Refining prognosis of patients with hepatocellular carcinoma through incorporation of metabolic imaging biomarkers

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Abstract

Purpose: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) has been proven to be useful for imaging of many types of cancer; however, the role of FDG-PET/CT is less well defined in hepatocellular carcinoma (HCC). We assessed the prognostic value of metabolic imaging biomarkers as established by baseline pretreatment FDG-PET/CT in patients with HCC.

Methods: We retrospectively analyzed the records of patients with HCC who underwent FDG-PET/CT before initial treatment from May 2013 through May 2014. Four PET/CT parameters were measured: maximum standardized uptake value (SUV_{max}), total lesion glycolysis (TLG), metabolic tumor volume (MTV), and tumor-to-normal-liver ratios of SUV (TNR). Optimal cut-off values for PET/CT parameters to stratify patients in terms of OS were determined. Multivariate analysis was performed to evaluate whether PET/CT parameters could provide additional prognostic information beyond that provided by Cancer of the Liver Italian Program (CLIP) scoring system and Barcelona-Clinic Liver Cancer (BCLC) staging system.

Results: Fifty-six patients were included in the analysis. Univariate analysis of the association between OS and continuous variables, including PET/CT parameters SUVmax, TLG, tumor size, total bilirubin level, and alkaline phosphatase level were significant predictors of OS in this analysis. $SUV_{max} \geq 11.7$, TLG $\geq$ 1341, MTV $\geq$ 230 mL, and TNR $\geq$ 4.8 were identified as cut-off values. Multivariate analysis revealed that SUVmax $\geq$ 11.7 and TNR $\geq$ 4.8 were independent poor prognostic factors for both the CLIP scoring system and BCLC staging system, so too was TLG in the BCLC staging system.

Conclusion: Pretreatment FDG-PET/CT can provide prognostic information in patients with HCC beyond

standard clinical measures. Incorporation of imaging biomarkers derived from FDG-PET/CT into HCC staging systems should be considered.

Keywords: FDG-PET/CT; hepatocellular carcinoma; CLIP scoring system; BCLC staging system

Introduction

Liver cancer is the second leading cause of cancer-related death in the world [1]. The most common form of liver cancer is hepatocellular carcinoma (HCC). The occurrence of liver cancer is closely associated with chronic liver damage, such as that caused by chronic hepatitis due to hepatitis virus infection, liver cirrhosis, or fatty liver disease [2]. Also, other metabolic diseases (such as obesity and diabetes mellitus) and alcohol intake are well-known risk factors for liver cancer [3, 4].

In patients with cancer, prognostic modeling can facilitate decision making regarding treatment; however, in patients with HCC, evaluating prognosis is difficult and complicated because cirrhosis is involved in many cases [5]. Both tumor features and functional hepatic reserve must be taken into account. At present, several different staging systems for HCC are available, and there is no universally accepted staging system [6]. The Cancer of the Liver Italian Program (CLIP) scoring system for HCC accounts for both liver function and tumor characteristics relevant to prognosis [7]. The Barcelona-Clinic Liver Cancer (BCLC) staging system was constructed on the basis of the results from several cohort studies and randomized controlled trials conducted by the Barcelona group [8]. Other staging systems are also available for HCC, including the American Joint Committee on Cancer staging system, Japanese Integrated Staging (JIS) system, Okuda staging system, GRoupe d'Etude et de Traitement du Carcinoma Hépatocellulaire (GRETCH), and Chinese University Prognostic Index (CUPI) [5, 9-11]. Some of these staging systems have been shown to be applicable for all stages of HCC and are widely accepted; however, none of these staging systems is predictive in every situation, so there is room for improvement. Although both the CLIP scoring system and BCLC staging system have been validated in

different cohorts of patients, a more reliable prognostic classification for HCC is still needed.

In patients with cancer, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been used for surveillance after treatment and for evaluation of response to therapy. During the past decade, combined FDG-PET and computed tomography (FDG-PET/CT) has also been used for imaging of various malignancies [12]. However, use of FDG-PET/CT in HCC has been limited because whereas FDG uptake in cholangiocarcinoma, hepatocholangiocarcinoma, and liver metastases has been reported to be higher than uptake in normal liver tissue [13-15], FDG uptake in well-differentiated HCC has been reported to be similar to uptake in normal liver tissue because of a high rate of gluconeogenesis in well-differentiated HCC [16]. In patients with many types of cancer, not only highest metabolic activity within the tumor (maximum standard uptake value; SUV_{max}) in a 2-dimensional region of interest but also total lesion glycolysis (TLG) and maximum tumor volume (MTV) in a 3-dimensional region of interest are thought to provide valuable information with regard to prognosis. However, the prognostic value of findings on baseline pretreatment FDG-PET/CT in patients with HCC remains to be elucidated.

The aim of this study was to determine the associations between overall survival (OS) and established prognostic factors and FDG-PET/CT parameters and to determine whether baseline pretreatment FDG-PET/CT parameters provide additional prognostic information beyond that provided by CLIP score or BCLC staging system in patients with HCC.

Materials and methods

Patients

This study was approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center, which waived the requirement for informed consent, and was performed in compliance with the Health Insurance Portability and Accountability Act. We retrospectively reviewed the database of MD Anderson's Tumor Registry and identified 98 consecutive patients with liver tumors who were referred to our institution for treatment during the period from May 2013 through May 2014. Of these patients, 30 patients were excluded because they did not undergo FDG-PET/CT before initial treatment. An additional 12 patients were excluded because OS data were unavailable (n=5); the patient had another type of liver cancer (cholangiocarcinoma, gallbladder carcinoma, hepatic adenoma, or adenomatosis) (n=4); the patient had already had surgery at the time of referral to MD Anderson Cancer Center (n=2); or no HCC was detected by FDG-PET/CT because of false negative (n=1). The remaining 56 patients were included in the analysis. For all patients, diagnosis of HCC was confirmed at MD Anderson as part of the institution's standard practice based on pathological or radiological HCC characteristics.

Patient information was obtained by direct chart review. Information extracted from charts included demographic, HCC risk factors, clinical characteristics, Eastern Cooperative Oncology Group (ECOG) performance status, and pathological differentiation. Furthermore, we reviewed patients' radiological images to retrieve different tumor parameters mandatory for stage calculation including number of tumor nodules, tumor size, endovascular invasion, lymph node and distance metastasis. Accordingly, TNM staging system, seventh

edition, CLIP score and BCLC staging system were calculated specifically for the current analysis using information in the patients' charts. The CLIP score is calculated by assigning a score (0, 1, or 2) to each of 4 clinical factors: a) Child-Turcotte Pugh score (CTP); b) number of tumor nodules and the percentage of the liver occupied by tumor whether it is ≤ 50% or > 50% by reviewing the radiological images that patients did when they present to MD Anderson for the first time; c) alfa-fetoprotein level; and d) portal vein thrombosis. These scores are summed to calculate a CLIP score of 0-6 [7]. The BCLC staging system classify disease into four categories: a) early stage, b) intermediate stage, c) advanced stage, and d) end stage based on several independent prognostic factors identified in several studies. These factors are variables related to tumor stage including number of tumor nodules, tumor size by centimeter, distance metastasis, lymph node involvement, and vascular invasion. Also, it includes parameters to asses underlying liver functional status by CTP score, and patients' performonus status by Eastern Cooperative Oncology Group (ECOG), and cancer-related symptoms to [17].

FDG-PET/CT imaging

FDG-PET/CT scans were performed using standard clinical protocol. Briefly, patients fasted for 6 hours before ^{18}F-FDG administration. All patients were confirmed to have a serum blood glucose level of ≤ 200 mg/dL prior to injection of the radiopharmaceutical. ^{18}F-FDG (typically 259-444 MBq / 7-12 mCi) was administered intravenously. Approximately 60 minutes later, an integrated PET/CT system (Discovery ST, STe, or RX; GE Healthcare) was used to acquire imaging data. CT was performed concomitantly with each PET acquisition for

anatomical localization and attenuation correction; parameters included 3.75-mm axial slice placement, 140 kV, and 120 mA at a 13.5-mm table speed. PET was performed in 3-dimensional mode at 3 to 5 minutes per bed station based on BMI. PET, CT, and fusion images were displayed in 3.75-mm slices. Attenuation-corrected and non-attenuation-corrected datasets were reconstructed. FDG-PET/CT was always performed within 30 days prior to initiation of treatment.

Image review and tumor analysis

Imaging data were reviewed by experienced nuclear medicine physicians and radiologists at MD Anderson. Four PET/CT parameters, SUV_{max}, TLG, MTV, and tumor-to-normal-liver ratios of SUV (TNR), were measured specifically for the current analysis using a MIM workstation (MIM Software, Cleveland, OH, USA). Volumetric parameters were defined using MIM contouring software as described previously [18]. SUV was defined as measured activity concentration (Bq/g) multiplied by body weight (g) divided by injected activity (Bq). TLG was defined as average metabolic activity within the tumor multiplied by tumor volume. MTV was defined using an automated contouring program based on the SUV.

Statistical analysis

Statistical analyses were performed with Splus Software, version 8.2 (TIBCO, Palo Alto, CA), and SAS software, version 9.3 (SAS Institute Inc., Cary, NC). OS was defined as the time from the date of initial treatment to death from any cause or last follow-up. A univariate Cox model was used to determine the

association of OS with continuous variables, including PET/CT parameters. The log-rank test was used to compare OS stratified by various potential prognostic factors. Martingale residual plots and recursive partitioning and regression trees analysis were used to determine cut-off values for PET/CT parameters to stratify patients in terms of OS. A Cox proportional hazards regression model was used for multivariate analysis to evaluate significant PET/CT parameters for both the CLIP scoring system and the BCLC staging system. Fisher's exact test was used to assess the association between variables. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Patient characteristics are summarized in Table 1. Thirty-nine patients (71%) had stage III or IV disease. The median time from initial treatment to last follow-up was 5.3 months (range, 0.1 - 26.9 months). Twenty-four patients (43%) died during follow-up. The estimated median OS was 17.0 months (95% confidence interval: 5.1 months - not assessable). Twenty-six patients (46%) had well or moderately differentiated HCC. Twenty-seven patients (48%) were infected with hepatitis B or C virus. Multifocality and capsular nodularity were seen in 29 patients (52%) and 37 patients (66%), respectively. Thirty-one patients (55%) had a history of alcohol consumption. Moderate or slight ascites was seen in 23 patients (41%). Portal vein thrombosis was seen in 23 patients (41%). The median alfa-fetoprotein value was 60.7 ng/mL (range, 1.3 - 76717.2). The median tumor size was 8.2 cm (range, 1.1 - 18.2). Twenty patients (36%) had tumor volume accounting for more than 50% of the liver volume.

Association between OS, established prognostic factors, and FDG-PET/CT parameters

The median values of FDG-PET/CT parameters for the primary lesion were as follows: SUV_{max}, 6.0 (range, 2.2-20.0); TLG, 541.0 (range, 4.6-5631.7); MTV, 151.9 mL (range, 8.3-2003.8); and TNR, 2.0 (0.8-12.9). Table 2 shows the results of univariate analysis of the association between OS and continuous variables, including PET/CT parameters. SUV_{max}, TLG, tumor size, total bilirubin level, and alkaline phosphatase level were significant predictors of OS in this analysis. MTV and TNR were not significant predictors of OS. Table 3

shows the results of log-rank test to compare OS between patient subgroups. There are blanks for 2-year OS rate. This is because there was no follow-up data beyond 1 year if patients either died or censored within 1-year. ECOG performance score 0-1, no endovascular invasion, CTP-A, tumor volume $\leq$ 50% of liver volume, TNM stage I/II, and CLIP score 0 were significant good predictors of OS in this analysis.

Evaluation of whether PET/CT parameters provide additional prognostic value to scoring systems

Martingale residual plots and recursive partitioning and regression trees analysis revealed the following optimal cut-off points for PET/CT parameters to stratify patients in terms of OS: SUV_{max}, 11.7; TLG, 1341; MTV, 230 mL; and TNR, 4.8. Figure 1 shows Kaplan-Meier survival curves for patients by the determined cut-off values of PET/CT parameters. OS was significantly worse in patients with SUV $\geq$ 11.7 (Figure 1A), TLG $\geq$ 1341 (Figure 1B), MTV $\geq$ 230 (Figure 1C), and TNR $\geq$ 4.8 (Figure 1D). The results of multivariate analysis to determine whether PET/CT parameters provide additional prognostic value beyond that provided by CLIP score and BCLC staging system for OS are shown in Table 5 and Table 6, respectively. Each table includes 4 different sets of data. These correspond to 4 different models, one for each of the PET/CT parameters. For the CLIP scoring system, both SUV_{max} $\geq$ 11.7 and TNR $\geq$ 4.8 were independent poor prognostic factors (Table 4). For the BCLC staging system, both SUV $\geq$ 11.7 and TNR $\geq$ 4.8 were independent poor prognostic factors; so too was TLG $\geq$ 1341 (Table 5).

Discussion

Our study confirmed an association between established prognostic factors and overall survival, and also found a statistically significant association between OS and metabolic imaging biomarkers. In this analysis that included 56 consecutive patients with HCC who underwent FDG-PET/CT before initial treatment, we found that FDG-PET/CT derived parameters were significant predictors of OS, and we determined optimal cut-off values for these parameters. Patients with higher values than cut-off values had significantly worse survival. We also demonstrated that PET/CT parameters, especially SUV_{max} and TNR, could provide additional prognostic value beyond that provided by CLIP score and BCLC staging system, so too was TLG in the BCLC staging system. To our knowledge, this is the first analysis showing that incorporation of initial pretreatment PET/CT parameters can improve the prognostic utility of prognostic scoring systems for patients with untreated HCC.

Previous publications on the role of FDG-PET/CT in the evaluation of patients with HCC have suggested that the utility of FDG-PET/CT may depend on degree of differentiation or tumor size. Torizuka et al. proposed that in well-differentiated HCC, FDG-PET/CT may not be an appropriate modality because a high rate of gluconeogenesis comparable with normal liver tissue results in similar uptake of FDG [16]. Trojan et al. reported that high FDG uptake was frequently seen in patients with HCC with moderately or poorly differentiated tumors, tumors > 5 cm, or elevated alfa-fetoprotein levels [19]. Hayakawa et al. reported that less well-differentiated HCC express more hexokinase, resulting in higher FDG uptake [20]. In our study reported here, many patients already had large tumors before initiation of treatment: the median tumor size at pretreatment FDG-PET/CT was 8.2 cm. Thus, our patient cohort might be suitable for PET/CT. Information

with regard to tumor differentiation was not available in all our patients.

Our findings were partly consistent with a previous report by Ahn et al., who reported that preoperative FDG-PET/CT can predict early recurrence after curative resection of HCC [21]. In their report, both TNR ≥ 2 and $SUV_{max} \geq 4$ were significant predictors in univariate analysis. However, their examined factors were not significant independent predictors on multivariate analysis.

To our knowledge, this is the first report about association between PET/CT parameters and staging systems. In the present study, we demonstrated on multivariate analysis that SUV_{max} and TNR provided additional prognostic information beyond that provided by CLIP score and BCLC staging system, so too was TLG in the BCLC staging system. Our results suggested that both SUV_{max} and TNR clearly added prognostic value beyond that provided by CLIP score and BCLC staging system, and TLG might be also prognostic; in contrast, TLG was not independent poor prognostic factors on multivariate analysis. Tumor volume is not taken into account in the calculation of either SUV_{max} or TNR. These results contrast with previous findings that volume-based PET/CT parameters aid in predicting prognosis in many types of malignancy, including non-small cell lung cancer, head and neck cancer, ovarian cancer, and soft tissue sarcoma [22-25]. However, which PET/CT parameter is the most reliable to predict outcome in patients with HCC is still unknown. Further prospective study is necessary to clarify this issue.

Although we focused on FDG-PET/CT, tracers other than FDG might also be promising for predicting prognosis in patients with HCC. PET tracers that visualize lipid metabolism have been proposed to be superior to FDG for the detection of HCC. ^{11}C-acetate was reported to be beneficial because of its better sensitivity for

the detection of well-differentiated HCC [27, 28]. Talbot et al. reported that a prospective study showed that ^{18}F-fluorocholine PET/CT was significantly more sensitive than FDG-PET/CT in the detection of well-differentiated HCC but had sensitivity similar to that of FDG-PET/CT in the detection of less differentiated HCC [29]. On the other hand, these authors also reported that FDG seemed better than these other tracers in the detection of poorly differentiated HCC. The prognostic value of ^{11}C-acetate and ^{18}F-fluorocholine PET/CT in patients with HCC has not yet been examined.

Our study had several potential limitations. This was a single-center retrospective study, with relatively small patients numbers. Cut-off values in the present study should be validated in a larger patient group. Additionally, we were not able to categorize patients according to type of systemic therapy, which could be a factor in patient outcome. For example, the number of patients treated with a multikinase inhibitor such as sorafenib was unknown. It has been suggested that molecularly targeted therapy might prolong survival in patients with advanced HCC [30]. Additionally, information about tumor differentiation was not available in all patients. ^{18}F-FDG uptake varies between well-differentiated and poorly differentiated HCC [27]. Despite these limitations, this study is noteworthy because our data demonstrate that pretreatment FDG-PET/CT not only was important in terms of OS but also provided additional prognostic information beyond that provided by the CLIP scoring system or BCLC staging system.

Conclusion

This study demonstrates that metabolic imaging biomarkers as derived from FDG-PET/CT parameters are prognostic factors for OS in patients with newly-diagnosed hepatocellular carcinoma about to undergo initial treatment. Furthermore, the incorporation of FDG-PET/CT imaging biomarkers are additive and complimentary to the CLIP scoring system and BCLC staging system in patients with untreated HCC. Maximum lesion intensity (SUV_{max}) and tumor-to-nontumor radios (TNR) seem to be the most prognostically powerful of the FDG-PET/CT parameters, but total lesion glycolysis (TLG) may also impart important prognostic factor. We believe that incorporation of metabolic imaging biomarkers into HCC staging systems should be considered, with future studies aimed at further defining the use of these biomarkers.

Compliance with Ethical Standards

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Conflicts of interest

The author and all other coauthors have no conflicts of interest to disclose.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of our institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This retrospective study was approved by the local institutional review board and the requirement for written informed consent was waived. This article does not contain any studies with animals performed by any of the authors.

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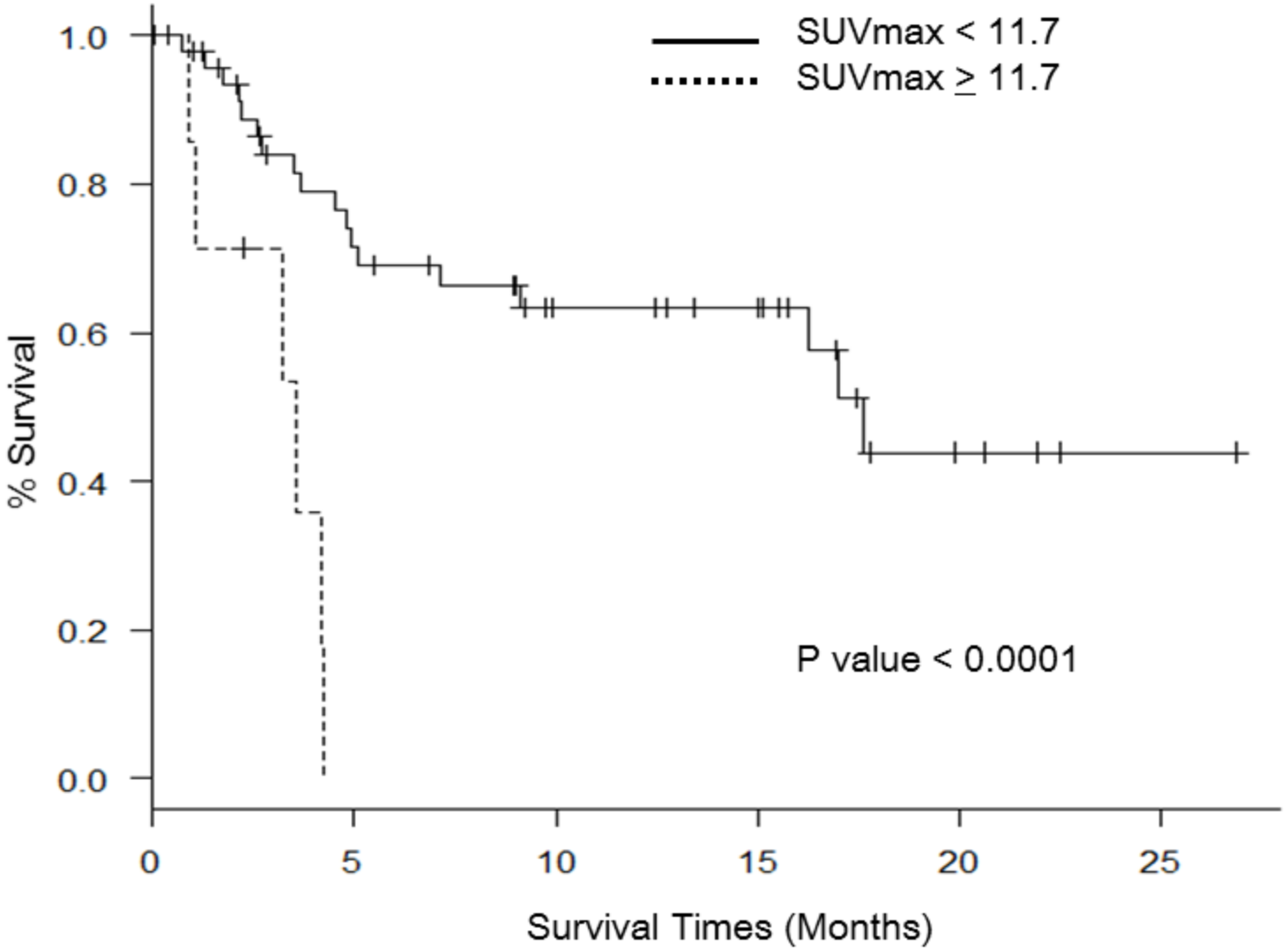
Figure Caption

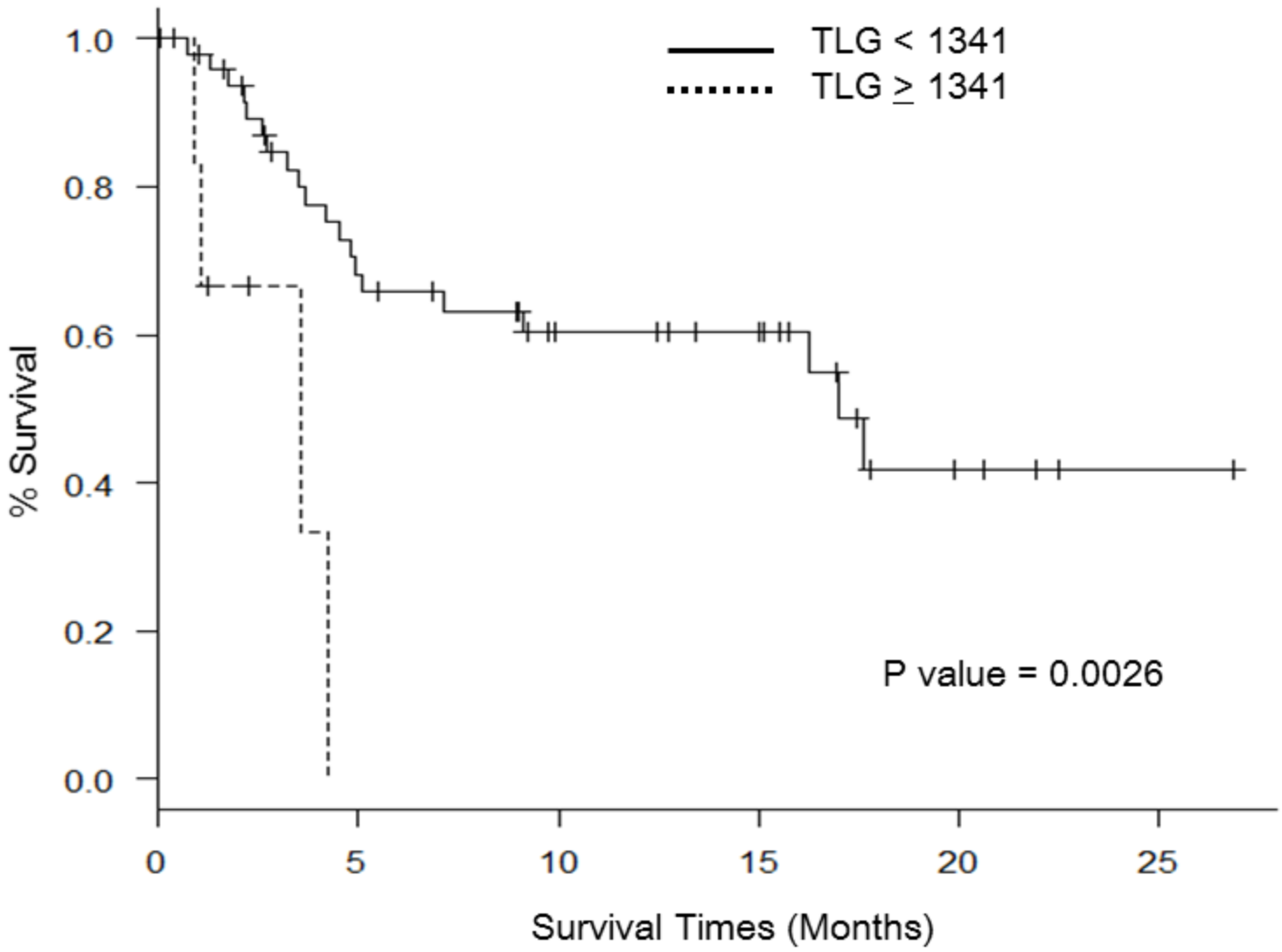
Fig. 1 Survival curves for patients by determined cut-off values of PET/CT parameters. A, SUV_{max} (maximum standardized uptake value). B, TLG (total lesion glycolysis). C, MTV (metabolic tumor volume). D, TNR (tumor-to-normal-liver ratios of SUV). NA, not assesable; OS, overall survival; CI, confidence interval

A



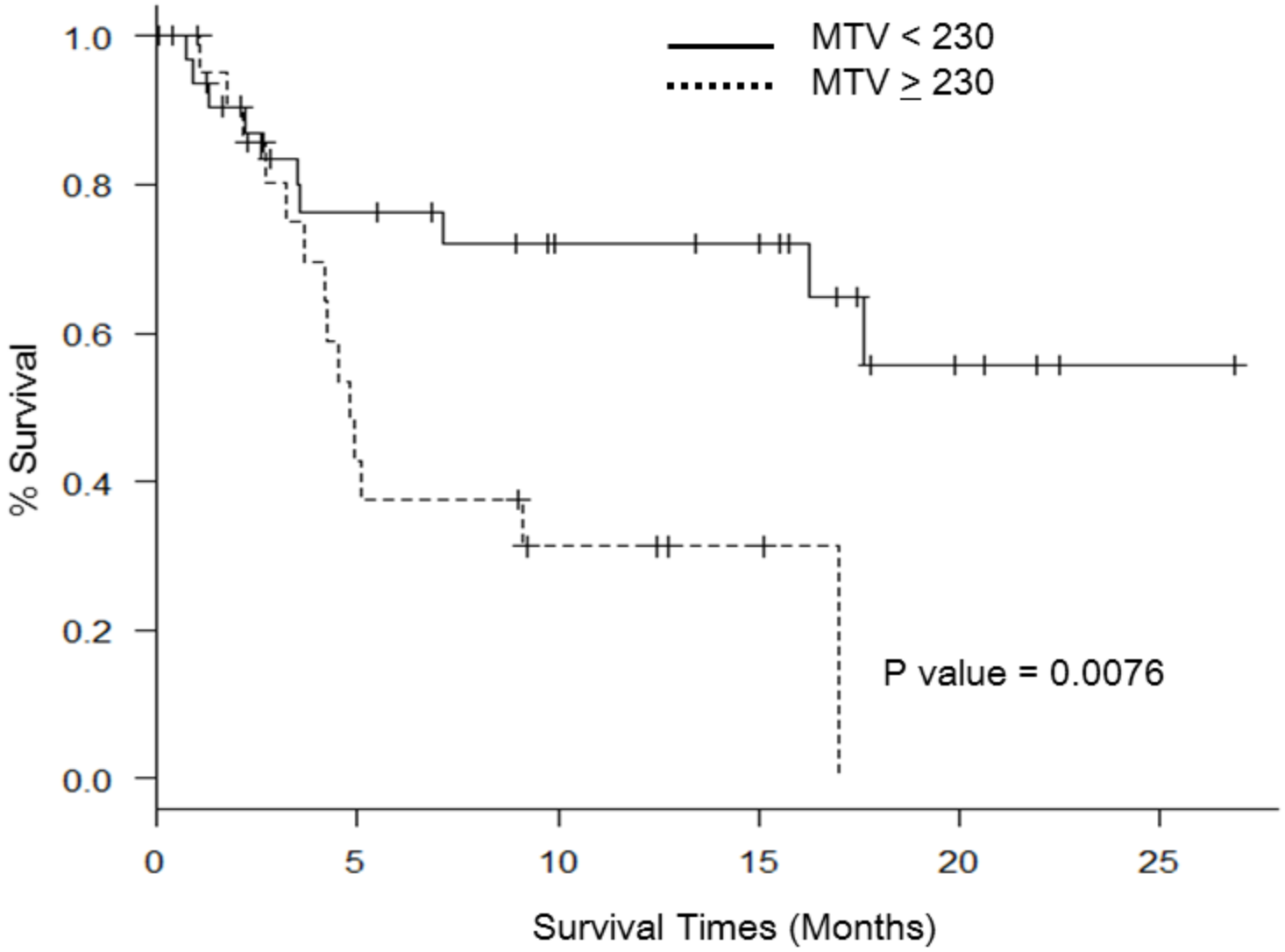
	death/N	Median OS (95% CI)
SUVmax < 11.7	18/49	17.6 (16.3-NA)
SUVmax ≥ 11.7	6/7	3.5 (1.1-NA)

B



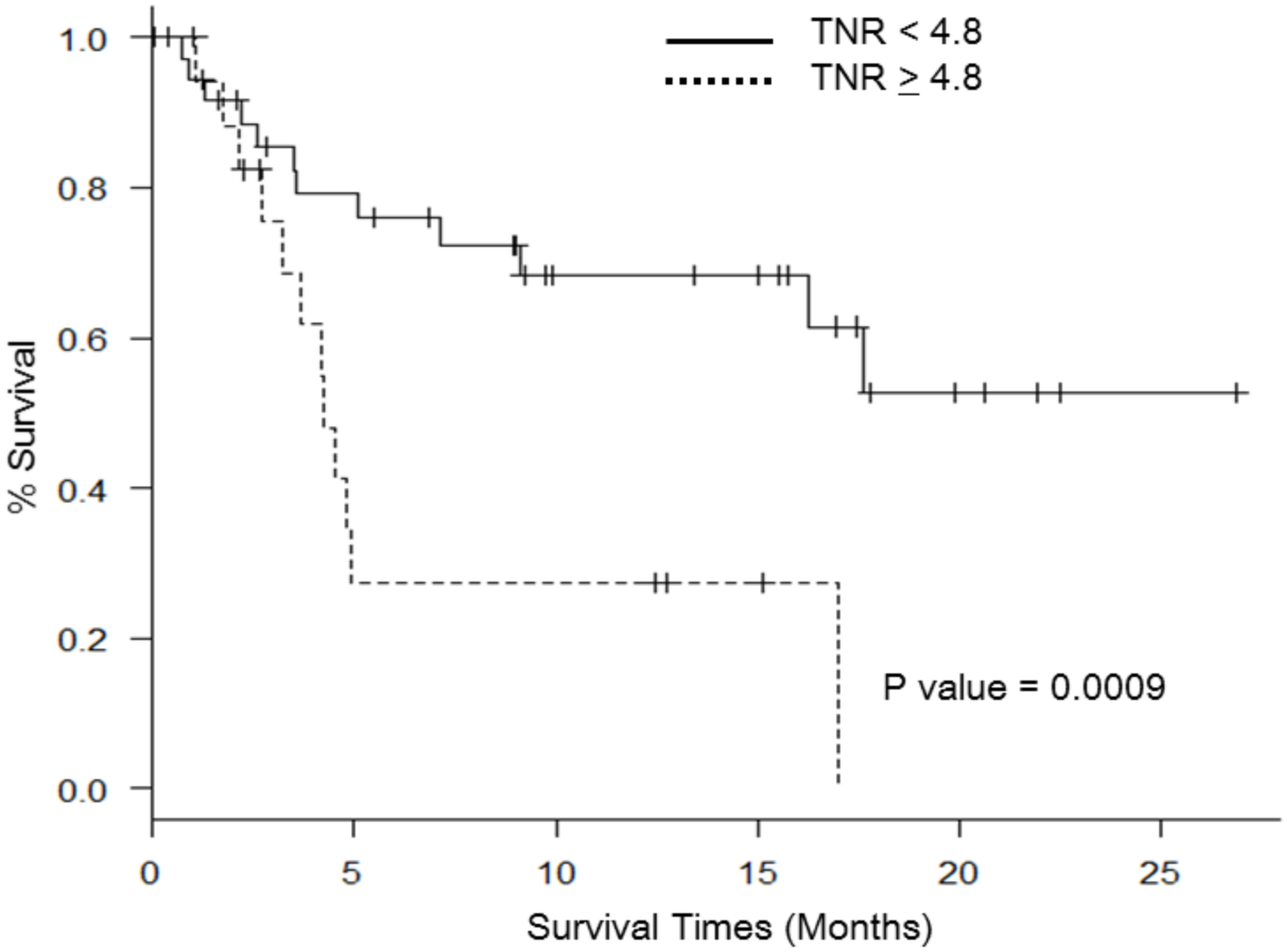
	death/N	Median OS (95% CI)
TLG < 1341	12/37	NA (9.1-NA)
TLG ≥ 1341	12/19	44.2 (2.7-NA)

C



	death/N	Median OS (95% CI)
MTV < 230	10/33	NA (16.3-NA)
MTV ≥ 230	14/23	4.8 (3.2-NA)

D



	death/N	Median OS (95% CI)
TNR < 4.8	20/49	17.0 (9.1-NA)
TNR ≥ 4.8	4/7	3.5 (1.1-NA)

Table 1 Patient demographics and clinical characteristics

Characteristic	No. of patient (%) (n=56)
Age, median (range)	65 years (21-91 years)
Sex	
Male	49 (88)
Female	7 (12)
Race/ethnicity	
Caucasian	36 (64)
Latino	10 (18)
African American	7 (13)
Asian	3 (5)
ECOG performance status	
0-1	45 (80)
2-3	9 (16)
Unknown	2 (4)
Tumor differentiation	
Well	8 (14)
Moderately	18 (32)
Poorly	6 (11)
Unknown	24 (43)
Hepatitis infection	
HBV	6 (11)
HCV	20 (36)
HBV and HCV	1 (1)
None	29 (52)
Cirrhosis	
Yes	33 (59)

No	23 (41)
Varices	
Yes	15 (27)
No	41 (73)
Endovascular invasion	
Yes	30 (54)
No	26 (46)
Child-Pugh score	
A	37 (66)
B	17 (30)
C	1 (2)
Unknown	1 (2)
TNM stage	
I	6 (11)
II	8 (14)
III	18 (32)
IV	24 (43)
CLIP score	
0	8 (14)
1	8 (14)
2	12 (21)
3	14 (25)
4	4 (8)
5	3 (5)
Unknown	7 (13)
BCLC stage	
0	1 (2)
A	4 (7)

B	6 (11)
C	42 (75)
D	3 (5)

BCLC, Barcelona-Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus.

Table 2 Univariate analysis of the association between OS and continuous variables

Variable	HR	95% CI	*P* value
SUV_{max}	1.11	1.0026-1.23	0.045
TLG	1.00020	1.0000-1.00050	0.024
MTV	1.00050	0.99-1.0010	0.099
TNR	1.17	0.97-1.42	0.11
Age	1.00030	0.97-1.032	0.98
Creatinine level	1.74	0.74-4.11	0.20
Albumin level	0.72	0.38-1.36	0.31
Tumor size	1.11	1.015-1.21	0.022
PT	1.084	0.81-1.46	0.59
PT-INR	8.58	0.50-147.25	0.14
Total bilirubin level	1.20	1.011-1.41	0.037
ALK	1.0033	1.00050-1.0061	0.020

OS, overall survival; SUVmax, maximum standardized uptake value; TLG, total lesion glycolysis; MTV, maximum tumor volume; TNR, tumor-to-normal liver ratios of SUV; PT, prothrombin time; PT-INR, prothrombin time-international normalized ratio; ALK, alkaline phosphatase; HR, hazard ratio; CI, confidence interval.glycolysis; TNR, tumor-to-normal liver ratios of SUV.

Table 3 Log-rank test to compare OS among patient subgroups

Variable	No. of patients	No. of events	Median OS (95% CI), mo	1-year OS rate (95% CI)	2-year OS rate (95% CI)	*P* value
Age, years						
≤ 60	22	10	4.9 (3.67-NA)	0.40 (0.22-0.73)		0.16
> 60	34	14	17.0 (9.13-NA)	0.64 (0.49-0.84)	0.41 (0.23-0.73)	
Sex						
Female	7	2	NA (7.1-NA)	0.64 (0.34-1.00)		0.66
Male	49	22	16.3 (4.8-NA)	0.55 (0.41-0.72)	0.38 (0.23-0.63)	
Race/ethnicity						
Other	20	8	17.0 (3.7-NA)	0.55 (0.35-0.87)	0.28 (0.060-1.00)	0.87
Caucasian	36	16	16.3(4.9-NA)	0.56 (0.41-0.76)		
ECOG PS						
0-1	45	20	17.0 (5.1-NA)	0.57 (0.43-0.75)	0.4 (0.24-0.66)	0.02
2-3	9	4	2.9 (1.3-NA)	0.25 (0.05-1.00)		
Hepatitis infection						
HBV/HCV	27	13	4.9 (3.7-NA)	0.49 (0.32-0.76)	0.26 (0.10-0.72)	0.21

None	29	11	17.0 (7.1-NA)	0.61 (0.44-0.84)		
Cirrhosis						
No	23	10	17.0 (5.1-NA)	0.61 (0.43-0.87)	0.38 (0.18-0.81)	0.47
Yes	33	14	17.6 (4.2-NA)	0.51 (0.34-0.75)		
Varices						
No	41	18	17.0 (4.5-NA)	0.53 (0.39-0.72)	0.42 (0.25-0.72)	0.69
Yes	15	6	17.6 (7.1-NA)	0.65 (0.42-1.00)		
Endovascular invasion						
No	26	8	NA (16.3-NA)	0.74 (0.57-0.94)	0.55 (0.33-0.89)	0.0025
Yes	30	16	4.5 (3.2-NA)	0.37 (0.21-0.63)		
Focality						
Multifocal	29	14	5.1 (3.5-NA)	0.47 (0.30-0.74)		0.058
Unifocal	27	10	NA (9.1-NA)	0.64 (0.47-0.86)	0.56 (0.37-0.83)	
AFP level, ng/mL						
< 400	34	12	NA (9.1-NA)	0.63 (0.47-0.83)	0.55 (0.37-0.81)	0.16
≥ 400	20	10	7.1 (4.2-NA)	0.5 (0.3-0.82)		
Child-Pugh score						
A	37	14	17.6 (7.1-NA)	0.63 (0.48-0.82)	0.47 (0.28-0.77)	0.0016

B	17	8	5.1 (2.6-NA)	0.47 (0.26-0.84)		
C	1	1	1.3 (NA-NA)			
Tumor volume as a percentage of liver volume						
≤ 50%	32	10	NA (16.3-NA)	0.71 (0.56-0.91)	0.55 (0.36-0.85)	0.019
> 50%	20	11	4.8 (3.7-NA)	0.38 (0.21-0.72)		
TNM stage						
III/IV	42	22	5.1 (4.2-NA)	0.43 (0.29-0.64)		0.0059
I/II	14	2	NA (NA-NA)	0.92 (0.77-1.00)	0.76 (0.51-1.00)	
Ascites						
Moderate	8	4	2.1 (1.1-NA)	0.34 (0.11-1.00)		0.059
None	33	14	17.6 (7.1-NA)	0.61 (0.46-0.81)	0.43 (0.24-0.77)	
Slight	15	6	16.97 (3.5 , NA)	0.51 (0.28 , 0.94)		
CLIP score						
0	8	1	NA (16.3-NA)	1.00 (1.00-1.00)	0.75 (0.43-1.00)	0.018
1	8	4	7.1 (4.9-NA)	0.47 (0.21-1.00)		
2	12	3	17.6 (17.6-NA)	0.82 (0.63-1.00)		
3	14	7	4.8 (3.7-NA)	0.37 (0.17-0.80)		

4	4	2	3.1 (1.7-NA)			
5	3	2	17.0 (2.6-NA)	0.67 (0.30-1.00)		
BCLC stage						
0	1	0	NA (NA-NA)			0.18
A	4	1	17.0 (16.3-NA)	1.00 (1.00-1.00)		
B	6	2	NA (17.6-NA)	0.83 (0.58-1.00)	0.56 (0.23-1.00)	
C	42	20	9.1 (4.5-NA)	0.47 (0.33-0.67)		
D	3	1	1.8 (1.3-NA)			

OS, overall survival; AFP, alfa-fetoprotein; CI, confidence interval; CLIP, Cancer of the Liver Italian Program; BCLC, Barcelona-Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NA, not available.

Table 4 Multivariate Cox regression analysis using PET/CT parameters and Cancer of the Liver Italian Program (CLIP) score

Variable	Coefficient	*P* value	HR (95% CI)
CLIP 1 (vs. 0)	1.52	0.181	4.59 (0.49-42.97)
CLIP 2 (vs. 0)	1.16	0.318	3.18 (0.33-30.78)
CLIP 3 (vs. 0)	1.92	0.100	6.82 (0.69-67.01)
CLIP 4 (vs. 0)	3.78	0.004	43.96 (3.36-574.48)
CLIP 5 (vs. 0)	2.15	0.084	8.60 (0.75-99.12)
$SUV_{max} \geq 11.7$ (vs. < 11.7)	2.08	0.004	8.00 (1.96-32.76)
CLIP 1 (vs. 0)	1.67	0.140	5.31 (0.58-48.84)
CLIP 2 (vs. 0)	1.11	0.340	3.03 (0.31-29.49)
CLIP 3 (vs. 0)	2.25	0.054	9.44 (0.96-93.04)
CLIP 4 (vs. 0)	3.14	0.025	23.04 (1.50-354.97)
CLIP 5 (vs. 0)	1.88	0.149	6.57 (0.51-84.38)
TLG $\geq$ 1341 (vs. < 1341)	0.38	0.509	1.46 (0.47-4.55)
CLIP 1 (vs. 0)	1.71	0.129	5.54 (0.61-50.46)
CLIP 2 (vs. 0)	1.12	0.336	3.06 (0.31-29.70)

CLIP 3 (vs. 0)	2.28	0.050	9.76 (1.00-94.79)
CLIP 4 (vs. 0)	3.22	0.018	25.13 (1.72-367.09)
CLIP 5 (vs. 0)	1.95	0.128	7.04 (0.57-86.91)
MTV ≥ 230 mL (vs. < 230 mL)	0.33	0.571	1.39 (0.45-4.30)
CLIP 1 (vs. 0)	1.74	0.122	5.69 (0.63-51.72)
CLIP 2 (vs. 0)	1.14	0.327	3.11 (0.32-30.15)
CLIP 3 (vs. 0)	2.09	0.070	8.11 (0.84-78.33)
CLIP 4 (vs. 0)	3.60	0.005	36.57 (2.91-459.45)
CLIP 5 (vs. 0)	2.13	0.088	8.38 (0.73-95.94)
TNR ≥ 4.8 (vs. < 4.8)	1.58	0.047	4.85 (1.02-22.92)

CI, confidence interval; HR, hazard ratio; SUV_{max}, maximum standardized uptake value; TLG, total lesion glycolysis; MTV, maximum tumor volume; TNR, tumor-to-normal liver ratios of SUV.

Table 5 Multivariate Cox regression analysis using PET/CT parameters and Barcelona-Clinic Liver Cancer (BCLC) stage

Variable	Coefficient	*P* value	HR (95% CI)
BCLC B (vs. A/0)	0.20	0.870	1.22 (0.11-13.64)
BCLC C (vs. A/0)	1.07	0.300	2.92 (0.38-22.23)
BCLC D (vs. A/0)	1.63	0.284	5.09 (0.26-100.01)
$SUV_{max} \geq 11.7$ (vs. < 11.7)	1.65	0.003	5.19 (1.73-15.56)
BCLC B (vs. A/0)	0.20	0.869	1.22 (0.11-13.65)
BCLC C (vs. A/0)	0.87	0.411	2.38 (0.30-18.84)
BCLC D (vs. A/0)	2.11	0.160	8.29 (0.44-157.75)
TLG ≥ 1341 (vs. < 1341)	0.97	0.033	2.64 (1.08-6.45)
BCLC B (vs. A/0)	0.05	0.968	1.05 (0.09-11.80)
BCLC C (vs. A/0)	0.83	0.436	2.29 (0.28-18.41)
BCLC D (vs. A/0)	2.17	0.150	8.73 (0.46-166.13)
MTV ≥ 230 mL (vs. < 230 mL)	0.89	0.053	2.44 (0.99-6.02)
BCLC B (vs. A/0)	0.22	0.861	1.24 (0.11-13.82)
BCLC C (vs. A/0)	1.16	0.260	3.19 (0.42-24.08)
BCLC D (vs. A/0)	1.69	0.273	5.43 (0.26-112.19)

TNR ≥ 4.8 (vs. < 4.8)	1.48	0.021	4.37 (1.24-15.38)

CI, confidence interval; HR, hazard ratio; SUV_{max}, maximum standardized uptake value; TLG, total lesion glycolysis; MTV, maximum tumor volume; TNR, tumor-to-normal liver ratios of SUV.