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The clinical utility of splenic fluorodeoxyglucose uptake for diagnosis and prognosis in patients with macrophage activation syndrome

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Abstract

The aim of the study was to evaluate splenic glucose metabolism in macrophage activation syndrome (MAS), characterized by overwhelming systemic inflammation. Splenic ^{18}F-fluorodeoxyglucose (FDG) uptake was compared in patients with MAS and sepsis using positron emission tomography/computed tomography (PET/CT).

Clinical and FDG-PET/CT findings from patients with MAS and those with culture-proven sepsis were evaluated. The standardized uptake value (SUV) for the spleen and liver were measured. The maximum of the spleen to liver SUV ratio (SLR_{max}) was calculated as spleen SUV_{max}/liver SUV_{mean}. The radiological splenic volume was also measured, and splenic metabolic volume (MV) was defined as the total splenic volume with an $SLR_{mean} > 1.14$. The association between clinical features, laboratory variables, and SLR_{max} was analyzed.

The median SLR_{max} and splenic MV were significantly higher in patients with MAS (n = 38) than they were in those with sepsis (n = 15) (SLR_{max}: 1.51 vs 1.09, $P = .001$; MV: 346.0 vs 154.0, $P = .015$). Multivariate analyses revealed that $SLR_{max} > 1.31$ was useful for discriminating between MAS and sepsis. SLR_{max} positively correlated with ferritin and lactate dehydrogenase level in MAS. Furthermore, MAS patients with high splenic FDG uptake ($SLR_{max} > 1.72$) had higher in-hospital mortality compared to those with moderate to low splenic FDG uptake ($P = .013$).

This study was the first to demonstrate that splenic FDG uptake is significantly elevated in patients with MAS compared to those with sepsis. This may be useful to differentiate between MAS and sepsis, and to predict poor prognosis in patients with MAS.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BLR = bone marrow to liver SUV ratio, CI = confidence interval, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, FDG = ^{18}F-fluorodeoxyglucose, HLH = hemophagocytic lymphohistiocytosis, IL = interleukin, IQR = interquartile range, LDH = lactate dehydrogenase, MAS = macrophage activation syndrome, MV = metabolic volume, OR = odds ratio, ROC = receiver operating characteristic, RV = radiologic volume, SLR = spleen to liver SUV ratio, SUV = standardized uptake value, VOI = volume of interest, WBC = white blood cell.

Keywords: glycolysis, macrophage activation syndrome, sepsis, spleen glucose metabolism

1. Introduction

Macrophage activation syndrome (MAS) is a "cytokine storm syndrome" of excessive immune activation that leads to high fever, cytopenia, hepatosplenomegaly, and multiorgan injury.[1,2] Although MAS is characterized by the uncontrolled expansion and activation of T lymphocytes and macrophages,[3] the underlying pathogenesis of MAS remains unknown. MAS can arise in clinical settings with systemic inflammation owing to infection, malignancy, or autoimmune diseases. MAS is known as a secondary form of hemophagocytic lymphohistiocytosis (HLH), because in both HLH and MAS, severe hemophagocytosis (i.e., phagocytosis of erythrocytes, platelets, and leukocytes by histocytes) in the bone marrow is often observed.[4] However, the role of bone marrow biopsy in the diagnosis of MAS is limited because hemophagocytosis is occasionally not detected in the early stages, and mild hemophagocytosis can be observed in many other inflammatory diseases.[5] Consequently, the diagnosis of MAS in patients with systemic inflammatory conditions has been very challenging for clinicians. Multiple biomarkers including interleukin (IL)-18, soluble IL-2 receptor, and natural killer cell activity have been evaluated.[6] Unfortunately, these biomarkers are not well-validated and accessible to clinicians in their daily practice; thus, evaluation of other markers associated with macrophage activation to identify MAS is necessary.

It has been reported that MAS is a fatal disease with a poor prognosis and, as such, early recognition and treatment are critical for the survival of the patient.[7,8] However, because there is no disease-specific clinical manifestation in MAS, it is often difficult to differentiate MAS from systemic inflammatory diseases such as sepsis, since fever, hypotension, tachycardia,

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and thrombocytopenia can be present in both diseases. Indeed, being able to accurately differentiate between MAS and sepsis is critical, as the treatment strategies for these 2 diseases are very different. Although potent immune suppression with glucocorticoid, cyclophosphamide, or etoposide is helpful in patients with MAS, it can be harmful in patients with sepsis.

Recent studies have suggested that ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) may be useful for detecting inflammatory conditions according to FDG uptake in the inflamed tissues of individuals with vasculitis, myositis, and arthritis.[9,10] Furthermore, we recently demonstrated that FDG uptakes are increased in spleen of patients with febrile autoimmune diseases than in patients with localized infections.[11] It suggests that spleen glucose metabolism is increased in autoimmune diseases because of abnormal immune cell activation. Therefore, spleen FDG uptake might be a biomarker to systemic immune activation. However, it is not clear whether spleen FDG uptake can differentiate systemic autoimmune diseases from systemic infection because both conditions are associated with systemic immune activation. In the present study, we compared splenic FDG uptake on PET/CT to differentiate patients with MAS from those with sepsis, and to determine whether these data can predict the prognosis of patients with MAS.

2. Materials and methods

2.1. Patient selection

The medical records of MAS patients who underwent ^{18}F-FDG PET/CT and were admitted to Severance Hospital, Seoul, South Korea, from December 2005 to December 2015, were retrospectively reviewed. The inclusion criteria were as follows: (i) patients with documented fever (≥37.8°C) during hospital admission and (ii) patients diagnosed with MAS according to the 2016 European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative classification criteria for MAS (i.e., patients with fever, a ferritin level ≥ 684 ng/mL, and who fulfilled more than 2 of the following criteria: platelet count ≤ 181,000/μL, aspartate aminotransferase (AST) level > 48 units/L, triglyceride level >156 mg/dL, and fibrinogen level ≤ 360 mg/dL).[12,13] Patients were excluded if they fulfilled the classification criteria for MAS with a definite focus of infection and/or residual cancer. As a result, a total of 38 patients with MAS were enrolled. For comparison, 15 patients with sepsis who had a positive blood culture at the time of PET/CT imaging and 40 randomly selected healthy control subjects who had undergone a routine health check-up were also enrolled. This study was approved by the Institutional Review Board of Severance Hospital (IRB approval number 4-2016-1114) and conducted in accordance with the principles set forth in the Declaration of Helsinki.

2.2. Clinical and laboratory data collection

We collected the following clinical data: age, sex, in-hospital duration, and mortality. As for the laboratory data, we reviewed the white blood cell (WBC), neutrophil, lymphocyte, monocyte, and platelet counts, as well as the hemoglobin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), blood urea nitrogen, creatinine, AST, alanine aminotransferase (ALT), total bilirubin, total protein, albumin, ferritin, and lactate dehydrogenase (LDH) levels, which were measured within 3 days of the ^{18}F-FDG PET/CT scan. In-hospital mortality was defined as all-cause mortality during hospital admission.

2.3. Evaluation of the hemophagocytic syndrome score (HScore) in patients with MAS and with sepsis

We further evaluated the HScore in our study population to validate patients classified as having MAS according to the 2016 EULAR/ACR/PRINTO classification criteria. As previously described, the HScore and probability of having hemophagocytic syndrome were calculated by using the calculator available online (http://saintantoine.aphp.fr/score/).[14]

2.4. ^{18}F-FDG PET/CT image acquisition and assessment

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

Semi-quantitative and volumetric measurements, including the maximum standardized uptake value (SUV_{max}), mean SUV (SUV_{mean}), spleen radiologic volume (RV), and spleen metabolic volume (MV), were performed using the MIMvista software (MIMvista Corp., Cleveland, OH). The spleen radiologic volume was calculated by drawing a volume of interest (VOI) manually using the CT image obtained during PET/CT image acquisition. Spleen SUVs were obtained on 3 non-adjacent slices and bone-marrow SUVs were obtained separately from the lumbar vertebrae 1–5 and averaged. Three spherical 1-cm sized VOI were drawn in the liver, 2 in the right lobe and 1 in the left lobe. The SUV_{mean} of the liver was calculated as the mean SUV value of 3 VOIs. The maximum of the spleen to liver SUV ratio (SLR_{max}) was calculated by dividing the spleen SUV_{max} by the liver SUV_{mean}, and the maximum of the bone marrow to liver SUV ratio (BLR_{max}) was calculated by dividing the bone marrow SUV_{max} by the liver SUV_{mean}. The spleen MV was defined as the total spleen volume with an $SLR_{mean} > 1.14$, which corresponds to the maximal cut-off value of SLR_{mean} in the discrimination between MAS and sepsis.

2.5. Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences software version 21 (SPSS Inc., Chicago, IL). Continuous variables are presented as the median with the interquartile range (IQR), and categorical variables are expressed as frequencies and percentages. Continuous variables were compared using the Mann–Whitney *U* test, and categorical data were compared using the chi-square or the Fisher's exact test. Correlations between the ^{18}F-FDG PET/CT variables and laboratory variables and the presence of hemophagocytosis in MAS were calculated with the Pearson and Spearman correlation analyses, respectively.

The maximal cut-off values for SLR_{max} in discriminating MAS and sepsis, and predicting in-hospital mortality, were calculated

Table 1

Baseline characteristics of patients with macrophage activation syndrome and sepsis.

Variable	Macrophage activation syndrome (n = 38)	Sepsis (n = 15)	P
Clinical variables			
Age	41.5 (21.0)	67.0 (26.5)	**.003**
Sex, female	25 (65.7)	10 (66.6)	.952
In-hospital duration, days	21.5 (29.0)	19.0 (30.0)	.999
In-hospital mortality	6 (15.7)	0 (0.0)	.167
Laboratory variables			
WBC count, /μL	4060.0 (4120.0)	7780.0 (3157.5)	**<.001**
Hemoglobin, g/dL	10.3 (2.3)	10.5 (3.1)	.649
Platelet count, ×1000/μL	117.5 (81.0)	272.0 (222.0)	**<.001**
Neutrophil count, /μL	2592.8 (4170.0)	5660.0 (3922.5)	**.006**
Lymphocyte count, /μL	670.0 (900.0)	1320.0 (620.0)	**.017**
Monocyte count, /μL	214.0 (260.0)	440.0 (292.5)	**<.001**
ESR, mm/h	40.0 (41.0)	67.0 (41.5)	**.019**
CRP, mg/L	33.8 (72.5)	42.3 (119.8)	.160
Creatinine, mg/dL	0.6 (0.4)	0.8 (0.3)	**.040**
AST, IU/L	107.5 (223.0)	29.0 (15.8)	**<.001**
ALT, IU/L	64.0 (141.0)	30.0 (18.5)	**<.001**
Total bilirubin, mg/dL	0.5 (0.9)	0.5 (0.6)	.874
Albumin, mg/dL	3.0 (0.7)	3.2 (0.9)	.068
Ferritin, ng/mL	2280.3 (11446.1)	267.6 (233.2)*	**<.001**
LDH, IU/L	622.0 (694.0)	249.0 (107.0)*	**<.001**
Underlying autoimmune disease			
Idiopathic	17 (44.7)	n/a	
Kikuchi disease	9 (23.6)	n/a	
Systemic lupus erythematosus	7 (18.4)	n/a	
Adult onset Still's disease	3 (7.8)	n/a	
Dermatomyositis	1 (2.6)	n/a	
Sjogren syndrome	1 (2.6)	n/a	

Data expressed as median (interquartile range) or n (%).

Bold values indicate statistically significant differences.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, LDH = lactate dehydrogenase, n/a = not applicable, WBC = white blood cell.

* Number confined to patients who underwent each test (n = 6).

using the area under the receiver operating characteristic (ROC) curve analyses. Multivariate logistic regression analyses using the backward method were used to compare ^{18}F-FDG PET/CT and laboratory variables to discriminate between MAS and sepsis. Comparison of the cumulative survival rate in patients with $SLR_{max} > 1.72$ and $SLR_{max} \leq 1.72$ was performed using the Kaplan–Meier method and the log-rank test. In all statistical analyses, differences were considered to be significant at $P < .05$ (2-tailed).

3. Results

3.1. Patients' baseline characteristics

The median ages of the patients with MAS were significantly lower than those of the patients with sepsis (41.5 vs 67.0, $P = .003$). No difference in in-hospital duration was identified between the 2 patient groups. In patients with MAS, 6 patients (15.7%) suffered in-hospital mortality, whereas there was no death in sepsis. Patients with MAS had significantly lower WBC, platelet, neutrophil, lymphocyte, and monocyte counts, as well as a lower ESR and creatinine level than patients with sepsis. Patients with MAS had significantly higher AST, ALT, ferritin, and LDH levels than patients with sepsis (all $P < .001$; Table 1). Although the cause of MAS was idiopathic in most cases (17/38 [44.7%]), Kikuchi disease (9/38 [23.6%]), and systemic lupus erythematosus (7/38 [18.4%]) were the 2 most common causes of MAS in patients with a known primary disorder, followed by adult-onset Still's disease (3/38 [7.8%]), dermatomyositis, and Sjögren's syndrome (both 1/38 [2.6%], respectively) (Table 1). In patients with sepsis, the most prevalent source of origin was the abdomen (4/15 [26.6%]), followed by the urinary tract, lung, and musculoskeletal area (3/15 [20.0%], respectively). In addition, 1 patient's source of infection was the heart and the other patient's was the brain (6.6%, respectively). Among 38 MAS patients, 28 patients had undergone a bone marrow study and hemophagocytosis was observed in 15 patients.

3.2. Evaluation of the HScore in patients with MAS and with sepsis

The absolute HScore and probability of having hemophagocytic syndrome was compared among patients who were classified as having MAS according to the 2016 EULAR/ACR/PRINTO classification criteria and patients with sepsis. Comparison of the HScore between 2 groups showed that patients with MAS had a higher HScore and probability of having hemophagocytic syndrome than patients with sepsis ($P < .001$, respectively) (Fig. 1A and B).

3.3. Comparisons of ^{18}F-FDG PET/CT variables

Evaluation of FDG uptake in spleen and bone marrow among patients with MAS, patients with sepsis, and healthy controls

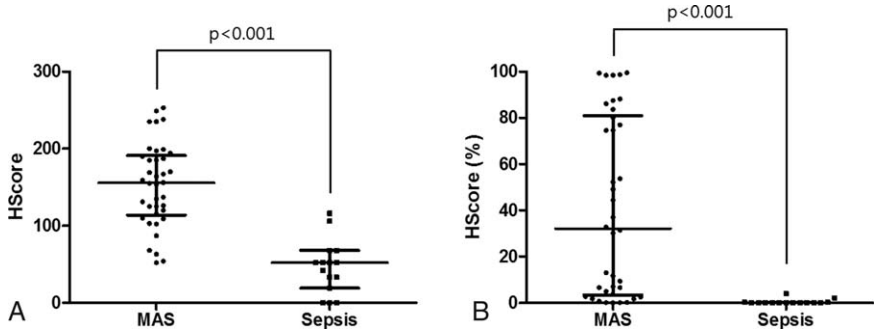

Figure 1. Evaluation of the HScore and probability of having hemophagocytic syndrome in patients with MAS and sepsis. (A) Comparison of the absolute HScore between the groups. (B) Comparison of the probability of having hemophagocytic syndrome between the groups. Data are expressed as the median and the interquartile range. *HScore (%)* = probability of having the hemophagocytic syndrome, MAS = macrophage activation syndrome.

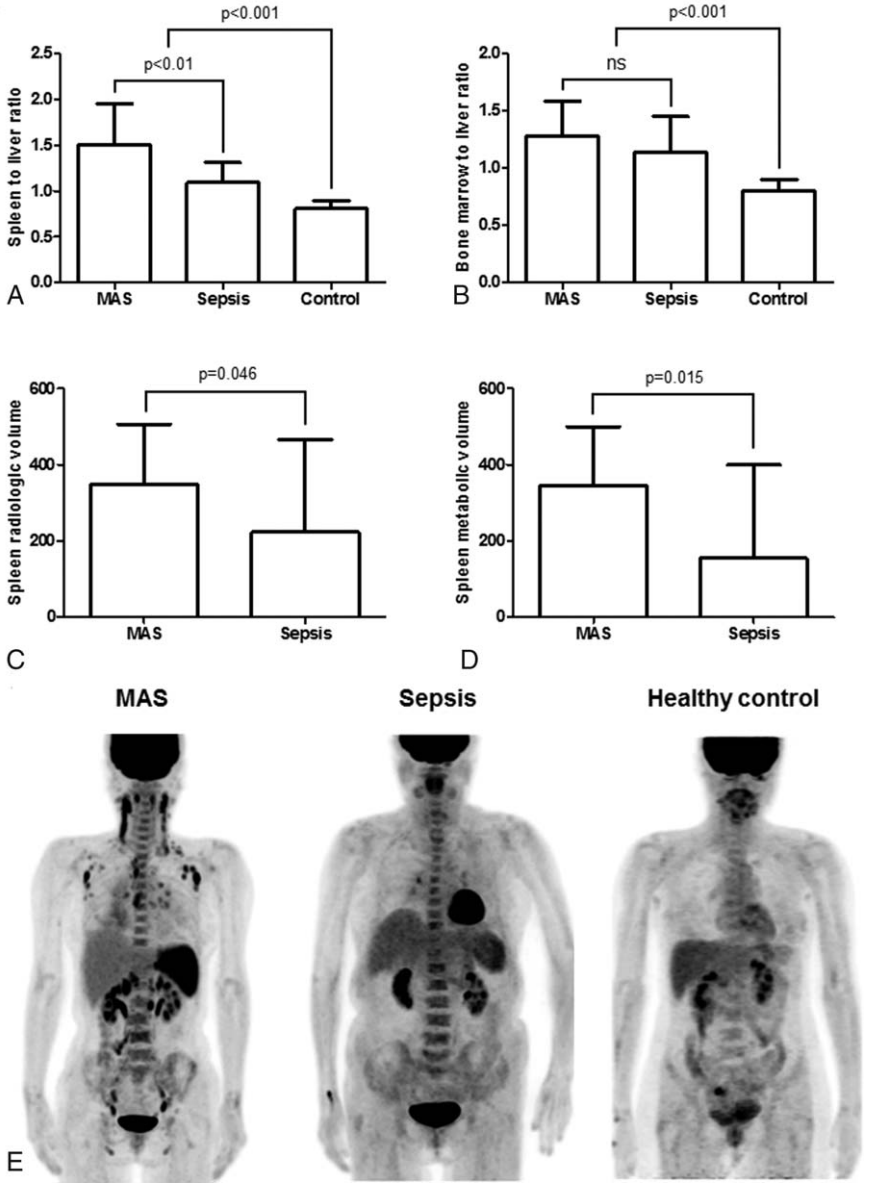

Figure 2. Comparison of the standardized ^{18}F-fluorodeoxyglucose uptake values (SUV) in patients with macrophage activation syndrome (MAS; n = 38), patients with sepsis (n = 15), and healthy controls (n = 40). (A) The SUV_{max} of spleen to liver ratio. (B) The SUV_{max} of bone marrow to liver ratio. (C) Spleen radiologic volume. (D) Spleen metabolic volume. (E) Representative 18F-FDG PET/CT images in patient with MAS (left), patient with sepsis (middle), and healthy control subject (right). Data are expressed as the median; error bars indicate the interquartile range. ^{18}F-FDG PET/CT = 18-fluoro-2-deoxyglucose positron emission tomography/computed tomography, MAS = macrophage activation syndrome, *ns* = not significant, SUV = standardized uptake value.

showed that the SLR and BLR were significantly higher in patient groups than they were in healthy controls ($P < .001$, respectively) (Fig. 2A and B). Patients with MAS had significantly higher SLR than patients with sepsis (median SLR_{max}: 1.51 [IQR 0.71] vs 1.09 [IQR 0.28], $P = .001$) (Fig. 2A). However, the BLR did not differ between patients with MAS and patients with sepsis (median BLR_{max}: 1.28 [IQR 0.61] vs 1.14 [IQR 0.56], $P = .290$) (Fig. 2B). When the volumetric parameters of FDG PET/CT were applied, patients with MAS had a significantly higher median spleen RV (348.5 cm^3 [IQR 221.7] vs 222.9 cm^3 [IQR 314.2], $P = .046$) and median spleen MV (346.0 cm^3 [IQR 272.1] vs 154.0 cm^3 [IQR 274.9], $P = .015$) than patients with sepsis (Fig. 2 C and D). Representative FDG PET/CT images in patients with MAS, sepsis, and a healthy control subject are shown in Fig. 2E.

3.4. Utility of the FDG PET/CT and laboratory variables for differentiating between MAS and sepsis

Using ROC analyses, an SLR_{max} cut-off > 1.31 was found to have the highest discriminating power in both groups (Table 2 and Fig. 3). Univariate analysis showed that $SLR_{max} > 1.31$, WBC, platelet, monocyte counts, ESR, AST, ALT, and albumin levels were significant for discriminating between MAS and sepsis. However, in the multivariate analysis, $SLR_{max} > 1.31$ (odds ratio [OR]: 8.175, 95% confidence interval [CI],

Table 2

Comparison of the abilities of ^{18}F-FDG PET/CT variables to differentiate between macrophage activation syndrome and sepsis using receiver operating characteristic analyses.

	Cut-off	Sensitivity, %	Specificity, %	AUROC	*P*
SLR_{max}	1.31	71.0	80.0	0.785	**<.001**
BLR_{max}	1.17	60.5	66.6	0.594	.297
Spleen RV	224.25	76.3	60.0	0.677	.059
Spleen MV	154.00	92.1	53.3	0.716	**.024**

Bold values indicate statistically significant differences.
^{18}F-FDG PET/CT = 18-fluoro-2-deoxyglucose positron emission tomography/computed tomography, AUROC = area under receiver operator curve, BLR = bone marrow to liver ratio, MV = metabolic volume, RV = radiologic volume, SLR = spleen to liver ratio.

1.543–43.306, $P = .013$) and platelet count (OR: 0.989, 95% CI: 0.983–0.996, $P = .004$) were statistically significant factors (Table 3).

3.5. Association of laboratory variables with FDG-PET/CT variables in patients with MAS

We evaluated the associations between the laboratory variables and FDG PET/CT variables in patients with MAS. In patients with MAS, the SLR_{max} was positively correlated with the ferritin and LDH levels (Table 4). The strongest correlation was between the SLR_{max} and LDH values ($r = 0.571$, $P < .001$). In contrast, the BLR_{max} showed a different correlation pattern as they were positively correlated with the WBC, platelet, and neutrophil counts, and with the ESR and CRP levels (Table 4). The strongest correlation was between the BLR_{max} and WBC count ($r = 0.597$, $P < .001$). The spleen MV values were negatively correlated with the lymphocyte ($r = -0.377$, $P = .019$) and monocyte counts ($r = -0.375$, $P = .02$) and strongly correlated with the total bilirubin levels ($r = 0.672$, $P < .001$).

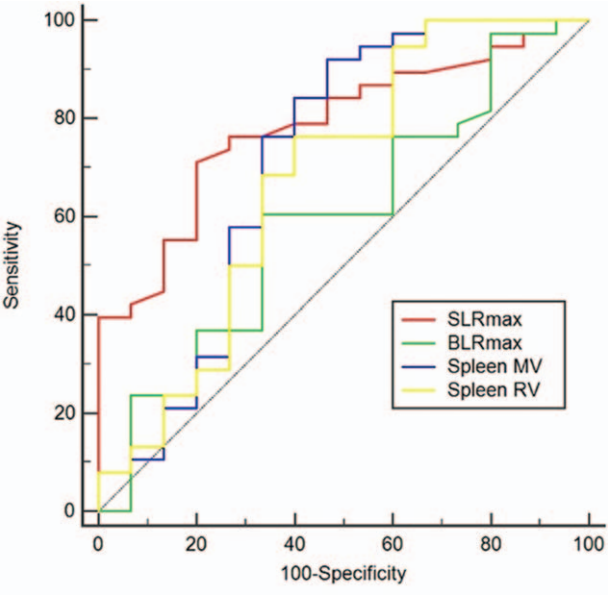

Figure 3. Receiver operating characteristic curves for the FDG PET/CT variables to differentiate between macrophage activation syndrome and sepsis. ^{18}F-FDG PET/CT = 18-fluoro-2-deoxyglucose positron emission tomography/computed tomography.

3.6. Comparison of in-hospital mortality of patients with MAS according to SLR_{max}

There were 6 in-hospital mortalities among patients with MAS. The area under the ROC curve analysis revealed that $SLR_{max} > 1.72$ was the best cut-off to predict in-hospital mortality in patients with MAS. In patients with $SLR_{max} > 1.72$, 5 died, whereas there was only 1 death in those with $SLR_{max} \leq 1.72$.

Table 3

Comparison of the abilities of ^{18}F-FDG PET/CT and laboratory variables to differentiate between macrophage activation syndrome and sepsis by logistic regression analyses.

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*P*	Odds ratio	95% CI	*P*
^{18}F-FDG PET/CT variables						
SLR_{max}	22.774	2.285–226.948	**.007**			
$SLR_{max} > 1.31$	9.818	2.311–41.707	**.002**	8.175	1.543–43.306	**.013**
BLR_{max}	1.279	0.428–3.818	.658			
Spleen MV	1.003	0.999–1.007	.099			
Laboratory variables*						
WBC, /μL	0.999	0.999–1.000	**.037**			
Hemoglobin, g/dL	1.155	0.790–1.688	.456			
Platelet count, ×1000/μL	0.988	0.982–0.995	**.001**	0.989	0.983–0.996	**.004**
Neutrophil count, /μL	0.999	0.999–1.000	.154			
Lymphocyte count, /μL	0.999	0.998–1.000	.077			
Monocyte count, /μL	0.993	0.989–0.997	**.002**			
ESR, mm/h	0.979	0.961–0.998	**.038**			
CRP, mg/L	0.994	0.986–1.003	.230			
Creatinine, mg/dL	0.880	0.349–2.217	.786			
AST, IU/L	1.054	1.017–1.093	**.004**			
ALT, IU/L	1.069	1.018–1.123	**.007**			
Total bilirubin, mg/dL	1.437	0.643–3.213	.376			
Albumin, mg/dL	0.220	0.049–0.979	**.046**			

* Laboratory variables with missing data were excluded from the analysis.
Bold values indicate statistically significant differences.
^{18}F-FDG PET/CT = 18-fluoro-2-deoxyglucose positron emission tomography/computed tomography, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BLR = bone marrow to liver ratio, CI = confidence interval, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, MV = metabolic volume, SLR = spleen to liver ratio, WBC = white blood cell.

Table 4

Correlations between laboratory variables and 18F-FDG PET/CT variables in patients with macrophage activation syndrome.

	Macrophage activation syndrome (n = 38)		
	SLR_{max}	BLR_{max}	Spleen MV
WBC count, /μL	0.307 (0.060)	**0.597 (<0.001)**	−0.200 (0.226)
Hemoglobin, g/dL	0.168 (0.312)	−0.225 (0.172)	−0.103 (0.536)
Platelet count, ×1000/μL	0.088 (0.596)	**0.397 (0.013)**	−0.257 (0.119)
Neutrophil count, /μL	0.219 (0.186)	**0.542 (<0.001)**	−0.152 (0.361)
Lymphocyte count, /μL	0.281 (0.087)	−0.214 (0.196)	**−0.377 (0.019)**
Monocyte count, /μL	−0.092 (0.582)	−0.271 (0.099)	**−0.375 (0.020)**
ESR, mm/h	0.130 (0.434)	**0.372 (0.021)**	−0.311 (0.057)
CRP, mg/L	0.065 (0.696)	**0.549 (<0.001)**	0.022 (0.892)
Creatinine, mg/dL	−0.188 (0.257)	−0.276 (0.092)	−0.176 (0.288)
AST, IU/L	0.276 (0.092)	−0.202 (0.222)	0.077 (0.644)
ALT, IU/L	0.188 (0.257)	−0.074 (0.656)	0.104 (0.534)
Total bilirubin, mg/dL	0.004 (0.976)	0.039 (0.815)	**0.672 (<0.001)**
Albumin, mg/dL	−0.163 (0.327)	−0.206 (0.213)	−0.206 (0.214)
Ferritin, ng/mL	**0.494 (0.001)**	0.146 (0.379)	0.067 (0.686)
LDH, IU/L	**0.571 (<0.001)**	−0.029 (0.860)	0.115 (0.488)
Presence of hemophagocytosis*	−0.372 (0.051)	−0.239 (0.219)	0.102 (0.605)

Values indicate the correlation coefficient (*r*) and *P*-value (in parentheses).

Bold text indicates statistically significant differences.

^{18}F-FDG PET/CT = 18-fluoro-2-deoxyglucose positron emission tomography/computed tomography, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BLR = bone marrow to liver ratio, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, LDH = lactate dehydrogenase, MV = metabolic volume, SLR = spleen to liver ratio, WBC = white blood cell.

* Number confined to patients who underwent bone marrow biopsy (n = 28).

Kaplan–Meier analysis with the log-rank test revealed an in-hospital mortality rate that was higher in patients with $SLR_{max} > 1.72$ than in those with $SLR_{max} \leq 1.72$ ($P = .013$) (Fig. 4).

4. Discussion

Recent discoveries in immunometabolism suggest that, similar to cancer cells, proliferating immune cells demonstrate a high rate of glycolysis, whereas the rate in resting immune cells is lower.[15] The rate of glycolysis in cancer cells is known to be up to 200 times higher than in normal cells, even though oxygen is available for oxidative phosphorylation.[16] This phenomenon of aerobic glycolysis is known as the Warburg effect, which is the underlying mechanism of increased FDG uptake in cancer cells on PET/CT. Taking advantage of this high metabolism, PET/CT parameters, such as SUV and MV, are able to provide clinically useful information regarding the characteristics of cancer (progression, drug resistance, etc.).[17] Similar to cancers, FDG PET/CT have been useful for diagnosing and monitoring disease activity in autoimmune diseases, such as vasculitis, immunoglobulin G4-related disease, and rheumatoid arthritis, by measuring local inflammatory responses by the degrees of FDG uptake.[18] In the present study, we evaluated FDG uptake of the spleen and bone marrow in patients with MAS, a disease characterized by overwhelming systemic immune activation. Patients with MAS demonstrated significantly increased splenic FDG uptake compared to patients with sepsis and healthy controls. Although bone marrow FDG uptake was higher in patients with MAS and sepsis than in healthy controls, it was not different between those with MAS and sepsis. Therefore, splenic FDG uptake is important in differentiating pathologically activated immune cell in MAS from physiologically activated immune cells in sepsis.

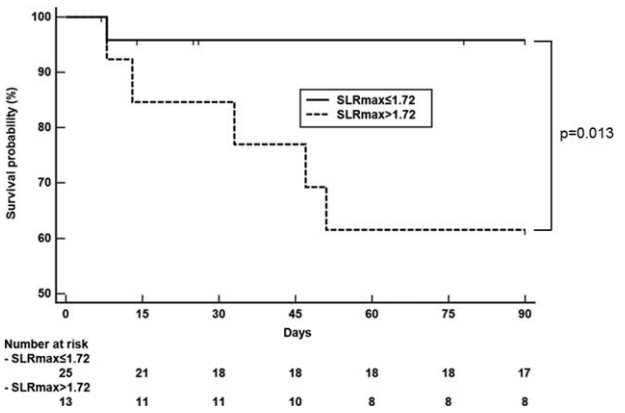

Figure 4. Comparison of the cumulative survival rate in those with a spleen to liver standardized uptake value ratio (SLR_{max}) ≤ 1.72 versus SLR_{max} > 1.72 in patients with macrophage activation syndrome. SLR = spleen-to-liver ratio.

In current clinical practice, the most common method to evaluate the spleen is measuring its size using ultrasound or CT. Since immune activation is associated with splenomegaly, we evaluated the additive values of volumetric compared with SUV-derived PET/CT parameters to gain better insight to splenic glucose metabolism in differentiating MAS from sepsis. Although the spleen MV cutoff (154.00 cm^3) had a higher area under the curve than the spleen RV cutoff (224.25 cm^3) in differentiating MAS from sepsis, splenic MV was insignificant in univariate analysis. In contrast, SLR_{max} values were statistically significant in differentiating MAS from sepsis in the univariate and the multivariate analyses. The degree of metabolic derangement appeared to be more reflective of the severity of inflammation than the volume of the spleen and, thus, more important in differentiating MAS from sepsis. Of the laboratory parameters, platelet count was the only significant discriminator between MAS and sepsis in the multivariate analyses, with MAS showing lower counts.

FDG-PET/CT variables were associated with different clinical parameters in MAS. SLR was positively correlated with ferritin and LDH levels, but not with nonspecific inflammatory markers such as ESR, CRP, and WBC and neutrophil counts. Given the

fact that extremely high levels of ferritin in MAS are due to immune cell activation,[1,19] splenic FDG uptake could be associated with the pathogenesis of MAS rather than a nonspecific consequence of inflammation. Interestingly, Ruscitti et al[20] reported older age and increased serum ferritin levels were associated with poor prognosis in MAS. Since SLR_{max} is associated with poor prognosis in MAS and there is significant association between ferritin and SLR_{max}, further studies are necessary to evaluate the relationship between ferritin and spleen glucose metabolism in MAS. In contrast, BLR was positively correlated with ESR, CRP, and WBC and neutrophil counts. As there was no difference in BLR between MAS and sepsis, bone marrow FDG uptake may represent nonspecific immune cell production in bone marrow in systemic inflammation. Splenic MV was negatively correlated with lymphocyte and monocyte count and positively correlated with bilirubin. As the underlying mechanisms of increased glucose metabolism in the spleen and bone marrow in systemic inflammation have been poorly studied, further experimental investigation appears to be necessary to understand the different patterns of correlation between clinical parameters and FDG PET/CT variables.

Taking together the results, our study demonstrated novel benefits of PET/CT in MAS patients in diagnosis and treatment by evaluating splenic FDG uptake. First, it might help to differentiate MAS and sepsis. Differentiating between MAS and sepsis is a very challenging task for clinicians because the clinical manifestations of systemic inflammation are similar, and both are potentially fatal diseases that require different treatment strategies. Second, it might identify MAS patients with poor prognosis in the early stage. Of note, $SLR_{max} > 1.72$ was predictive of in-hospital mortality in MAS. Therefore, the use of FDG-PET/CT may provide an opportunity to initiate anti-cytokine therapy in MAS, which may decrease in-hospital mortality. Although the incidence of MAS is rather low, early differentiation of MAS from sepsis has become increasingly important given the promising results of anticytokine therapy against IL-1, IL-6, and TNF in MAS.[21] Because PET/CT has been known to evaluate hidden malignancy or infection which can be underlying cause of MAS, our findings provide additional evidence that PET-CT can be helpful in MAS patients for proper medical care.

The strength of our study is the large number of MAS patients who underwent PET/CT, given the very low incidence of MAS in the general population. There are, however, limitations to this study. First, the data for this study were collected retrospectively, which may have led to bias in patient selection and analysis. Second, as critically ill patients with sepsis could not undergo FDG PET/CT, the exclusion of such patients might have influenced the results of in-hospital mortality in patients with sepsis.

In conclusion, splenic FDG uptake was significantly higher in patients with MAS than in those with sepsis. FDG uptake also showed a distinct pattern of correlation with laboratory markers and was useful in predicting the in-hospital mortality in patients with MAS. These results should encourage the use of FDG-PET/CT as a novel approach to early differentiation of MAS from sepsis, which may have potential prognostic implications for patients presenting with systemic inflammation.

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