Evaluation of Spleen Glucose Metabolism Using ^{18}F-FDG PET/CT in Patients with Febrile Autoimmune Disease

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The purpose of this study was to evaluate the clinical significance of ^{18}F-FDG uptake by the spleen in patients with autoimmune disease. **Methods:** We retrospectively reviewed Severance Hospital's electronic medical records of patients hospitalized for the evaluation of fever who underwent ^{18}F-FDG PET/CT. We found 91 patients with autoimmune diseases and 101 patients with localized infection. ^{18}F-FDG uptake was assessed by measuring SUV in the spleen and liver. The spleen-to-liver ratio of the SUV_{mean} (SLR_{mean}) was calculated. Clinical and laboratory parameters were collected and evaluated for association with SLR_{mean}. In-hospital mortality was defined as all-cause mortality during hospital admission for fever. **Results:** SLR_{mean} was significantly higher in autoimmune disease than in localized infectious disease (1.28 ± 0.43 vs. 0.91 ± 0.21, $P < 0.001$). In autoimmune disease, SLR_{mean} was correlated with monocytes, aspartate aminotransferase, alanine aminotransferase, albumin, and ferritin. Analysis of receiver-operating-characteristic curves revealed that in comparison with laboratory parameters, SLR_{mean} had the highest performance in differentiating autoimmune from localized infectious disease. Multivariate logistic regression analysis demonstrated that high SLR_{mean} and low platelets were significantly associated with in-hospital mortality in febrile autoimmune disease. **Conclusion:** These findings suggest that spleen glucose metabolism is increased in febrile autoimmune disease. Spleen ^{18}F-FDG uptake may provide information useful in differentiating febrile autoimmune disease from localized infectious disease and predicting clinical outcomes in febrile autoimmune disease.

Key Words: ^{18}F-FDG PET/CT; spleen; bone marrow; autoimmune disease; immunometabolism

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The radiotracer ^{18}F-FDG, which is used in PET/CT, is an analog of glucose; its concentration reflects regional glucose uptake in tissue (*1*). Increased ^{18}F-FDG uptake indicates high glycolytic activity and is associated with various conditions that have active cellular metabolism, such as cancer and localized infection (*2*). Inflammation is also accompanied by high glycolytic activity, and several studies have investigated the role of ^{18}F-FDG PET/CT in the diagnosis of autoimmune disease, such as arthritis, myositis, and vasculitis (*3,4*). In autoimmune disease, specific patterns of ^{18}F-FDG uptake are detected in multiple target organs, such as joints, muscles, and arteries, which can be helpful for diagnosis. The pattern of ^{18}F-FDG distribution in multiple sites throughout the body is consistent with the systemic nature of autoimmune diseases.

Autoimmune diseases are accompanied by activation of systemic inflammation, whereas most infection is caused by local invasion of microorganisms. The general principles of treatment can be very different depending on the underlying condition; immune suppression can be therapeutic in autoimmune diseases, though potentially deleterious in infection. Despite the distinct pathogeneses and treatments, both diseases share common clinical features, including leukocytosis and elevated acute-phase reactants, such as erythrocyte sedimentation rate and C-reactive protein (*5*). Fever can be the main clinical feature of both autoimmune and infectious diseases, posing diagnostic challenge for distinguishing autoimmune diseases from infection.

The spleen filters blood, monitors blood-borne antigens, and is involved in innate and adaptive immune responses. Leukocytes in the spleen include various subsets of T and B cells, dendritic cells, and macrophages. Recent findings suggest that proliferating effector T cells require high metabolic flux through growth-promoting pathways (*6*). Energy metabolism of stimulated lymphocytes is shifted from oxidative metabolism to glycolysis to provide additional energy for activation and proliferation (*7*). We hypothesized that spleen glucose metabolism is different in autoimmune and localized infectious diseases as a consequence of systemic inflammation in autoimmune disease. Hence, we evaluated the correlation between spleen ^{18}F-FDG uptake and laboratory data, the usefulness of ^{18}F-FDG uptake in differentiating between autoimmune and localized infectious diseases, and the role of ^{18}F-FDG uptake in predicting patient outcome.

MATERIALS AND METHODS

Patient Selection

The medical records of patients who underwent ^{18}F-FDG PET/CT at Severance Hospital in Seoul, South Korea, from December 2005 to December 2015 were reviewed. The inclusion criteria were as follows: patients 15–75 y old, patients with documented fever (≥37.8°C) during hospital admission, and patients with a definite cause of fever. The exclusion criteria were as follows: patients with an elucidated origin of fever within 3 d of admission, patients with septic shock or sepsis, and patients with cancer. Finally, 192 patients were enrolled; 91 patients were classified as having an autoimmune disease and 101 as having localized infectious disease. Two groups of age- and sex-matched healthy controls were selected for the autoimmune and infectious disease groups. This

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TABLE 1
Baseline Characteristics and Comparison of Patients with Autoimmune and Infectious Diseases

Variable	Autoimmune (n = 91)	Infectious (n = 101)	P
Clinical variables			
Age	48.1 ± 17.6	55.0 ± 15.9	0.005
Sex (Female)	64 (70.3%)	48 (47.5%)	0.001
In-hospital duration (d)	22.6 ± 15.1	21.7 ± 23.4	0.72
Laboratory variables			
WBC count (/μL)	8,060.3 ± 6,611.2	8,285.8 ± 3,453.5	0.76
Hemoglobin (g/dL)	10.4 ± 1.4	12.8 ± 11.1	0.041
Platelet count (×1,000/μL)	259.3 ± 163.7	343.5 ± 131.8	<0.001
Neutrophil count (/μL)	6,561.2 ± 6,409.8	5,925.0 ± 3,226.5	0.37
Lymphocyte count (/μL)	1,047.9 ± 632.7	1497.1 ± 684.7	<0.001
Monocyte count (/μL)	339.7 ± 256.3	481.3 ± 236.0	<0.001
ESR (mm/h)	66.2 ± 34.7	75.3 ± 31.8	0.007
CRP (mg/L)	73.4 ± 69.6	56.6 ± 50.5	0.059
BUN (mg/dL)	12.1 ± 7.0	11.9 ± 6.1	0.83
Cr (mg/dL)	0.7 ± 0.5	0.9 ± 1.1	0.12
AST (IU/L)	107.5 ± 253.8	27.0 ± 22.0	0.001
ALT (IU/L)	54.9 ± 79.3	28.6 ± 32.7	0.002
Total bilirubin (mg/dL)	0.6 ± 0.7	0.6 ± 1.2	0.70
Total protein (mg/dL)	6.1 ± 0.9	6.8 ± 0.8	<0.001
Albumin (mg/dL)	2.9 ± 0.5	3.4 ± 0.6	<0.001
Ferritin (ng/mL)	3,537.8 ± 5,616.5*	598.4 ± 723.6†	0.005

*Number is confined to patients who underwent each test (n = 82).
†Number is confined to patients who underwent each test (n = 30).
WBC = white blood cell; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; BUN = blood urea nitrogen; Cr = creatinine; AST = aspartate aminotransferase; ALT = alanine aminotransferase.
Data are mean ± SD or number.

study was approved by the Institutional Review Board of Severance Hospital (4-2016-0150), and the requirement to obtain informed consent was waived because of the retrospective nature of the study.

Clinical and Laboratory Data Collection

Clinical data collected included age, sex, and in-hospital duration. Laboratory data included white blood cell, neutrophil, lymphocyte, monocyte, and platelet counts and hemoglobin, erythrocyte sedimentation rate, C-reactive protein, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, total bilirubin, total protein, albumin, and ferritin levels, which were measured within 3 d of the date of the PET/CT scan. In-hospital mortality was defined as all-cause mortality during hospital admission.

^{18}F-FDG PET/CT Image Acquisition

All ^{18}F-FDG PET/CT scans were obtained on a dedicated PET/CT scanner (Discovery STE [GE Healthcare] or Biograph 40 TruePoint [Siemens Medical Systems]). All patients fasted for 6 h before the PET/CT scan, and a blood glucose level below 140 mg/dL was confirmed. The PET/CT scan was performed 60 min after the intravenous administration of 5.5 MBq of ^{18}F-FDG per kilogram. The CT scan was performed at 30 mA and 130 kVp on the Discovery STE or at 36 mA and 120 kVp on the Biograph 40 TruePoint. The PET scan was performed with an acquisition time of 2.5 min per bed position in 3-dimensional mode. PET images were reconstructed using an ordered-subset expectation maximization algorithm with attenuation correction.

Assessment of SUV Acquired by ^{18}F-FDG PET/CT Scans

Radiotracer accumulation was analyzed semiquantitatively using both SUV_{mean} and SUV_{max}. Spleen ^{18}F-FDG SUV was obtained on 3 nonadjacent slices and averaged. Bone marrow SUV was separately obtained from lumbar vertebrae 1 through 5 and averaged. In the case of bone infection directly involving the lumbar spine (n = 1) and liver abscess (n = 3), the region involved was excluded from analysis. To measure normal liver activity, 3 spheric 1-cm regions of interest were drawn on the liver: 2 on the right lobe and 1 on the left lobe. The SUV_{mean} of the liver was defined as the mean of the 3 regions of interest. Because 2 different PET scanners were used in this study, liver was used as an internal reference organ to reduce problems related to different scanners. The spleen-to-liver ratio of the SUV (SLR) was calculated by dividing the spleen SUV_{max} or SUV_{mean} by the liver SUV_{mean}, and the bone marrow–to–liver ratio of the SUV (BLR) was calculated by dividing the bone marrow SUV_{max} or SUV_{mean} by the liver SUV_{mean}.

Statistical Analysis

Data were analyzed using SPSS, version 21 (SPSS Inc.). Continuous variables are presented as mean with SD, and categoric variables are expressed as frequencies and percentages. Continuous variables were compared using the Student t test, and categoric data were compared using the χ^2 test. Correlations between laboratory variables and SLR or BLR were calculated by the Pearson correlation analysis.

The discriminative ability of SLR or BLR for autoimmune disease was analyzed using area under the receiver-operating-characteristic (ROC) curve. The area under the ROC curve was presented with 95%

TABLE 2
Clinical Spectrum of Autoimmune and Infectious Diseases

Autoimmune		Infectious	
Type	*n*	Type	*n*
Total	91	Total	101
Hemophagocytic lymphohistiocytosis	19 (20.8%)	Chest*	57 (56.4%)
Systemic lupus erythematosus	17 (18.6%)	Abdomen*	35 (34.6%)
Kikuchi disease	14 (15.3%)	Bone*	9 (8.9%)
Vasculitis	12 (13.1%)	Biliary system*	7 (6.9%)
Adult-onset Still disease	11 (12.0%)	Urinary tract*	6 (5.9%)
Rheumatoid arthritis	6 (6.5%)	Brain	3 (2.9%)
Inflammatory myositis	5 (5.4%)	Orofacial*	2 (1.9%)
Behçet disease	4 (4.3%)		
IgG4-related disease	2 (2.1%)		
Sjögren syndrome	1 (1.0%)		

*Multiple affected sites were counted.

confidence interval (CI), and the Youden index was used to identify the maximal cutoff. Risk factors for in-hospital mortality were calculated by univariate and multivariate logistic regression analyses. For estimation of the best cutoff for SLR_{mean} in predicting in-hospital mortality, ROC curve analysis was used. A P value of less than 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics of Patients

The mean age was 48.1 y in the autoimmune disease group and 55.0 y in the infectious disease group ($P = 0.005$). Sixty-four patients (70.3%) were female in the autoimmune disease group, whereas 48 patients (47.5%) were female in the infectious disease group ($P = 0.001$) (Table 1). During the admission period, 14 patients died: 12 in the autoimmune disease group and 2 in the infectious disease group. The autoimmune disease group had lower platelets, lymphocytes, monocytes, erythrocyte sedimentation rate, total protein, and serum albumin than the infectious disease group (Table 1). However, the autoimmune disease group had higher aspartate aminotransferase, alanine aminotransferase, and ferritin than the infectious disease group.

Spectrum of Disease

Most patients were diagnosed with hemophagocytic lymphohistiocytosis, systemic lupus erythematosus, Kikuchi disease, adult-onset Still disease, vasculitis, or rheumatoid arthritis (Table 2). In patients with infectious disease, the most prevalent regions affected were the chest, followed by the abdomen, bone, biliary system, urinary tract, brain, and orofacial area (Table 2).

Comparison of SLR and BLR

Patients with autoimmune disease had higher SLRs than patients with localized infectious disease (SLR_{max}, 1.46 ± 0.49 vs. 1.09 ± 0.25, $P < 0.001$; SLR_{mean}, 1.28 ± 0.43 vs. 0.91 ± 0.21, $P < 0.001$ [Fig. 1]). Also, patients with autoimmune disease had higher mean BLRs than patients with localized infectious disease (BLR_{max}, 1.36 ± 0.51 vs. 1.18 ± 0.37, $P = 0.004$; BLR_{mean}, 1.19 ± 0.46 vs. 0.98 ± 0.31, $P < 0.001$ [Fig. 1]). Representative images (Fig. 2) demonstrate that diffuse ^{18}F-FDG uptake in the spleen is detected with strong contrast to liver ^{18}F-FDG uptake in autoimmune disease. Because the autoimmune and infectious disease groups had different mean ages and sex distributions, we selected 2 healthy control groups matched by age and sex to compare with the autoimmune disease group (control group A) and the infectious disease group (control group B). There was no difference in SLRs or BLRs between the two control groups, suggesting that SLRs and BLRs were not affected by age or sex in our control groups. Interestingly, SLRs and BLRs were higher in the infectious disease group than in the healthy control groups,

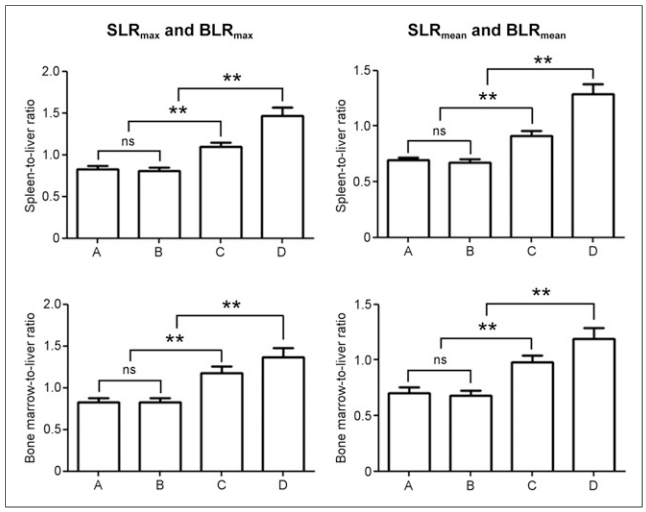

FIGURE 1. ^{18}F-FDG uptake in patients with autoimmune disease (n = 91), patients with infectious disease (n = 101), and age- and sex-matched healthy controls (n = 50). SLRs and BLRs were compared among autoimmune disease controls (A), infectious disease controls (B), patients with infectious disease (C), and patients with autoimmune disease (D). Error bars indicate 95% CI. ns = not significant. **$P < 0.01$.

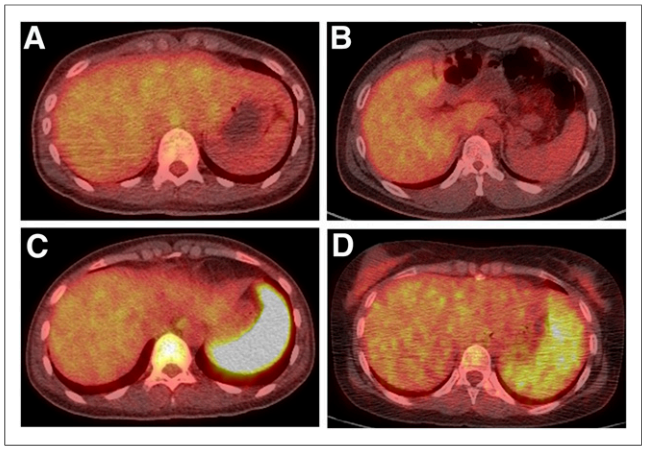

FIGURE 2. Representative ^{18}F-FDG PET/CT images in age- and sex-matched healthy controls for autoimmune disease (A) and infectious disease (B) and patients with autoimmune disease (C) and infectious disease (D).

suggesting that, even in localized infectious disease, spleen and bone marrow glucose metabolism was increased (Fig. 1).

Association of Laboratory Variables with SLR and BLR

In patients with autoimmune disease, SLR_{mean} correlated positively with aspartate aminotransferase, alanine aminotransferase, and ferritin and negatively with serum albumin and monocytes. SLR_{mean} had the highest correlation with ferritin ($r = 0.649$, $P < 0.001$). BLR_{mean} correlated positively with white blood cells, neutrophils, C-reactive protein, and ferritin (Table 3). However, in localized infectious diseases, SLR_{mean} correlated positively with C-reactive protein and negatively with total protein and serum albumin. BLR_{mean} correlated negatively with serum albumin (Table 3). We also analyzed the association of laboratory variables with SLR_{max} and BLR_{max}. Although not included in Table 3, the correlations between laboratory values and SLR_{max} and BLR_{max} were similar to the correlations between laboratory values and SLR_{mean} and BLR_{mean} included in the table.

Differentiation Between Autoimmune and Localized Infectious Diseases

ROC analysis was performed to compare the laboratory variables and SLRs and BLRs for differentiation between autoimmune and localized infectious diseases (Table 4). SLRs had higher ROC values than BLRs, and an SLR_{mean} cutoff of 1.06 had a sensitivity of 62.6% and specificity of 84.2%, with the highest ROC value compared with hemoglobin, platelets, lymphocytes, monocytes, erythrocyte sedimentation rate, aspartate aminotransferase, alanine aminotransferase, total protein, albumin, and ferritin (area under the ROC curve, 0.782; 95% CI, 0.717–0.839; $P < 0.001$).

Risk Factors for In-Hospital Mortality in Autoimmune Disease

We next evaluated the risk factors for in-hospital mortality in patients with autoimmune disease. In univariate analysis, platelet count (odds ratio [OR], 0.993; 95% CI, 0.987–0.998; $P = 0.014$) and

TABLE 3
Correlation Between Laboratory Variables and SLR_{mean} and BLR_{mean} in Autoimmune and Infectious Diseases

Variable	Autoimmune		Infectious	
	SLR_{mean}	BLR_{mean}	SLR_{mean}	BLR_{mean}
WBC count (/μL)	0.168 (0.10)	0.452 (<0.0001)	0.036 (0.71)	0.146 (0.14)
Hemoglobin (g/dL)	0.016 (0.87)	−0.104 (0.32)	−0.087 (0.38)	−0.126 (0.20)
Platelet count (×1,000/μL)	−0.185 (0.077)	0.083 (0.43)	0.110 (0.27)	0.151 (0.13)
Neutrophil count (/μL)	0.189 (0.071)	0.452 (<0.0001)	0.050 (0.61)	0.170 (0.088)
Lymphocyte count (/μL)	0.028 (0.79)	−0.081 (0.43)	−0.132 (0.18)	−0.090 (0.36)
Monocyte count (/μL)	−0.235 (0.024)	−0.095 (0.369)	0.097 (0.333)	−0.030 (0.764)
ESR (mm/h)	−0.091 (0.38)	0.171 (0.10)	0.081 (0.46)	0.089 (0.42)
CRP (mg/L)	0.147 (0.16)	0.356 (<0.001)	0.315 (0.001)	0.198 (0.054)
BUN (mg/dL)	−0.043 (0.68)	−0.124 (0.23)	−0.135 (0.17)	−0.038 (0.70)
Cr (mg/dL)	−0.027 (0.79)	−0.165 (0.11)	−0.023 (0.81)	−0.014 (0.88)
AST (IU/L)	0.359 (<0.001)	−0.098 (0.35)	0.023 (0.81)	−0.014 (0.88)
ALT (IU/L)	0.334 (0.001)	−0.011 (0.91)	−0.035 (0.72)	−0.044 (0.65)
Total bilirubin (mg/dL)	0.135 (0.20)	0.013 (0.89)	0.088 (0.38)	−0.067 (0.50)
Total protein (mg/dL)	−0.119 (0.25)	−0.030 (0.77)	−0.219 (0.027)	−0.063 (0.53)
Albumin (mg/dL)	−0.231 (0.027)	−0.168 (0.10)	−0.441 (<0.001)	−0.355 (<0.001)
Ferritin (ng/mL)	0.649 (<0.001)*	0.283 (0.009)*	−0.076 (0.68)†	−0.075 (0.69)†

*Number is confined to patients who underwent each test ($n = 82$).
†Number is confined to patients who underwent each test ($n = 30$).
WBC = white blood cell; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; BUN = blood urea nitrogen; Cr = creatinine; AST = aspartate aminotransferase; ALT = alanine aminotransferase.
Data are correlation coefficient followed by *P* value in parentheses.

TABLE 4
Comparison of ROC Curve of Spleen and Bone Marrow SUV and Laboratory Variables in Differentiating Between Autoimmune and Infectious Diseases

Variable	Cutoff	Sensitivity	Specificity	PPV (%)	NPV (%)	Area under curve
Spleen SUVs						
SLR_{max}	1.27	59.3	83.1	75.9	69.4	0.738 (0.670–0.799)
SLR_{mean}	1.06	62.6	84.2	78.3	72.0	0.782 (0.717–0.839)
Bone marrow SUVs						
BLR_{max}	1.17	58.2	60.4	56.8	61.6	0.607 (0.534–0.677)
BLR_{mean}	1.22	37.4	85.1	69.2	60.2	0.642 (0.570–0.710)
Laboratory variables*						
Hemoglobin (g/dL)	10.4	58.2	80.2	72.5	67.5	0.734 (0.665–0.795)
Platelet count (×1,000/μL)	216.0	48.4	86.1	75.7	65.0	0.659 (0.588–0.726)
Lymphocyte count (/μL)	870.0	49.4	85.1	74.8	65.2	0.714 (0.645–0.777)
Monocyte count (/μL)	270.0	49.5	85.1	74.8	65.2	0.693 (0.622–0.757)
ESR (mm/h)	27.0	19.7	93.9	74.3	56.5	0.574 (0.496–0.648)
AST (IU/L)	26.0	72.5	72.2	70.0	74.5	0.752 (0.685–0.812)
ALT (IU/L)	35.0	41.8	79.2	64.3	60.2	0.606 (0.533–0.676)
Total protein (mg/dL)	6.2	59.3	79.2	71.9	68.4	0.733 (0.665–0.794)
Albumin (mg/dL)	3.3	81.3	60.4	70.4	80.5	0.749 (0.682–0.809)
Ferritin (ng/mL)	1,126.8	42.6	93.3	85.0	64.4	0.711 (0.618–0.793)

*Laboratory variables with differences with clinical significance in baseline characteristics were evaluated.
PPV = positive predictive value; NPV = negative predictive value; ESR = erythrocyte sedimentation rate; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

SLR_{mean} (OR, 3.625; 95% CI, 1.013–12.967; $P = 0.047$) were identified as prognostic predictors. Furthermore, using ROC analysis, an SLR_{mean} cutoff of more than 1.61 revealed the greatest risk for in-hospital mortality (OR, 5.076; 95% CI, 1.413–18.230; $P = 0.012$). The multivariate logistic regression model showed that platelet count (OR, 0.993; 95% CI, 0.988–0.999; $P = 0.020$) and an SLR_{mean} of more than 1.61 (OR, 4.796; 95% CI, 1.228–18.723; $P = 0.024$) were still significantly associated with in-hospital mortality (Table 5).

DISCUSSION

The spleen is the largest organ in the lymphatic system. Unlike lymph nodes, the spleen has no afferent lymph vessels but only efferent lymph vessels (*8*). Therefore, the spleen is specialized to monitor blood for microorganisms and blood cells, whereas lymph nodes monitor lymphatics for local inflammation. However, the diagnostic methods to evaluate spleen conditions have been limited. Although measuring spleen size is the most common method for evaluating the spleen in current clinical practice, our study is the first, to our knowledge, to show that spleen ^{18}F-FDG uptake is elevated in autoimmune disease compared with localized infectious disease and also provides prognostication for febrile patients hospitalized with autoimmune disease.

There is a biologic rationale for using ^{18}F-FDG uptake to evaluate spleen immunometabolism in systemic inflammation (*9*). In the spleen, dendritic cells and T cells interact for antigen processing and also become directly exposed to proinflammatory cytokines in the blood (*10*). During activation, dendritic cells and T-cell metabolism change; the aerobic glycolysis pathway is used during this high-energy-demand state (*6,11,12*). Recent studies demonstrated that inhibition of glycolysis or oxidative phosphorylation improves systemic inflammation in animal models of lupus as well as in human lupus (*10,11,13*). Monitoring spleen energy metabolism may be useful in systemic inflammatory disease for evaluating disease activity and possibly providing guidance for metabolism-targeted therapy (*14*).

We excluded sepsis and cancer patients because our hypothesis was to evaluate the role of spleen and bone marrow ^{18}F-FDG uptake in febrile patients who are without a definite diagnosis. Sepsis is a diagnosis based on clinical presentation, vital signs, and identification of microorganisms and is beyond our research scope. Spleen ^{18}F-FDG uptake in cancer is also an interesting topic, and a recent study demonstrated that high spleen ^{18}F-FDG uptake is associated with poor prognosis in patients with cholangiocarcinoma (*15*). Although cancer patients can develop fever of various causes, such as chemotherapy, neutropenia, thrombosis, and infection, we did not include cancer patients because it is not common to perform PET/CT on cancer patients for fever evaluation. Because of the relatively narrow clinical focus of our study, the results from our study cannot be generalized and should be interpreted with caution when evaluating patients with fever.

Although lymphoma is known to be one of the most frequent malignant conditions associated with elevated splenic SUVs, focal mass or infiltrative patterns of ^{18}F-FDG uptake in the spleen suggests a primary pathology (*16*) that is different from a diffuse uptake pattern in systemic autoimmune diseases. However, it will be difficult to differentiate diffuse infiltrative patterns of splenic lymphoma from increased spleen ^{18}F-FDG uptake secondary to inflammation.

TABLE 5
Univariate and Multivariate Logistic Regression Models for Prediction of In-Hospital Mortality During Admission in Patients with Autoimmune Diseases

Variable	Univariate analysis		Multivariate analysis	
	Odd ratio	*P*	Odd ratio	*P*
Spleen SUV				
SLR_{max}	3.062 (0.971–9.654)	0.056		
SLR_{mean}	3.625 (1.013–12.967)	0.047		
$SLR_{mean} \geq 1.61$	5.076 (1.413–18.230)	0.012	4.796 (1.228–18.723)	0.024
Bone marrow SUV				
BLR_{max}	1.793 (0.639–5.032)	0.267		
BLR_{mean}	1.885 (0.592–6.001)	0.282		
Clinical variables				
Age	1.015 (0.979–1.052)	0.396		
Sex	0.432 (0.088–2.119)	0.301		
In-hospital day	1.033 (0.998–1.068)	0.057		
Laboratory variables				
WBC (/μL)	1.000 (0.999–1.000)	0.829		
Hemoglobin (g/dL)	0.804 (0.500–1.293)	0.368		
Platelet count (×1,000/μL)	0.993 (0.987–0.998)	0.014	0.993 (0.988–0.999)	0.020
Neutrophil count (/μL)	1.000 (0.999–1.000)	0.937		
Lymphocyte count (/μL)	0.998 (0.997–1.000)	0.118		
Monocyte count (/μL)	0.997 (0.994–1.000)	0.149		
ESR (mm/h)	0.984 (0.966–1.002)	0.085		
CRP (mg/L)	1.001 (0.993–1.010)	0.698		
BUN (mg/dL)	1.045 (0.974–1.121)	0.213		
Cr (mg/dL)	1.685 (0.714–3.974)	0.233		
AST (IU/L)	0.999 (0.994–1.003)	0.640		
ALT (IU/L)	0.988 (0.968–1.008)	0.266		
Total bilirubin (mg/dL)	1.176 (0.589–2.348)	0.644		
Total protein (mg/dL)	0.543 (0.269–1.098)	0.089		
Albumin (mg/dL)	0.345 (0.105–1.125)	0.077		
Ferritin (ng/mL)	1.000 (1.000–1.000)	0.345		

WBC = white blood cell; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; BUN = blood urea nitrogen; Cr = creatinine; AST = aspartate aminotransferase; ALT = alanine aminotransferase.
Data in parentheses are 95% CI.

Bone marrow and spleen play different roles in systemic inflammation. Bone marrow is the site of hematopoietic progenitor cell production (*17*), whereas spleen is the site of interaction of activated immune cells (*8,18*). Although both SLRs and BLRs were higher in autoimmune disease than in localized infectious disease, SLRs were better at differentiating autoimmune from localized infectious diseases than were BLRs. This finding may be due to nonspecific progenitor cell activation in bone marrow in both autoimmune and localized infectious diseases, whereas immune cell activation in the spleen is more specific in febrile autoimmune diseases (*17*). In fact, an SLR_{mean} cutoff of 1.06 showed the highest area under the ROC among all imaging and laboratory variables.

Comparison of laboratory variables with SLRs and BLRs also showed distinct patterns. In autoimmune disease, SLR_{mean} was most strongly associated with ferritin level, whereas BLR_{mean} was most strongly associated with white blood cell and neutrophil counts. Ferritin is an acute-phase reactant that is elevated in several autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and adult-onset Still disease (*19*). The association between serum ferritin level and spleen glucose metabolism is an interesting novel finding, and further studies are necessary to understand their relationship to systemic inflammation.

Identification of prognostic factors is important for the proper immunosuppressive treatment of autoimmune diseases. In this study, SLR_{mean} with a cutoff greater than 1.61 was associated with in-hospital mortality during the admission period. Increased spleen ^{18}F-FDG uptake may represent an early sign of severe systemic inflammatory response that is not detectable by conventional laboratory parameters. Therefore, closer monitoring may be needed in

autoimmune disease patients with high SLRs. Although our findings cannot be simply generalized due to heterogeneity of disease, they suggest the importance of quantitative evaluation of SLRs in clinical practice.

The strength of our study is the large number of patients who were clearly diagnosed as having either autoimmunity or infection as the cause of fever. Although previous studies have evaluated the role of PET/CT in diagnosing autoimmune and infectious diseases (*3,4,20,21*), they were limited by relatively small sample sizes and focused mainly on detection of localized infection or inflammation. However, previous studies demonstrated that specific patterns of ^{18}F-FDG uptake in inflamed tissue can provide important information. In rheumatoid arthritis, ^{18}F-FDG uptake in joints is associated with disease activity (*22*). In large-vessel vasculitis, the patterns of ^{18}F-FDG uptake in blood vessels are useful for diagnosis and predict poor outcome (*23*). Also, hidden localized infection can easily be identified by PET/CT scanning, especially in chronic infections of bone or adjacent structures (*4*). Therefore, PET/CT can provide multiple useful findings in febrile patients in addition to SLR or BLR.

Limitations to our study include those that are inherent in all single-institution retrospective observational studies, including bias in patient selection and analysis. Also, only patients who had autoimmune or localized infectious diseases as the cause of fever were included. Other causes of fever, such as cancer or systemic infectious diseases, may have different spleen ^{18}F-FDG uptake values and patterns from our study. Further studies will be required to investigate this possibility.

CONCLUSION

Spleen ^{18}F-FDG uptake is increased in febrile autoimmune disease and is associated with an increased risk of all-cause in-hospital mortality. Evaluation of spleen glucose metabolism might be useful for differentiating systemic inflammatory diseases from localized infectious diseases when other causes of fever are excluded. Further studies to evaluate the molecular mechanism for glucose energy metabolism during systemic inflammation are necessary.

DISCLOSURE

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