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The Relationship Between ^{18}F-FDG Uptake on PET/CT and Markers of Systemic Inflammatory Response in Patients Undergoing Surgery for Intrahepatic Cholangiocarcinoma

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Abstract. *Background/Aim: This study evaluated the prognostic relationship between tumor ^{18}F-fluorodeoxyglucose (FDG) uptake on positron-emission tomography (PET)/computed tomography (CT) imaging and markers of systemic inflammatory response (SIR) in patients undergoing surgery for intrahepatic cholangiocarcinoma (ICC). Patients and Methods: Between 2002 and 2016, 94 patients with ICC who underwent ^{18}F-FDG-PET scans before surgery were analyzed. ^{18}F-FDG uptake was quantified as a maximum standardized uptake value (SUVmax). The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and C-reactive protein (CRP) were selected as SIR markers. Results: There was no strong correlation between SUVmax and, NLR, PLR and CRP (all Pearson's |r| <0.40). Multivariate Cox regression analyses identified high tumor SUVmax (≥8) and high NLR (≥5) as independent predictors of poor overall survival (p=0.013 and p=0.002) and disease-free survival (p<0.001 and p=0.004). Conclusion: Prognostic information provided by tumor SUVmax and SIR markers may be independent prognostic factors in patients undergoing surgery for ICC.*

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer after hepatocellular carcinoma (HCC) (1). To decide administration of therapy for ICC in the era of multidisciplinary strategy, prognostic biomarkers may play an increasingly crucial role (2). Uptake of ^{18}F-fluorodeoxyglucose (FDG) positron-emission tomography (PET)/computed tomography (CT) is a widely used imaging biomarker in liver malignancies (3-5). In particular, tumor ^{18}F-FDG uptake, which is commonly quantified as the maximum standardized uptake value (SUVmax), can be seen as characteristic of tumor glucose metabolism and is noteworthy in prognostication in patients with ICC (3, 6).

The relationship between tumor ^{18}F-FDG uptake and systemic inflammatory responses (SIR) has become of interest in several malignancies (7-12). The underlying basis for this is as follows: Elevation of SIR markers, for example, C-reactive protein (CRP), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) is regarded as a surrogate for immune cell activation; tumor ^{18}F-FDG uptake is not tumor cell-specific and as a result it can include metabolically dynamic cells, for example, immunity cells. These two facts prompted us to explore the relationship between tumor ^{18}F-FDG uptake and SIR markers, yet this topic has not still been investigated in patients with ICC.

Clearly, elevation of SIR markers and high tumor SUVmax are now known to be associated with poor prognosis in patients with ICC after surgery (2, 3, 13). Therefore, the primary purpose of this study was to investigate whether tumor uptake on ^{18}F-FDG PET/CT and SIR markers were independent prognostic factors or not in patients undergoing surgery for ICC. If these markers are independent, patients who have a high SUVmax and high levels of SIR markers would be expected to have a dismal prognosis, which allows a clinician better insight as to the best therapeutic strategy. This can contribute to a better understanding of the prognostic value of these markers in patients with ICC.

Patients and Methods

Patients. All data of patients with histologically confirmed ICC (excluding patients with combined ICC–HCC) who underwent surgery at the Kyoto University Hospital, Kyoto, Japan between

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2002 and 2016 were retrieved from a prospectively maintained institutional database. ICC is defined as a tumor whose center of the mass is judged to be located in the second or more distal branch of intrahepatic bile duct (14). The inclusion criteria were the following: Patients who experienced upfront surgery; and patients who underwent ^{18}F-FDG-PET/CT study before surgery. The exclusion criteria were patients who experienced surgery-related death within 90 days; and patients with apparent distant metastases detected on CT, magnetic resonance imaging (MRI) or ^{18}F-FDG-PET scans. Primary tumor characteristics and resection margins were confirmed on the basis of final historical findings. Tumor stages were assessed according to the American Joint Committee on Cancer (AJCC) classification system, 8th edition (15). Operative morbidity was evaluated according to the Clavien–Dindo classification system (16). The follow-up protocol and recurrence criteria were reported previously (17, 18). Namely, multiple image-based modalities, including CT, MRI, and ^{18}F-FDG-PET, were used for documenting the appearance of new lesion(s), or any progression of a suspicious disease. The follow-up data were updated in February 2018. The study protocol was approved by the Ethical Committee of the Graduate School of Medicine, Kyoto University (R-0597). All the study participants gave their relevant written informed consent.

^{18}F-FDG-PET study and SIR markers. All the relevant data and information were estimated when there were no symptoms of infection depicted by the patients. All ^{18}F-FDG-PET imaging procedures were performed as previously reported (3-5). In this study, three PET or PET/CT scanners were used (Advance, Discovery ST Elite, and Discovery IQ, GE Healthcare, Waukesha, WI). ^{18}F-FDG-PET imaging was performed at least 2 weeks before surgery and interpreted by at least two experienced nuclear medicine physicians by consensus. For quantitative analyses of tumor FDG uptake, the SUVmax was calculated. In this investigation, the following SIR markers were assessed: CRP, PLR, and NLR (2). They were all measured preoperatively at the time of admission and at least 3 days before surgery.

Surgical procedures and treatment strategy. The surgical strategies and therapeutic alternatives were duly discussed on weekly basis in a Cancer Board that included senior hepatobiliary surgeons, dedicated hepatobiliary radiologists, and two healthcare oncologists. At the time of presentation, resectability was characterized as indicated by the following: liver function, tumor extent, and the tumor location. Routine sampling of para-aortic lymph nodes and lymph node dissection were performed around the hepatoduodenal ligament, common hepatic artery and retro-pancreatic area, except in patients in poor condition and those diagnosed preoperatively with HCC or other diseases. Postoperatively, tegafur-gimeracil-oteracil potassium (S-1; from 2007) and gemcitabine (from 2006), alone or in combination, was chiefly utilized as adjuvant chemotherapy for stage II-IV tumors, as classified by AJCC seventh and eighth editions (15, 19).

Statistical analysis. Continuous variables, expressed as medians (with range), were compared using the Mann–Whitney *U*-test. Categorical variables were compared using Fisher's exact test. Overall survival (OS) was calculated from the day of surgery to the date of death or end of the follow-up period, while disease-free survival (DFS) was calculated using the date of death or recurrence as the time of the terminal event according to the Kaplan–Meier method and a comparison was performed with the log-rank test. The correlation between SUVmax and SIR markers was analyzed using Pearson's correlation test and expressed as r. The following criteria of |r| were used: 0.8-1: very strong; 0.6-0.79: strong; 0.40-0.59: moderate; 0.2-0.39: weak; and 0-0.19: very weak. To assess the prognostic relationship among the SUVmax and SIR markers, multivariate Cox proportional hazards models using stepwise selection with the minimum Bayesian information criterion method (BIC) was used. The minimum BIC technique additionally decided the best indicators among the chosen factors. The cut-off value for SUVmax was calculated on the basis of the maximum significant OS differences that were calculated using the log-rank test (*i.e.* the minimum *p*-value approach). Differences were considered significant at $p<0.05$. Statistical analyses were performed using JMP ver. 12.1 software (SAS Institute, Cary, NC, USA).

Table I. *Patient demographics of 94 patients with intrahepatic cholangiocarcinoma*.

Variable	n=94
Preoperative factors	
Age, median, years, (range)	68 (32-84)
Male, n (%)	55 (58.5%)
SUVmax, median, (range)	6.35 (2.3-22.1)
NLR, median, (range)	2.2 (0.4-19.5)
PLR, median, (range)	129.7 (32.7-365.1)
CRP, mg/l (range)	2.0 (0-64)
Postoperative factors, n (%)	
AJCC T stage, n (%)	
T1	26 (27.7%)
T2-T4	68 (72.3%)
AJCC N stage, n (%)	
N0	57 (60.6%)
Nx	11 (11.7%)
N1	26 (27.7%)
Poorly differentiated, n (%)	16 (17.0%)
R0 resection, n (%)	81 (86.2%)
Treatment factors, n (%)	
Major hepatectomy (≥3 segments), n (%)	72 (76.6%)
Biliary reconstruction, n (%)	24 (25.5%)
Vascular resection, n (%)	13 (13.8%)
Postoperative adjuvant chemotherapy, n (%)	40 (42.6%)
Surgical outcome – Morbidity, n (%)	
None, n (%)	54 (57.5%)
Class I/II, n (%)	16 (17.0%)
Class III/ VI, n (%)	24 (25.5%)

SUVmax, Maximum standardized uptake value; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein: AJCC, American Joint Committee on Cancer; R0 resection, no macroscopic and microscopic tumor remaining.

Results

Patient demographics. During the study period, 134 patients with pathologically proven ICC underwent surgery. Of these, 101 patients (75.3%) underwent ^{18}F-FDG-PET/CT and subsequent surgery, the remaining 33 did not undergo

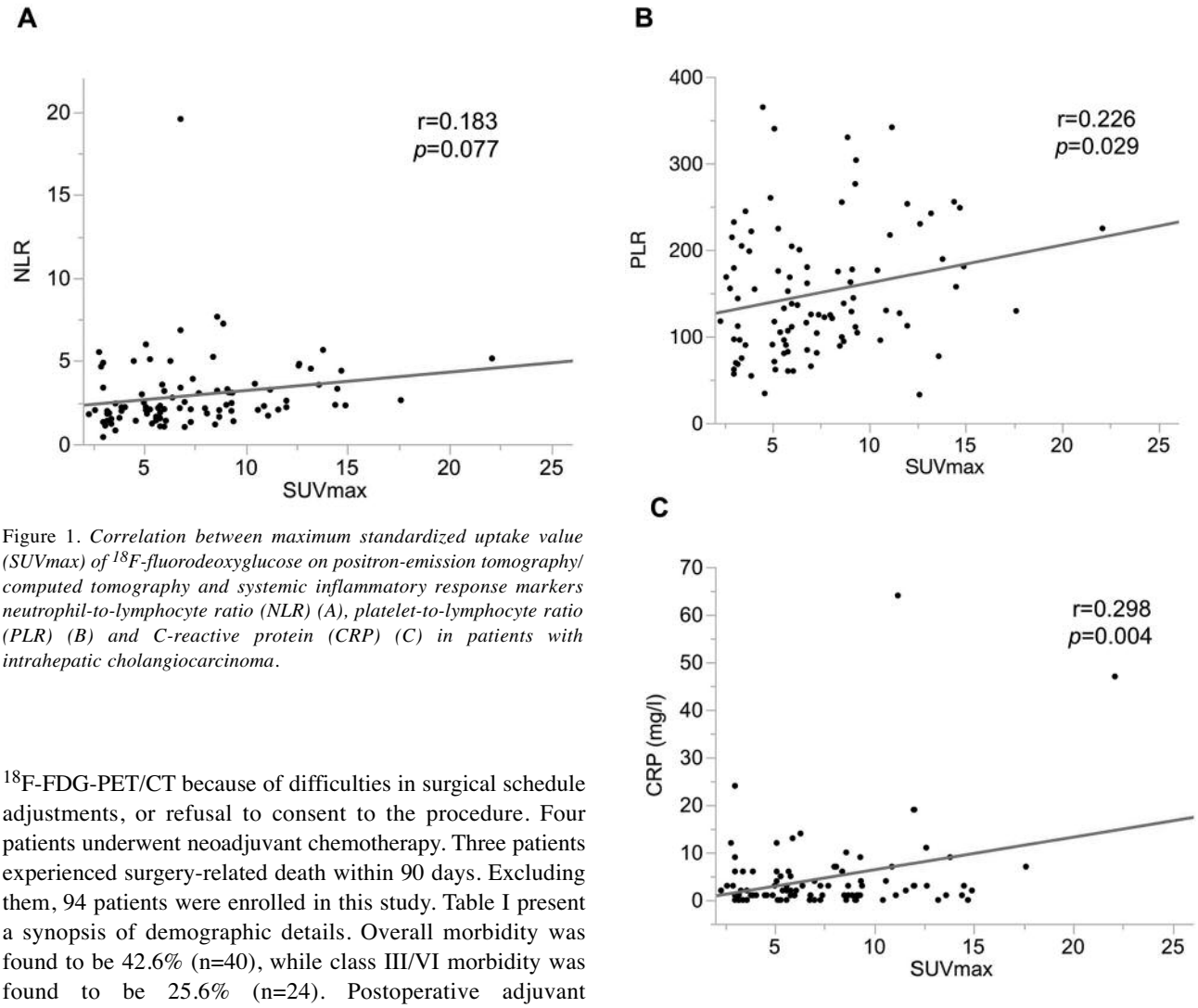

Figure 1. *Correlation between maximum standardized uptake value (SUVmax) of ^{18}F-fluorodeoxyglucose on positron-emission tomography/computed tomography and systemic inflammatory response markers neutrophil-to-lymphocyte ratio (NLR) (A), platelet-to-lymphocyte ratio (PLR) (B) and C-reactive protein (CRP) (C) in patients with intrahepatic cholangiocarcinoma.*

^{18}F-FDG-PET/CT because of difficulties in surgical schedule adjustments, or refusal to consent to the procedure. Four patients underwent neoadjuvant chemotherapy. Three patients experienced surgery-related death within 90 days. Excluding them, 94 patients were enrolled in this study. Table I present a synopsis of demographic details. Overall morbidity was found to be 42.6% (n=40), while class III/VI morbidity was found to be 25.6% (n=24). Postoperative adjuvant chemotherapy was performed on 40 patients (42.6%).

Correlation between tumor SUVmax and SIR markers. To start with, we examined the relationship between markers of inflammation and SUVmax as indicated by Figure 1. Amongst the three chosen SIRs, PLR and CRP indicated significant, however, quite weak positive relationships with tumor SUVmax (PLR, r=0.226, p=0.029; CRP, r=0.298, and p=0.004). NLR was not significantly related to tumor SUVmax (r=0.183, p=0.077).

Prognostic correlation between tumor SUVmax and SIR markers. Subsequently, we assessed whether the prognostic data given by SIR markers and tumor SUVmax are independent or not. The median follow-up time after surgery was 36.0 months. The median OS time was 47.6 months, with 1-, 3- and 5-year OS rates of 88.1%, 56.7%, and 43.2%, respectively. The median DFS time was 18.0 months, with 1-, 3- and 5-year DFS rates of 59.1%, 32.5%, and 27.6%, respectively.

Multivariate analyses were performed to assess the prognostic correlation between tumor SUVmax and SIR markers. To facilitate understanding the prognostic values of tumor SUVmax and SIR markers in patients with ICC after surgery, we determined the optimal cut-off values. Using the minimum p-value approach based on the maximum difference in OS, the optimal cut-off values were determined to be tumor SUVmax of 8, NLR of 5, PLR of 120, and CRP of 5 mg/l, respectively. Table II shows the results of univariate and multivariate analyses for predicting OS and DFS in patients with ICC after surgery. As a result, multivariate analyses using the minimum BIC method identified high tumor SUVmax (≥8) and high NLR (≥5) as significant independent predictors of poor OS (p=0.013 and p=0.002) as well as DFS (p<0.001 and p=0.004). These results confirmed that the individual prognostic value of tumor SUVmax and NLR was independent as well as strong.

Table II. *Univariate and multivariate analysis of preoperative quantitative factors.*

Variable		Univariate analysis	Multivariate analysis	
		p-Value	HR (95% CI)	*p*-Value
Overall survival	Cutoff			
SUVmax	≥8.0	**0.019**	1.993 (1.160-3.416)	**0.013**
NLR	≥5	**0.002**	3.651 (1.699-7.172)	**0.002**
PLR	≥120	0.070	-	-
CRP (mg/l)	≥5	**0.002**	-	-
Disease-free survival				
SUVmax	≥8.0	**<0.001**	2.520 (1.531-4.131)	**<0.001**
NLR	≥5	**0.009**	2.510 (1.496-6.198)	**0.004**
PLR	≥120	**0.002**		
CRP (mg/l)	≥5	**<0.001**		

SUVmax, Maximum standardized uptake value; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein; HR, hazard ratio; CI, confidence interval. Multivariate models are determined by minimum Bayesian information criterion method. Significant differences are shown in bold ($p<0.05$).

Prognostic stratification using tumor SUVmax and NLR. Finally, a prognostic scoring system including tumor SUVmax and NLR was developed to interpret the clinical impact of these factors on survival outcomes. The prognostic scores were defined as follows: score 0, neither of these factors above the cutoff; score 1, the presence of only one factor above its cutoff, and score 2, the presence of both factors above cutoff. Amongst the 94 patients, 51, 38, and five patients were scored as 0, 1, and 2, respectively. The differences in clinicopathological features among patients with different preoperative prognostic scores are shown in Table III. There was no significant relationship between the clinicopathological features assessed and scores.

Figure 2 shows patient OS and DFS according to the preoperative prognostic scores. The median OS time of patients with preoperative prognostic score 0, 1, and 2 were 83.6, 28.8 and 12.2 months, respectively (Figure 2A, $p<0.001$). Differences in OS according to the preoperative prognostic scores were significant (0 *vs.* 1, $p<0.001$; 1 *vs.* 2, $p=0.004$). Similar results were obtained for DFS. The median DFS of patients with preoperative prognostic score 0, 1, and 2 were 30.0, 9.7, and 4.9 months, respectively (Figure 2B, $p<0.001$). Stratifications of DFS according to the prognostic scores was also significant (0 *vs.* 1, $p<0.001$; 1 *vs.* 2, $p=0.016$). All five patients scoring 2 exhibited recurrence within 6 months as well as dying within 3 years.

Discussion

The relationship between tumor ^{18}F-FDG uptake and SIR is of interest in several malignancies. This present study investigated the relationship between tumor SUVmax and SIR markers in patients undergoing surgery for ICC. In this setting, tumor SUVmax was found to be slightly correlated with some SIR markers (*i.e.* CRP and PLR were significant; NLR was marginally significant). Most importantly it should be noted that multivariate analyses identified tumor SUVmax and NLR as independent prognostic indicators for OS and DFS. Furthermore, we developed a scoring system using these independent factors and found that patients with high tumor SUVmax along with high NLR presented extremely poor prognosis after surgery for ICC. Prognostic information given by tumor SUVmax and SIR markers may be sufficiently independent in patients undergoing surgery for ICC. In particular, a therapeutic strategy for patients with high tumor SUVmax and high NLR may need to be discussed with caution because of their extremely poor prognosis.

To the best of our knowledge, this is the first investigation between tumor SUVmax and SIR markers in patients who underwent surgery for ICC. To date, a relationship between tumor SUVmax and SIR markers has been investigated in several cancer types, such as colorectal (8), lung (9, 10), nasopharyngeal (11) and breast (12), yet their conclusions varied. Our results in the ICC population showed that there was a weak correlation between tumor SUVmax and SIR markers. Theoretically, SUVmax is higher when local inflammation occurs, and the available data in this study suggest that the value of SIR markers may weakly influence tumor SUVmax. Although a clear answer was not obtained in this study, we speculate that tumor glucose metabolism was so activated in this ICC population that the influence of SIR markers was rather weak. The elevation of SIR may suggest an immunosuppressive status rather than local inflammation in patients with ICC, and therefore quantification of ^{18}F-FDG uptake in ICC might not be hampered in this condition.

In this study, the study population included only patients who underwent surgery for ICC. In this setting, evaluating tumor SUVmax and NLR, which were identified as independent prognostic predictors in multivariate analysis, allowed us to develop a scoring system for predicting OS and DFS. This scoring system was able to stratify patients into three prognostic subgroups with scores of 0, 1, and 2, respectively. In spite of a small study population, we discovered five patients with high tumor SUVmax along with high NLR who represented patients with extremely poor OS and DFS after surgery for ICC. All five patients exhibited recurrence within 6 months as well as dying within 3 years. At present, gemcitabine plus cisplatin is the standard treatment for advanced ICC, with a median survival time of 11.9 months (20). Surgery should be the best practice for selected patients with ICC because of its invasiveness (1, 21). Nevertheless, the fact that patients scoring 2 showed dismal prognosis implied that surgery for such patients might be not beneficial. In this study population, lack of

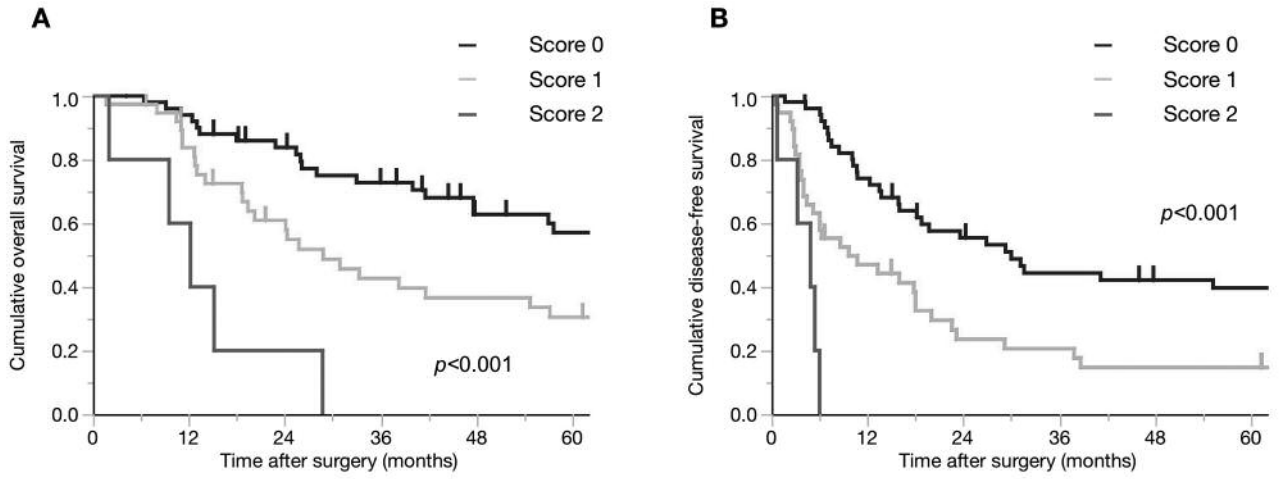

Figure 2. *Overall (A) and disease-free (B) survival according to a prognostic score incorporating maximum standardized uptake value of ^{18}F-fluorodeoxyglucose on positron-emission tomography/computed tomography and neutrophil to lymphocyte ratio in patients with intrahepatic cholangiocarcinoma. Score 0, Neither of these factors above the cutoff; score 1, the presence of only one factor above its cut-off; score 2, the presence of both factors above cutoff.*

Table III. *Differences of tumor characteristics between patients with ICC in the strata of the preoperative prognostic scores.*

Tumor characteristic	Score 0 (n=51), n (%)	Score 1 (n=38), n (%)	Score 2 (n=5), n (%)	*p*-Value
AJCC N1	10 (19.6%)	14 (36.8%)	2 (40.0%)	0.111
AJCC T stage (T2-T4)	34 (66.7%)	29 (76.3%)	5 (100%)	0.299
Poorly differentiation	6 (11.8%)	9 (23.7%)	1 (20.0%)	0.258
R1 resection	7 (13.7%)	6 (15.8%)	0 (0%)	>0.99

ICC, Intrahepatic cholangiocarcinoma; AJCC, American Joint Committee on Cancer; R1 resection, microscopic tumor remaining.

appropriate control patients meant we were unable to confirm this hypothesis; however, the evidence suggests that the therapeutic strategy for such patients should be discussed with caution.

The main limitation of the present study is its retrospective nature; certain biases such as the imaging modality [*e.g.* detector arrangement of ^{18}FDG-PET or advances of treatment variables (22, 23)] could not be completely avoided. However, it should be noted that ICC is a relatively rare disease; therefore, prospective evaluation of biological markers is difficult. We emphasize that this study included 94 consecutive patients with ICC, which to our knowledge is the largest study evaluating a relationship between tumor SUVmax and SIR. Another potential limitation is the interval between ^{18}FDG-PET/CT study and blood examinations. In this study, we attempted to measure SIR when patients showed no infectious symptoms to ensure the same clinical settings). Lastly, the variables which were selected in this study were NLR, PLR and CRP. A greater number of SIR markers or SIR scores may need to be addressed; however, they showed obvious multicollinearity.

Conclusion

Prognostic information provided by tumor SUVmax and SIR markers may be sufficiently independent in patients undergoing surgery for ICC. Therefore, we can interpret the significance of these parameters as they are. However, it should be noted that patients with high tumor SUVmax along with high NLR exhibited dismal prognosis even after surgery; therefore, a therapeutic strategy for such patients may need to be discussed with caution.

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