as the activity measured in a volume of interest (VOI) divided by the injected ^{18}F-FDG dose, based on body weight[10]:

$$SUV = \frac{Activity_{VOI}\ (MBq/mL)}{Dose_{injection}\ (MBq/kg)}$$

SUV_{liver} was measured in a 3-cm–diameter spherical VOI over the right lobe of the liver as recommended in the PERCIST 1.0 criteria.[4,5] No observable lesion was included in the liver VOI, except for the unavoidable multiple cysts in polycystic liver disease. $SUV_{blood\ pool}$ was measured in another spherical VOI with diameter > 2 cm in the descending thoracic aorta. Atherosclerotic plaque was avoided in the blood pool VOI as the diseased vessel wall was often ^{18}F-FDG–avid.[4,5] The mean HU of the liver and the spleen were recorded in two-dimensional circular regions of interest with diameters > 3 cm. The body weight was routinely recorded on the same day of the ^{18}F-FDG PET/CT acquisition, with mean weight of 63.4 ± 11.7 kg. Statistical analyses, including two-sided *t* tests and linear regression, were performed with SPSS (Windows version 20.0; IBM Corp, Armonk [NY], United States). The results were regarded as statistically significant if the corresponding p values were < 0.05.

RESULTS

Figure 1a shows a representative maximum intensity projection (MIP) of a control case. The ^{18}F-FDG uptake in the liver (orange arrow) was homogeneous without discernible hypermetabolic lesions. The degree of uptake was normal and greater than that in the mediastinal blood pool (purple arrow), i.e., $SUV_{liver}/SUV_{blood\ pool}$ ratio > 1, and in the spleen. All of the 50 control cases had $SUV_{liver}/SUV_{blood\ pool}$ ratios > 1, with a mean SUV ratio of 1.39 (Table 1).

In the hyperbilirubinaemia group, the serum bilirubin level ranged from 23 to 667 μmol/L (mean = 107). Four cases had elevated aspartate aminotransferase level (> 47 IU/L), four had elevated alkaline phosphatase level (> 140 IU/L), and 18 had both enzymes elevated. Thus, 26 subjects (89.7%) had elevated liver enzyme(s) in addition to the increased serum bilirubin level. The hyperbilirubinaemia cases had a mean SUV ratio of 1.49, which was greater than that of the controls. A two-sided *t* test showed that the difference in mean SUV ratios achieved statistical significance (p = 0.0053; Table 1). A representative MIP of the hyperbilirubinaemia cases demonstrates the higher degree of contrast between

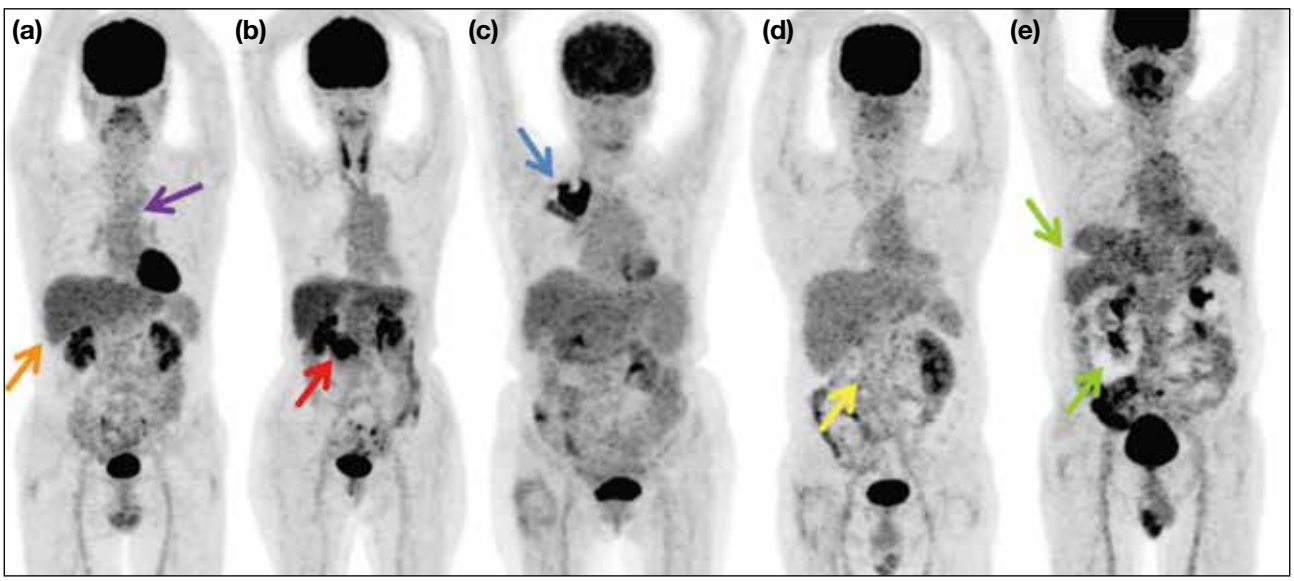

Figure 1. Maximum intensity projections of representative subjects of the five groups. (a) A control case showing liver uptake (orange arrow) is normally greater than that in the mediastinal blood pool (purple arrow) [standardised uptake value (SUV) ratio = 1.41]; (b) a hyperbilirubinaemia case with gallbladder tumour causing biliary obstruction (red arrow) [SUV ratio = 1.86]; (c) a cirrhosis case with right lung tumour (blue arrow) [SUV ratio = 1.24]; (d) a steatosis case with prior right nephrectomy for renal cell carcinoma (yellow arrow) [SUV ratio = 1.02]; and (e) a polycystic liver disease case with cold defects in liver and kidneys (green arrows) corresponding to cysts [SUV ratio = 0.79].

Table 1. Characteristics of the five groups (n = 168).

	Controls (n = 50)	Hyperbilirubinaemia (n = 29)	Cirrhosis (n = 27)	Steatosis (n = 52)	Polycystic liver disease (n = 10)
Definition	Normal liver	Bilirubin level ≥21 μmol/L	Cirrhotic features in US/CT/MRI/OGD	$HU_{liver} < HU_{spleen}$	No. of cysts > 20
Serum bilirubin, μmol/L	< 21	≥ 21	< 21	< 21	< 21
Steatosis	No	No	No	Yes	No
Cirrhosis	No	No	Yes	No	No
No. of cysts	≤ 20	≤ 20	≤ 20	≤ 20	> 20
SUV ratio (mean ± standard deviation)	1.39 ± 0.12	1.49 ± 0.19	1.29 ± 0.10	1.28 ± 0.15	0.75 ± 0.44
p Value*	N/A	0.0053	0.0003	0.0002	< 0.0001

Abbreviations: CT = computed tomography; HU_{liver} = density of the liver in Hounsfield units; HU_{spleen} = density of the spleen in Hounsfield units; MRI = magnetic resonance imaging; N/A = not applicable; OGD = oesophagogastroduodenoscopy; SUV = standardised uptake value; US = ultrasound.

* Two-sided *t* test.

hepatic and blood pool uptake compared with that of the controls (Figure 1b). The cause of hyperbilirubinaemia in Figure 1b was biliary obstruction secondary to a gallbladder tumour (red arrow). To investigate the correlation between bilirubin level and the SUV ratio, linear regression analysis was performed. Figure 2 shows that the SUV ratio was higher with increasing serum bilirubin level (black circles, bottom x-axis), with a corresponding slope of 0.0008 L/μmol and a correlation coefficient of 0.438. The relationship between serum bilirubin level and the SUV ratio was further examined by subdividing the hyperbilirubinaemia cases into two groups: mild (serum bilirubin level: 21-63 μmol/L, i.e., grade 1 to 2 hyperbilirubinaemia as defined by the Common Terminology Criteria for Adverse Events version 5.0[11]) and severe (serum bilirubin level > 63 μmol/L, i.e., grade 3 to 4 hyperbilirubinaemia). Table 2 shows that the mild hyperbilirubinaemia cases had a mean SUV ratio of 1.44, while the severe hyperbilirubinaemia cases had a mean SUV ratio of 1.59 (p = 0.0359).

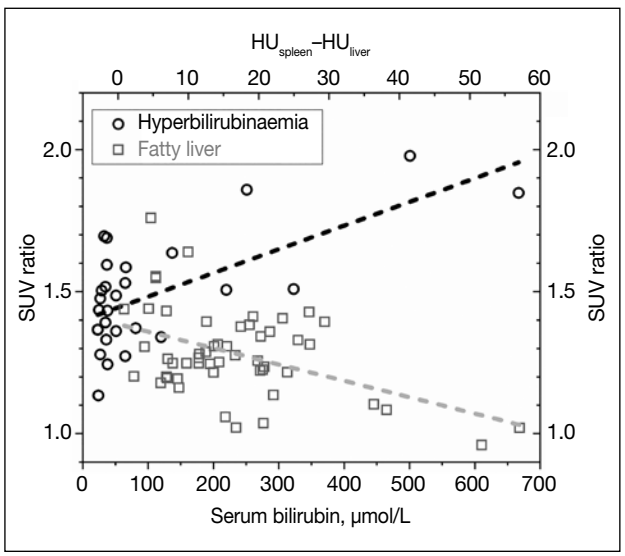

Figure 2. Linear regression plots of liver-to–blood pool standardised uptake value (SUV) ratio against the serum bilirubin level for the hyperbilirubinaemia cases (black circles, bottom x-axis) and the difference between the density of the spleen and the liver in Hounsfield units (HU_{spleen}–HU_{liver}) for the steatosis cases (grey squares, top x-axis). The hyperbilirubinaemia cases had a corresponding slope of 0.0008 L/μmoL and a correlation coefficient of 0.438. The steatosis cases had a corresponding slope of -0.0062 and a correlation coefficient of 0.209.

In the cirrhosis cases, 16 out of the 27 (59.3%) subjects had cirrhotic features documented by more than one modality (e.g., ultrasound, CT and oesophagogastroduodenoscopy). Twenty-three (85.2%) subjects had identifiable causes of cirrhosis (chronic hepatitis B: 51.9%, hepatitis C: 14.8%, chronic alcoholism: 18.5%). The cirrhosis cases had a mean SUV ratio of 1.29, which was less than that of the controls (p = 0.0003; Table 1). A representative MIP of a cirrhosis subject in Figure 1c shows that the visual contrast between liver and blood pool uptake was less than that of the control cases.

In the steatosis group, the HU_{liver} ranged from 5.5 to 55.2 (mean = 37.2) and the difference between HU_{spleen} and HU_{liver} (HU_{spleen}–HU_{liver}) ranged from 1 to 57 (mean = 16.6). The steatosis cases had a mean SUV ratio of 1.28, which was less than that of the controls (p = 0.0002; Table 1). The mean SUV ratio was still > 1, implying that liver had greater uptake than the blood pool. However, individuals with severe steatosis could have liver uptake as low as that of the blood pool, as illustrated in Figure 1d. To study if the SUV ratio depended on the severity of the steatosis, linear regression analysis was performed. The SUV ratios of the subjects with steatosis are plotted against the HU_{spleen}–HU_{liver} in Figure 2. It was observed that the SUV ratios decreased with increasing HU_{spleen}–HU_{liver} (grey squares, top x-axis). The corresponding slope in linear regression analysis was -0.0062 and the correlation coefficient was 0.209. The relationship between the steatosis severity and the SUV

Table 2. Subgroup analyses of hyperbilirubinaemia and steatosis groups.

	Hyperbilirubinaemia (n = 29)		Steatosis (n = 52)	
Subgroup	Mild (n = 19)	Severe (n = 10)	Mild (n = 17)	Moderate-to-severe (n = 35)
Criterion	Bilirubin level: 21-63 μmol/L	Bilirubin level > 63 μmol/L	HU_{spleen}–HU_{liver} ≤ 10	HU_{spleen}–HU_{liver} > 10
SUV ratio (mean ± standard deviation)	1.44 ± 0.14	1.59 ± 0.24	1.35 ± 0.18	1.25 ± 0.13
p Value*	0.0359		0.0201	

Abbreviations: HU_{liver} = density of the liver in Hounsfield units; HU_{spleen} = density of the spleen in Hounsfield units; SUV = standardised uptake value.
* Two-sided *t* test.

ratio was further evaluated by subdividing the subjects into mild (HU_{spleen}–$HU_{liver} \leq 10$) and moderate-to-severe (HU_{spleen}–$HU_{liver} > 10$) steatosis cases in accordance with Jacobs et al's study.[12] The mild steatosis cases had a higher mean SUV ratio of 1.35, while the moderate-to-severe steatosis cases had a lower mean SUV ratio of 1.25 ($p = 0.0201$; Table 2).

In the polycystic liver disease group, the mean SUV ratio was 0.75. This implies that unlike all the other cases which had mean ratios ≥ 1, the uptake in polycystic liver was generally less than that in the blood pool (Table 1). Figure 1e shows the MIP of a case of polycystic liver disease. The liver uptake was heterogeneous with a cold spot corresponding to a large hepatic cyst (upper green arrow). Table 1 shows that the SUV ratio of the polycystic liver disease cases had the greatest standard deviation (0.44) among all the cases (control group: 0.12, hyperbilirubinaemia group: 0.19, cirrhosis group: 0.10, steatosis group: 0.15) due to the variabilities in size, number and distribution of hepatic cysts with no uptake. Figure 3 shows another subject who had larger and more cysts compared with Figure 1e. The MIP and hybrid images in Figure 3 demonstrate almost no uptake in the right lobe of the liver and the corresponding SUV ratio was 0.12, while the left lobe of the liver (orange arrow in Figure 3b), with fewer and smaller cysts, demonstrated uptake similar to that of the blood pool and the spleen (yellow arrow in Figure 3b). Although the right hepatic lobe is commonly recommended as the standard metabolic reference in many international guidelines,[3-6] Figure 3 clearly illustrates that the right lobe is less appropriate for reference compared with the left lobe when the right lobe is more diseased.

DISCUSSION

^{18}F-FDG visual interpretation is advocated for oncological[3-5,13-15] and inflammatory[6,14] conditions, using liver and blood pool as metabolic references. While the PERCIST 1.0 criteria recommend that diseased liver is generally unsuitable for visual reference, the precise effects of different hepatic diseases on ^{18}F-FDG uptake have not been entirely elucidated.[4] The current study included a spectrum of liver diseases ranging from biochemical abnormality (hyperbilirubinaemia) to various structural changes (cirrhosis, steatosis, and polycystic liver disease) that can either increase or decrease the SUV ratio. They can be ranked in terms of their mean SUV ratios in descending order of hyperbilirubinaemia, control, cirrhosis and steatosis, and

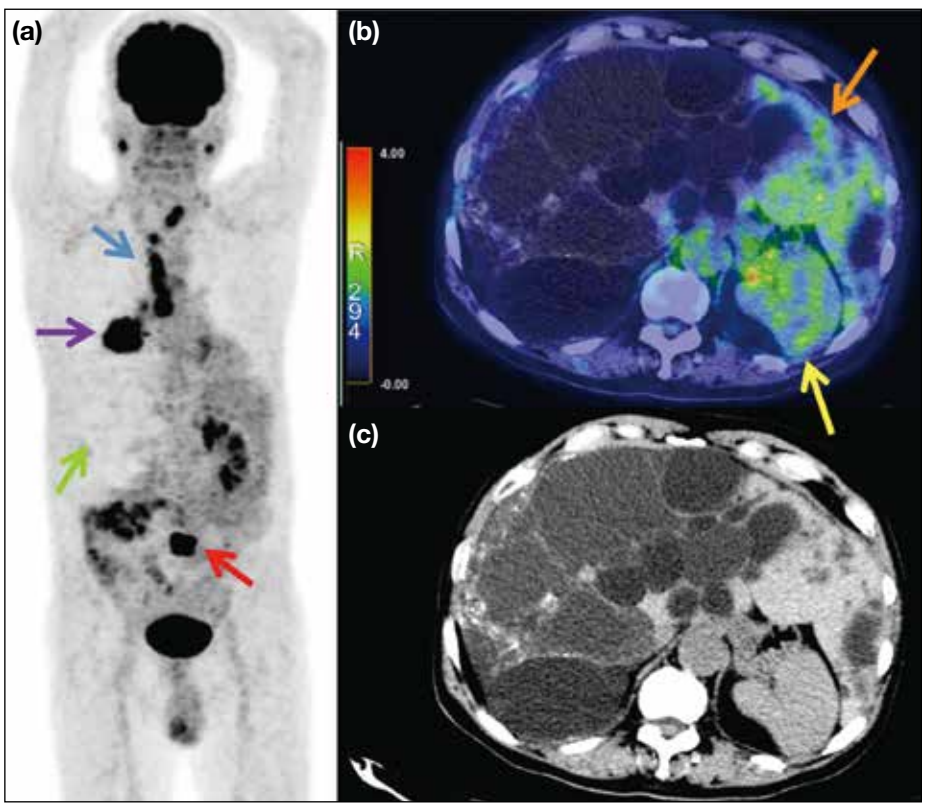

Figure 3. (a) Maximum intensity projection (MIP), (b) ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography, and (c) computed tomography images of a patient suffering from polycystic liver disease. The right hepatic region in MIP has no uptake (green arrow in [a]) because of numerous large liver cysts, with a corresponding standardised uptake value ratio of 0.12. The left hepatic lobe (orange arrow in [b]) has uptake similar to that of the spleen (yellow arrow in [b]) because of smaller and fewer cysts compared to the right lobe. A hypermetabolic right lung tumour (purple arrow in [a]) with metastases to lymph nodes (blue arrow in [a]) and the L5 level (red arrow in [a]) are seen.

polycystic liver disease.

The hyperbilirubinaemia cases showed higher SUV ratios than the controls. This is likely because jaundice implies hepatitis, and inflammation generally leads to increased ^{18}F-FDG uptake.[15] This hypothesis is supported by our findings that higher serum bilirubin levels were associated with higher SUV ratios (Figure 2). High SUV ratio raises the concern for increasing false negative rate in lesion delineation, particularly if the lesion is only mildly ^{18}F-FDG–avid. Clinical scenarios of hyperbilirubinaemia, due to biliary obstruction or acute hepatitis, are commonly encountered in oncology practice. In this study, hyperbilirubinaemia was used as an indicator of abnormal liver function and hepatitis. While serum bilirubin can be hepatic or haemolytic in origin, 89.7% of the hyperbilirubinaemia cases in this study exhibited elevated levels of other liver enzyme(s). This finding supports the hypothesis that the observed hyperbilirubinaemia was primarily hepatic in nature.

The cirrhosis cases had lower mean SUV ratios compared with the controls, probably as a result of the impaired glucose metabolism in liver fibrosis. Although liver biopsy is the gold standard for the diagnosis of cirrhosis, the procedure is invasive and not commonly employed. The cirrhosis subjects in this study were therefore selected based on radiological and endoscopic findings. For radiological findings, the sensitivity varies from 77% to 82% and the specificity ranges from 68% to 80%.[16] In this study, most cirrhotic cases (85.2%) had identifiable aetiologies of the cirrhosis. The majority (59.3%) also had cirrhotic features documented in more than one investigation.

The steatosis cases had lower SUV ratios than the control cases, consistent with previous observations.[17] We demonstrated that a more significant reduction in the SUV ratio can be expected in livers with higher degrees of steatosis. These results can be explained by the lower ^{18}F-FDG uptake in fat content compared with normal liver parenchyma and the impaired glucose metabolism in steatosis. Abele and Fung's study[18] showed that the SUV_{mean} in steatotic patients was lower than that of the controls (2.18 vs. 2.03). While this difference did not achieve statistical significance, the authors suggested that the limited power of their study might not have been sufficient to detect a true difference between the cases (i.e., type II error). The different sample sizes between Abele and Fung's study (n = 23)[18] and the current report (n = 52) may offer an explanation of this discrepancy. On the other hand, Keramida et al[19] demonstrated no difference in SUV_{mean} between steatosis cases and the controls; however, their SUV_{mean} had a complicated adjustment for hepatic fat content and the potential effect of such adjustment on the original SUV magnitude is still unclear. Most clinical scenarios and research studies, including our investigation, had no adjustment. The current study excluded any subject with biochemical or structural abnormality of steatotic livers, while previous studies did not specifically elaborate the biochemical or structural properties.[17-19] Most importantly, the current study emphasises the $SUV_{liver}/SUV_{blood\ pool}$ ratio instead of absolute SUV, because the ratio is more relevant to visual interpretation.

A simple cyst is defined as a thin-walled sac containing serous fluid.[20] Therefore, it has lower ^{18}F-FDG uptake compared with normal hepatic parenchyma. This explains why the mean SUV ratio observed in polycystic liver cases was the lowest among all the cases. While polycystic liver is not considered a reliable metabolic reference, its SUV was still evaluated in a 3-cm–diameter fixed-sized spherical VOI in accordance with the PERCIST 1.0 criteria for equivalent comparison with other cases.[4,5] The minimum SUV ratio among the polycystic liver cases was 0.12, which is clearly unsuitable as metabolic reference (Figure 3). This report further demonstrates that the hepatic uptake in polycystic liver disease depends on the size, number, and distribution of the cysts. The heterogeneous and variable uptake in the polycystic liver prohibits its application as a reliable metabolic reference.

Steatosis, cirrhosis and polycystic liver disease cases showed lower SUV ratios than those in the control cases. Their hepatic uptake could be similar to or even lower than blood pool or splenic uptake. This observation was distinct from the observation in the controls, in which normal liver uptake was always greater than blood pool and splenic uptake. A previous study of high-grade lymphoma indeed has suggested that lymphomatous involvement in spleen should be suspected if the spleen has greater uptake than the liver.[21] Therefore, the deceptively low liver-to–blood pool SUV ratio observed in steatosis, cirrhosis, and polycystic liver disease can potentially lead to higher false positive rates in lesion detection.

All disease cases had mean SUV ratios different from the controls and the differences were statistically significant in two-sided *t* tests. However, such quantitative

differences may not always appear conspicuous in the qualitative visual interpretation. For example, the visual contrast between liver/blood pool uptake in the cirrhosis cases was slightly less than that in the control cases. The visual differences between the mild hyperbilirubinaemia/steatosis cases and the controls were also subtle. On the other hand, in severe hyperbilirubinaemia, severe steatosis and polycystic liver disease cases, their visual contrast between liver/blood pool uptake was obviously different from that in the controls. Thus, severe liver diseases can have significant quantitative and qualitative effects on the liver/blood pool references. This can eventually affect the diagnostic accuracy of visual interpretation.

Limitations

The current study had some limitations. First, subtle hepatic tumour or metastasis may be present. To minimise this pitfall, subjects with a histological diagnosis or radiological suspicion of liver malignancy were excluded from this study. Second, the number of cases of polycystic liver disease (10 patients) was lower compared to other groups because of its inherently low prevalence. Third, the liver function tests were obtained within 2 weeks, rather than on the same day, of ^{18}F-FDG PET/CT acquisition. Fourth, this study demonstrated that all disease cases had SUV ratios different from that of the controls in quantitative aspect. Future study is required to determine if this quantitative difference can be translated to significant changes in qualitative visual interpretation.

CONCLUSION

Liver/blood pool uptake in ^{18}F-FDG PET/CT can be influenced by various liver conditions, including hyperbilirubinaemia, cirrhosis, steatosis, and polycystic liver disease. As liver diseases progress in severity, their impact on liver/blood pool uptake becomes more prominent. Therefore, radiologists should exercise great caution in the utilisation of liver/blood pool uptake as metabolic references in cases of significant hepatic disease. Clinical history, biochemical function and imaging findings should be thoroughly reviewed before visual interpretation.

REFERENCES

1. Ziai P, Hayeri MR, Salei A, Salavati A, Houshmand S, Alavi A, et al. Role of optimal quantification of FDG PET imaging in the clinical practice of radiology. Radiographics. 2016;36:481-96.
2. Boellaard R. Standards for PET image acquisition and quantitative data analysis. J Nucl Med. 2009;50 Suppl 1:11S-20S.
3. Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, Müeller SP, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol. 2014;32:3048-58.
4. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. J Nucl Med. 2009;50 Suppl 1:122S-50S.
5. O JH, Lodge MA, Wahl RL. Practical PERCIST: a simplified guide to PET Response Criteria in Solid Tumors 1.0. Radiology. 2016;280:576-84.
6. Jamar F, Buscombe J, Chiti A, Christian PE, Delbeke D, Donohoe KJ, et al. EANM/SNMMI guideline for ^{18}F-FDG use in inflammation and infection. J Nucl Med. 2013;54:647-58.
7. Boellaard R, O'Doherty MJ, Weber WA, Mottaghy FM, Lonsdale MN, Stroobants SG, et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2010;37:181-200.
8. Park JW, Kim JH, Kim SK, Kang KW, Park KW, Choi JI, et al. A prospective evaluation of ^{18}F-FDG and ^{11}C-acetate PET/CT for detection of primary and metastatic hepatocellular carcinoma. J Nucl Med. 2008;49:1912-21.
9. Gevers TJ, Drenth JP. Diagnosis and management of polycystic liver disease. Nat Rev Gastroenterol Hepatol. 2013;10:101-8.
10. Nabi HA, Zubeldia JM. Clinical applications of ^{18}F-FDG in oncology. J Nucl Med Technol. 2002;30:3-9.
11. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. 2017. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf. Accessed 9 Oct 2023.
12. Jacobs JE, Birnbaum B, Shapiro MA, Langlotz CP, Slosman F, Rubesin SE, et al. Diagnostic criteria for fatty infiltration of the liver on contrast-enhanced helical CT. AJR Am J Roentgenol. 1998;171:659-64.
13. Barrington SF, Kluge R. FDG PET for therapy monitoring in Hodgkin and non-Hodgkin lymphomas. Eur J Nucl Med Mol Imaging. 2017;44:97-110.
14. Soussan M, Nicolas P, Schramm C, Katsahian S, Pop G, Fain O, et al. Management of large-vessel vasculitis with FDG-PET: a systematic literature review and meta-analysis. Medicine (Baltimore). 2015;94:e622.
15. Love C, Tomas MB, Tronco GG, Palestro CJ. FDG PET of infection and inflammation. Radiographics. 2005;25:1357-68.
16. Kudo M, Zheng RQ, Kim SR, Okabe Y, Osaki Y, Iijima H, et al. Diagnostic accuracy of imaging for liver cirrhosis compared to histologically proven liver cirrhosis. A multicenter collaborative study. Intervirology. 2008;51 Suppl 1:17-26.
17. Lin CY, Lin WY, Lin CC, Shih CM, Jeng LB, Kao CH. The negative impact of fatty liver on maximum standard uptake value of liver on FDG PET. Clin Imaging. 2011;35:437-41.
18. Abele JT, Fung CI. Effect of hepatic steatosis on liver FDG uptake measured in mean standard uptake values. Radiology. 2010;254:917-24.
19. Keramida G, Potts J, Bush J, Verma S, Dizdarevic S, Peters AM. Accumulation of ^{18}F-FDG in the liver in hepatic steatosis. AJR Am J Roentgenol. 2014;203:643-8.
20. Vachha B, Sun MR, Siewert B, Eisenberg RL. Cystic lesions of the liver. AJR Am J Roentgenol. 2011;196:W355-66.
21. Rini JN, Leonidas JC, Tomas MB, Palestro CJ. ^{18}F-FDG PET versus CT for evaluating the spleen during initial staging of lymphoma. J Nucl Med. 2003;44:1072-4.