Association of leukotrienes and prostaglandins with splenic ^{18}F-FDG uptake in hepatobiliary cancer patients

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Abstract

Objective: In this study, we aimed to evaluate the relationship between lipid metabolites and diffuse splenic ^{18}F-FDG uptake with the means of leukotriene (LT) and prostaglandin (PG). **Subjects and Methods:** We enrolled 36 patients with hepatobiliary malignancies who underwent fluorine-18-fluorodeoxyuglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) for staging workup. Patients were divided into two groups according to spleen to liver ratio (S/L ratio) of ^{18}F-FDG uptake. Blood sample of each patient was collected on the day of conducting PET/CT scanning. Several types of LT and PG, including LTB4, LTC4, LTE4, PGD2, PGE2, and PGF2α were measured from blood plasma samples from 36 patients using enzyme immunoassay (EIA kit, Cayman Chemical Co.). **Results:** White blood cell counts (P=0.0176) and C-reactive protein (P=0.0036) were higher in patients with splenic ^{18}F-FDG uptake exceeding hepatic ^{18}F-FDG uptake. Among the several types of PG and LT, PGD2 (P=0.0033) was higher in patients with hepatic ^{18}F-FDG uptake exceeding splenic ^{18}F-FDG uptake, however, LTC4 (P=0.0237) and LTE4 (P=0.0429) were higher in patients with splenic ^{18}F-FDG uptake over hepatic uptake. Higher levels of LTC4 and lower levels of PGD2 are shown in patients with splenic ^{18}F-FDG uptake. **Conclusion:** If the clinician incidentally finds splenic ^{18}F-FDG uptake exceeding hepatic uptake, concurrent inflammation should be considered.

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Introduction

Leukotrienes (LT) and prostaglandins (PG) are important lipid mediators in enhancing and modulating proinflammatory responses [1-3]. They are lipid metabolites derived from arachidonic acid [1]. Leukotrienes, formed by the 5-lipoxygenase-catalyzed oxidation of arachidonic acid, have potent proinflammatory activities [2]. Prostaglandins are formed when arachidonic acid is metabolized by the sequential actions of cyclooxygenase and other synthase [3]. Prostaglandins play a key role in the generation of the inflammatory response [3].

The spleen, is the largest lymphoid organ which combines the innate and adaptive immune system in a uniquely organized way [4]. The spleen performs multiple tasks, including clearance of pathogens and production of inflammatory substances and immunoglobulins [5]. In normal individuals, fluorine-18-fluorodeoxyuglucose (^{18}F-FDG) uptake in the spleen is less than that in the liver [6]. The splenic uptake exceeding hepatic uptake is considered abnormal [6]. Focal uptake in the spleen is considered pathologic, which may represent a lymphoma, primary splenic neoplasm, metastasis, or infection [7].

In contrast to focal uptake, diffusely increased ^{18}F-FDG uptake in spleen is more commonly observed on a whole-body ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) by chance, but its clinical significance is discussed sparsely in the literature. There are few reports that diffused increased splenic ^{18}F-FDG uptake frequently occurs in patients under inflammatory condition [8, 9]. In previous reports, we also suggested that diffuse splenic uptake may be associated with acute inflammatory condition [10, 11]. The purpose of this study was to assess the clinical implication of diffusely increased splenic ^{18}F-FDG uptake and to evaluate the relationship between lipid biocompounds and increased glucose metabolism in spleen.

Subjects and Methods

Study population

This study was a retrospectively reviewed the patients with pancreaticobillary malignancies (cholangiocarcinoma, pancreatic cancer, gallbladder cancer, and cancer of the ampulla of vater) who underwent PET/CT. All patients had undergone ^{18}F-FDG PET/CT for staging workup before treatment. Patients with known causes of splenic ^{18}F-FDG uptake, such as metastasis to spleen, lymphoma involvement and focal infection were excluded. Patients with prior histories of treatment with granulocyte colony stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (CSF) were excluded. There was no patients who had uncontrolled diabetes mellitus or high blood sugar level. Thirty-six patients were enrolled in this study, and they were divided into 2 groups according to splenic ^{18}F-FDG uptake relative to hepatic ^{18}F-FDG uptake. Eighteen patients were included in each group. We adopted the laboratory studies within 3 days before or after PET/CT, including C-reactive protein (CRP) level, complete blood cell count, which were routinely planned for the clinical baseline study of the patients. In addition, the reserved serum in the same day of routine laboratory study was obtained for the analysis of both LTs and PGs. This study was reviewed and approved by the Institutional Review Board of our institution and waived informed consent form for retrospective nature.

Measurement of prostaglandins and leukotrienes

Blood sample for immunoassay to analyze concentration of LT and PG was collected on the day of ^{18}F-FDG PET/CT. Concentration of LT and PG was measured by a specific enzyme immunoassay with a commercial kit (Cayman Chemical Co; Ann Arbor, MI, USA). Six lipid mediators were analyzed as follow: LTB4, LTC4, LTE4, PGD2, PGE2, and PGF2α. Procedures were followed as described by the manufacturer.

^{18}F-FDG PET/CT

All patients fasted for at least 6 hours before undergoing ^{18}F-FDG PET/CT. Serum glucose levels were less than 120mg/dL before ^{18}F-FDG administration. The patients were injected with 5.2MBq of ^{18}F-FDG per kilogram of body weight. ^{18}F-FDG PET/CT was performed 60min after intravenous injection of ^{18}F-FDG. Emission scan was conducted in the 3-dimensional mode. Emission scan time per bed position was 3min; 9 bed positions were acquired. Positron emission tomography data were obtained using a dedicated PET/CT scanner (Gemini, Philips, Milpitas, CA, USA) with an axial field of view of 18cm. The average axial resolution varied between 4.2mm full width at half maximum in the center and 5.6mm at 10cm. The average total PET/CT examination time was 30 minutes. After scatter and decay correction, PET data were reconstructed iteratively with attenuation correction and reoriented in axial, sagittal, and coronal slices. The row action maximum likelihood algorithm was used for 3-dimensional reconstruction.

Image analysis

Using CT images of the ^{18}F-FDG PET/CT, round region of interest (ROI) was placed on the lumbar vertebrae (L1-L3 vertebral bodies), which were averaged as the bone marrow (BM). We placed one circular ROI on the center of the spleen and the right lobe of the liver, in the middle part, to avoid mismatch between the CT and PET images and the artifact by respiratory motion. The ROI were used to measure SUVmax of BM, liver and spleen in each patient. Spleen SUVmax/liver SUVmax (S/L ratio), and spleen SUVmax/BM SUVmax were calculated.

Statistical analysis

Statistical analyses were performed using MedCalc® for Windows version 16.4.3 (MedCalc, Mariakerke, Belgium). All non-normally distributed variables were expressed as medians and interquartile ranges (IQR; 25–75%). A Mann–Whitney U-test was used to compare continuous variables between the two groups. For comparing the categorical data of the groups, the X^2-test was used. The correlation between splenic ^{18}F-FDG uptake and hematologic indicies was determined by Pearson correlation coefficient. Results were considered statistically significant when a P-value was less than 0.05.

Results

Patient's characteristics

Patients' characteristics are shown in Table 1. Patients were histologically confirmed as following disease: cholangiocarcinoma (n=22), pancreatic cancer (n=9) or gall bladder cancer (n=3), ampulla of Vater cancer (n=2). Endoscopic retrograde cholangiopancreatography (ERCP) was done in 25 patients in 5 days before performing ^{18}F-FDG PET/CT. Seven patients received ERCP after ^{18}F-FDG PET/CT and 4 patients did not underwent ERCP. Thirteen patients of 18 patients in the spleen group received ERCP before ^{18}F-FDG PET/CT.

Relation between Splenic ^{18}F-FDG uptake and hematologic indices

Patients were divided into 2 groups according to splenic ^{18}F-FDG uptake relative to hepatic uptake. Eighteen patients were included in each group. Images of patients from each group are shown in Figure 1. White blood cell counts (P=0.0176) and CRP (P=0.0036) were higher in patients with splenic ^{18}F-FDG uptake exceeding hepatic ^{18}F-FDG uptake. Liver maximum standardize uptake value (SUVmax) was not different between two groups (P=0.1403), however, BM SUVmax was higher in patients with splenic ^{18}F-FDG uptake over hepatic ^{18}F-FDG uptake (P=0.0124). Other hematologic indices were not significantly different; RBC (P=0.1839), Hb (P=0.1210), Hct (P=0.1137), and platelet (P=0.5583) (Table 1).

Comparison of prostaglandin and leukotrienes between two groups

Among PG and LT, PGD2 (P=0.0033) was higher in patients with hepatic ^{18}F-FDG uptake exceeding splenic ^{18}F-FDG uptake, however, LTC4 (P=0.0237) and LTE4 (P=0.0429) were higher in patients with splenic ^{18}F-FDG uptake over hepatic uptake. PGE2, PGF2a, and LTB4 were not different between patients (Table 2). Data comparison graphs of PG and LT are presented in Figures 2 and 3.

Table 1. *Patient characteristics.*

Variables	Spleen>Liver (n=18)	Spleen<Liver (n=18)	P
Age (yrs)	70 (42-83)	70 (55-84)	0.6016
Sex (female)	11	6	0.1811
Disease (cholangiocarcinoma)	12	10	0.7332
Spleen SUVmax	4.85 (2.9-15.5)	2.1 (1.4-3.6)	<0.0001
Liver SUVmax	3.4 (2.2-6.6)	2.6 (1.9-5.8)	0.1403
BM SUVmax	3.2 (1.7-5.1)	2.2 (1.3-4.4)	0.0124
SpleenSUVmax/liverSUVmax	1.39 (1.04-2.35)	0.74 (0.6-0.97)	<0.0001
Spleen SUVmax/BM SUVmax	1.53 (1.0-4.70)	1.0 (0.52-1.38)	<0.0001
WBC (x10^3/μL)	9.57 (3.43-27.31)	6.87 (4.14-11.26)	0.0176
RBC (x10^3/μL)	3.73 (2.56-5.25)	4.06 (2.75-5.0)	0.1839
Hb (g/dL)	11.2 (7.6-14.8)	12.3 (8.4-15.1)	0.1210
Hct (%)	32.9 (22.4-44.4)	36.1 (23.8-43.2)	0.1137
Platelet (x10^3/μL)	272 (52-358)	230 (143-434)	0.5583
CRP (mg/dL)	4.6 (0.4-26.3)	2.0 (0.1-5.52)	0.0036

SUVmax, Maximum standardized uptake value; BM, Bone marrow; WBC, White blood cell; RBC, Red blood cell; Hct, Hematocrit; CRP, C-reactive protein. Variables are expressed as the median (interquartile range; IQR), P - value using Mann-Whitney U - test

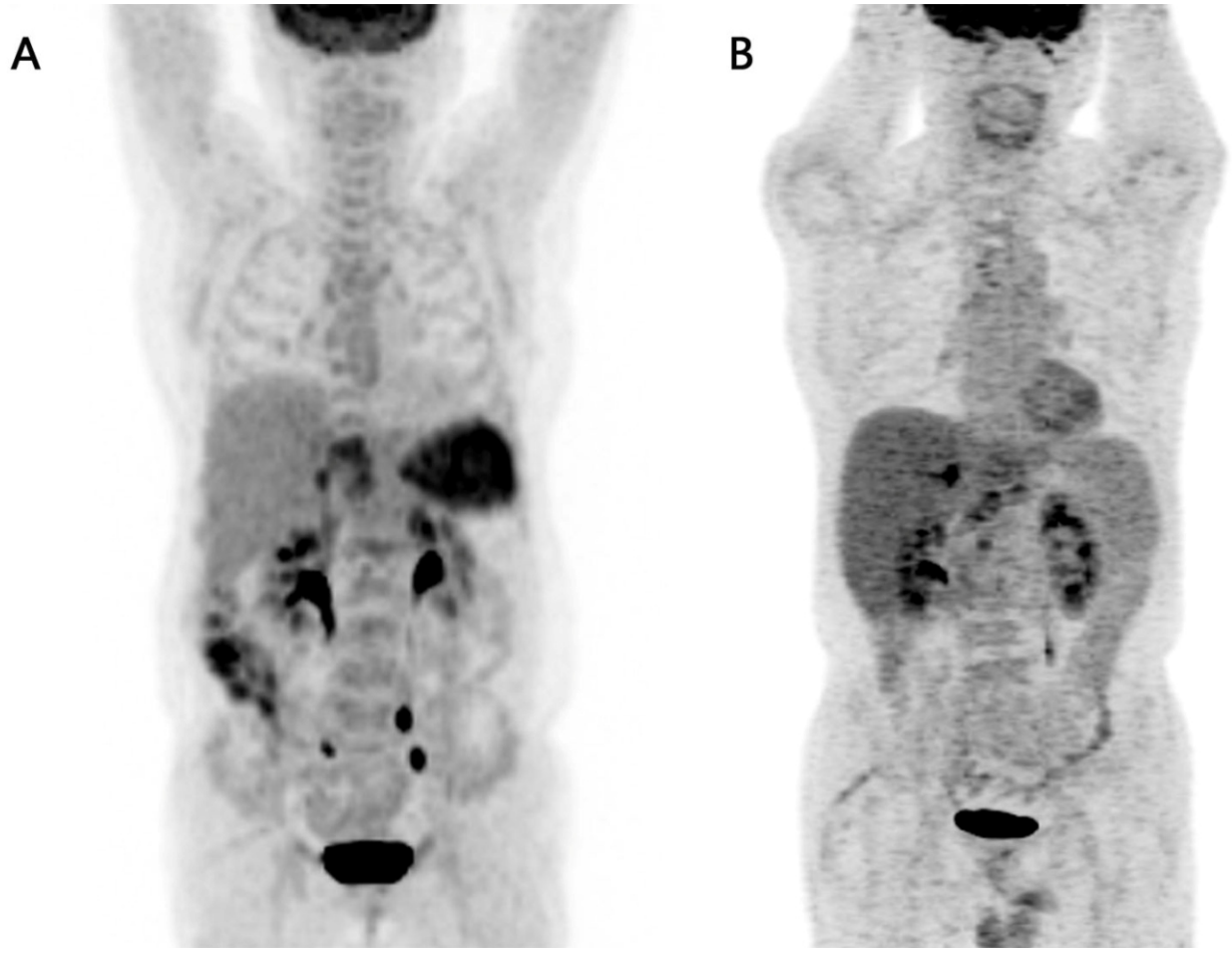

Figure 1. Maximum intensity projections of ^{18}F-FDG PET/CT. A 74 year-old woman with Klatskin tumor presenting increased splenic ^{18}F-FDG uptake (SUVmax 5.2) is exceeding hepatic ^{18}F-FDG uptake (SUVmax 2.3). Spleen to liver ratio was 2.23 (A). A 64 year-old man with intrahepatic cholangioc arcinoma showing splenic ^{18}F-FDG uptake (SUVmax 3.3) is lower than hepatic ^{18}F-FDG uptake (SUVmax 4.7). The spleen to liver ratio was 0.702. (B)

Table 2. *Comparison of prostaglandins and leukotrienes between 2 groups.*

Variables	Spleen>Liver (n=18)	Spleen<Liver (n=18)	P value
Prostaglandins (pg/mL)			
PGD2	1695.6 (548.3-11295.1)	3967.2 (1170.4-11874.2)	0.0033
PGE2	872.8 (233.6-1824.9)	963.3 (285.2-2167.3)	0.8371
PGF2a	504.3 (0-1997.8)	917.2 (929.9-2221.0)	0.0999
Leukotrienes (pg/mL)			
LTB4	28870.7 (9750.4-63433.5)	19654.1 (5039.6-51447.2)	0.1839
LTC4	160.1 (0-305.7)	98.5 (0-209.5)	0.0237
LTE4	6001.5 (1173.4-26023.8)	3625.5 (0-16815.8)	0.0429

PG, prostaglandin; LT, leukotriene, Variables are expressed as the median (interquartile range; IQR), P - value using Mann-Whitney U - test

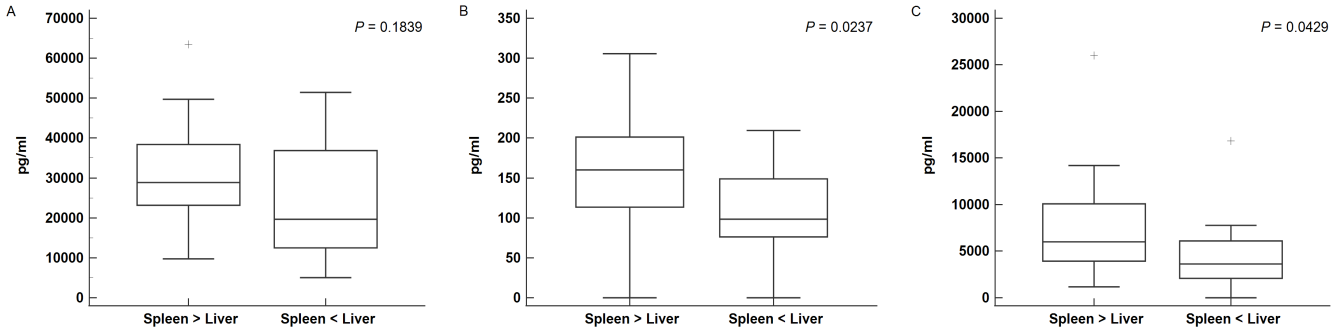

Figure 2. Comparison of leukotrienes level between two groups (In the box, the median and interquartile values are represented. Whiskers show values from minimum to maximum, excluding outliers. + expresses outliers).

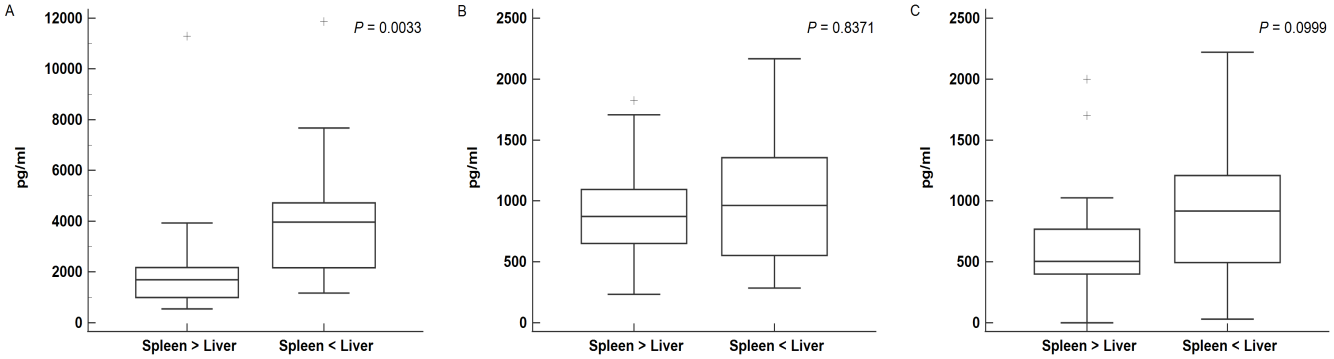

Figure 3. Comparison of prostaglandins levels between two groups (In the box, the median and interquartile values are represented. Whiskers show values from minimum to maximum, excluding outliers. + expresses outliers).

Correlations between ^{18}F-FDG uptake and hematologic indices

Correlations between spleen SUVmax, BM SUVmax, S/L ratio and hematologic indices are shown in Table 3. Correlations between LTB4 and BM SUVmax (r=0.3687, P=0.0269) and between PGD2 and S/L ratio (r=-0.3628, P=0.0296) were weakly significant, however the correlations between other variables were not statistically significant.

Discussion

We have observed splenic ^{18}F-FDG uptake exceeding hepatic ^{18}F-FDG uptake and proved the relation between that phenomenon and concurrent inflammation [10]. Interleukin (IL)-1b, IL-1receptor antagonist, IL-4, IL-6, IL-7, and IL-13 was associated with diffuse splenic ^{18}F-FDG uptake [11]. In addition, splenic ^{18}F-FDG uptake could predict worse prognosis in patients with cholangiocarcinoma [12]. In this study, we have found that PGD2 and LTC4 are associated with this phenomenon.

There are several assumptions that explain splenic ^{18}F-FDG uptake exceeding hepatic uptake. Infections such as HIV in-

Table 3. *Correlation plot between laboratory findings ad PET parameters.*

	P-value													
SpleenSUVmax /liverSUVmax	0.304	0.322	0.290	-0.174	-0.363	-0.017	-0.31	-0.290	-0.229	0.430	0.168	0.772	0.364	
BM SUVmax	0.369	0.208	0.309	0.077	-0.209	-0.096	0.081	0.038	0.068	0.444	0.019	0.594		0.364
Spleen SUVmax	0.224	0.163	0.283	-0.089	-0.300	-0.079	-0.172	-0.196	-0.113	0.395	-0.077		0.594	0.772
Platelet ($x10^3$/μL)	0.038	0.026	-0.091	-0.08	-0.096	-0.091	-0.038	-0.072	0.081	0.143		-0.077	0.019	0.168
WBC ($x10^3$/μL)	0.254	0.208	0.171	0.14	-0.251	0.049	0.047	-0.015	0.155		0.143	0.395	0.444	0.43
RBC ($x10^3$/μL)	0.039	-0.028	-0.167	0.278	0.039	0.188	0.929	0.922		0.155	0.081	-0.113	0.068	-0.229
Hct (%)	0.056	-0.028	-0.103	0.205	0.022	0.186	0.969		0.922	-0.015	-0.072	-0.196	0.038	-0.29
Hb(g/dL)	0.047	-0.05	-0.129	0.241	0.019	0.156		0.969	0.929	0.047	-0.038	-0.172	0.081	-0.31
PGE2	0.651	0.574	0.599	0.547	0.430		0.156	0.186	0.188	0.049	-0.091	-0.079	-0.096	-0.017
PGD2	-0.028	-0.015	0.041	0.571		0.430	0.019	0.022	0.039	-0.251	-0.096	-0.3	-0.209	-0.363
PGF2	0.295	0.383	0.213		0.571	0.547	0.241	0.205	0.278	0.14	-0.08	-0.089	0.077	-0.174
LTC4	0.76	0.758		0.213	0.041	0.599	-0.129	-0.103	-0.167	0.171	-0.091	0.283	0.309	0.29
LTE4	0.742		0.758	0.383	-0.015	0.574	-0.05	-0.028	-0.028	0.208	0.026	0.163	0.208	0.322
LTB4		0.742	0.76	0.295	-0.028	0.651	0.047	0.056	0.039	0.254	0.038	0.224	0.369	0.304
Pearson correlation coefficient	LTB4	LTE4	LTC4	PGF2	PGD2	PGE2	Hb (g/dL)	Hct (%)	RBC ($x10^3$/μL)	WBC ($x10^3$/μL)	Platelet ($x10^3$/μL)	Spleen SUVmax	BM SUVmax	SpleenSUVmax /liverSUVmax

PG, prostaglandin; LT, leukotriene; SUVmax, Maximum standardized uptake value; BM, Bone marrow; WBC, White blood cell; RBC, Red blood cell; Hct, Hematocrit;

fection, malaria infection, toxoplasmosis and varicella infection result in activation of immune system in the white pulp or compensatory expansion of the red marrow in the spleen, leading to increased glucose usage by this organ [5, 13-17]. In addition, concurrent inflammatory condition which was supported by leukocytosis and increased level of CRP may be associated with this phenomenon in accordance with previous studies [10, 11]. Spleen serves as a reservoir of cellular elements including leukocytes and the white pulp is the structure of the lymphoid region of the spleen [4, 5]. The correct organization and maintenance of the white pulp is controlled by specific chemokines that attract T and B cells to their respective domains [4]. Splenic uptake in malaria patients is proven to reflect the activation on B lymphocytes [15, 16]. Therefore, the phenomenon of splenic ^{18}F-FDG uptake may be linked with the activation of B and T lymphocytes activation in white pulp of spleen.

In this study, we compared PG and LT between 2 groups. Prostaglandins play a key role in the generation of the inflammatory response, however, their role in the resolution of inflammation is more controversial [3]. Among PG, PGD2 was lower in patients with splenic uptake exceeding hepatic uptake. Prostaglandins 2 is a major eicosanoid that functions in both an inflammatory and homeostatic capacity [3]. Prostaglandins 2 production is known to be increased during the proinflammatory phase, but not during resolution phase [3]. The role of PGD2 in cholangitis is not fully understood, however, PGE2 involves in development of cholangitis [18]. The worse prognosis of patients with splenic uptake may result from unresolvable cholangitis, not from expanding cholangiocarcinoma [19]. Patients with splenic uptake might be in the phase of resolution after acute inflammation by cholangitis. Among LT, LTC4 was higher in patients with splenic ^{18}F-FDG uptake. Leukotrienes C4, LTD4, and LTE4 are cysteinyl LT, potent proinflammatory mediators [20]. In patients with obstructive jaundice, the excretion of LT from blood by hepatobiliary elimination are increased with the severity of cholestasis and hepatic inflammation [20].

Several limitations should be considered in this study. This is the first study that evaluated the association of LT, and PG with splenic ^{18}F-FDG uptake, however, we could not explain the mechanism of this phenomenon. In addition, the current study is retrospectively designed and includes a relatively small sample size. Further prospective studies with a large sample size will be needed to explain the mechanism of this phenomenon.

In conclusion, higher levels of LTC4 and lower levels of PGD2 are shown in patients with splenic ^{18}F-FDG uptake. If the clinician incidentally finds splenic ^{18}F-FDG uptake exceeding hepatic uptake, concurrent inflammation should be considered.

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