JGH Open An open access journal of gastroenterology and hepatology
Open Access
JGHF Journal of Gastroenterology and Hepatology Foundation
doi:10.1002/jgh3.12676

ORIGINAL ARTICLE

Combination of psoas muscle mass index and neutrophil/lymphocyte ratio as a prognostic predictor for patients undergoing nonsurgical hepatocellular carcinoma therapy

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Key words
drug therapy, hepatocellular carcinoma, molecular targeted therapy, prognosis, sarcopenia.

Accepted for publication 4 November 2021.

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Declaration of conflict of interest: None.

Abstract

Background and Aim: Reliable predictors for hepatocellular carcinoma (HCC) are urgently needed. The psoas muscle index (PMI) is a simple and rapid method for evaluating muscle atrophy. Furthermore, the neutrophil/lymphocyte ratio (NLR) is a prognostic factor that is easy to calculate in everyday clinical practice. We aimed to investigate the value of the PMI and NLR as prognostic factors for patients receiving nonsurgical HCC therapy, hepatic arterial infusion chemotherapy (HAIC), transcatheter arterial chemoembolization (TACE), or molecular targeted drugs such as sorafenib (SOR) and lenvatinib (LEN).

Methods: We enrolled 87 patients with HCC who were treated with HAIC, TACE, SOR, or LEN. The primary endpoint was overall survival (OS) with variable PMI or NLR status. For Barcelona Clinic Liver Cancer (BCLC)-B patients, useful prognostic factors were examined by comparing the OS between stratified groups. Prognostic factors including PMI and NLR were evaluated by univariate and multivariate analysis.

Results: Analysis of HAIC or TACE (HAIC/TACE) and SOR or LEN (SOR/LEN) patients showed significant differences in OS between low and high PMI. In patients treated with TACE, there was a significant difference in OS between low and high NLR. For BCLC-B and low PMI, the prognosis was significantly worse for SOR/LEN than for TACE, although there was no difference for high PMI, suggesting that PMI may be useful for treatment selection. In addition, the prognostic formula composed of PMI, NLR, and up-to-seven criteria developed in the present study may be useful.

Conclusion: PMI and NLR are considered to be independent prognostic factors for HCC.

Introduction

Hepatocellular carcinoma (HCC) is a common cancer in patients with chronic liver disease and is the third most common cause of cancer mortality worldwide.[1] Although the principal treatment for HCC is surgical resection, some cases require treatments other than surgical resection such as radiofrequency ablation (RFA), hepatic arterial infusion chemotherapy (HAIC), transcatheter arterial chemoembolization (TACE), or molecular targeted drugs according to the status of tumor, hepatic reserve, and patient's performance status.[2] The up-to-seven criteria were initially developed by Mazzaferro and colleagues for patients who had undergone liver transplantation.[3] Because Barcelona Clinic Liver Cancer (BCLC)-B HCC comprises a heterogeneous population of patients with a wide range of tumor burdens, sub-classification of BCLC-B HCC using the up-to-seven criteria has recently been advocated.[4] Although TACE is the standard of care for BCLC-B HCC, not all BCLC-B patients are suitable candidates for TACE. TACE is not effective for substage B2 (up-to-seven criteria out) HCC and also impairs the hepatic functional reserve,[5] resulting in a poor prognosis.[6] However, if TACE is performed in appropriate cases, it can provide sufficient local tumor control.[7] Therefore, it is important to reliably predict the therapeutic effect. HAIC can be used for multiple lesions where TACE is likely to reduce hepatic reserve, but the predominantly used treatment drug, cisplatin, poses a risk of cumulative nephropathy.[8] Thus, it is important to predict the therapeutic effect in order to avoid renal failure. Molecular targeting therapy is the main treatment for HCC that

is not indicated for curative local therapy. Both sorafenib (SOR),[9] which has been used since 2009, and lenvatinib (LEN),[10,11] which has been used since 2018, are drugs that have been proven to prolong overall survival (OS) in phase 3 trials. In 2020, combination therapy with atezolizumab and bevacizumab[12] became an additional option for first-line treatment. In addition to TACE, drug therapy for HCC in BCLC-B stage may be an option in some cases. Therefore, it is important to identify predictors that can guide the selection of appropriate treatments.

In recent years, the clinical significance of sarcopenia has been reported relatively frequently in patients with primary HCC.[13] Skeletal muscle mass index (SMI) is usually used to measure muscle mass. There are two methods for examining SMI: the bioimpedance analysis method,[14] and the computed tomography (CT) image method,[15] but neither is simple to use in routine medical care because they are time consuming and require special equipment and software. Therefore, we focused on psoas muscle index (PMI), which is a very simple method that involves calculating the area of the psoas major muscle at the height of the third lumbar vertebra and the height.[16] It has the advantage that CT images are captured in most cases during medical treatment for HCC, and PMI can be easily measured in a very short time using the general radiation interpretation system attached to electronic medical records. While PMI has been shown to correlate with SMI, there is insufficient evidence regarding the relationship between PMI and treatment outcomes for HCC.[17]

The neutrophil/lymphocyte ratio (NLR), which refers to the ratio of neutrophil to lymphocyte count, is a readily available marker for assessing systemic inflammatory changes.[18] Because NLR reflects the potential balance between neutrophil-associated pro-tumor inflammation and lymphocyte-dependent anti-tumor immune function, it has been recognized as a prediction marker in the treatment of several types of cancer.[19,20]

The ability to estimate therapeutic effects in advance makes it possible to preserve the hepatic reserve and formulate a treatment strategy for HCC. We present here an investigation of the utility of PMI and NLR, which are predictors that can be easily obtained in routine clinical practice, as prognostic factors for patients undergoing nonsurgical HCC therapy, such as HAIC, TACE, SOR, or LEN.

Methods

Patients. We included 87 patients who received nonsurgical treatment including HAIC, TACE, SOR, or LEN for HCC from 1 April 2015 to 31 July 2019 at the Division of Medical Oncology, Sapporo Medical University Hospital. The diagnosis of HCC was primarily based on imaging using dynamic CT and/or Gd-EOB-DTPA-enhanced MRI. A few patients with atypical imaging findings underwent ultrasound-guided tumor biopsy for histologic assessment. Treatment for HCC was chosen mainly on the basis of HCC treatment guidelines published by the Japan Society of Hepatology.[21] According to the guidelines, HAIC is to be selected when the patient's Child−Pugh score is A or B and there is vascular infiltration or the number of tumors exceeds 3; TACE is to be selected when the patient's Child−Pugh score is A or B, there is vascular infiltration, and the number of tumors exceeds 3 or the maximum tumor diameter exceeds 3 cm; and SOR/LEN is to be selected when the Child−Pugh score is A and the patient has distant metastases, vascular infiltration, or more than three tumors.

Measurement of PMI. The sum of the left and right psoas major muscle area (cm^2) was measured from CT images at the mid-level of the third lumbar vertebra using a manual tracing method. The area was divided by height squared (m^2) to calculate PMI.[22] The measurements were performed by an investigator (SY) who was masked regarding the patient profile, treatment details, and treatment outcomes.

Measurement of NLR. Data from the most recent hematologic examination before treatment was used for the calculation of NLR. Pre-treatment NLR was calculated by dividing the neutrophil count by the lymphocyte count measured in peripheral blood.

Setting cut-off values. Receiver operating characteristic (ROC) curves were created by plotting sensitivity against 1-specificity for HAIC or TACE (HAIC/TACE) and SOR or LEN (SOR/LEN) with respect to PMI and NLR in binary form using median survival time. For PMI, cut-off values for males and females were individually calculated. Cut-off values were calculated using the Youden index.

Examination of treatment options for BCLC-B HCC. To examine treatment options for HCC patients with BCLC-B according to PMI, we set another cut-off value for PMI based on the OS rate of all patients, using ROC curves. We then divided patients into low-PMI and high-PMI groups based on the cut-off value, and we compared OS between HAIC/TACE and SOR/LEN.

Clinical parameters. Clinical characteristics, including general characteristics, demographic information, BCLC staging for HCC, up-to-seven criteria, PMI, and all laboratory data including neutrophil count, lymphocyte count, albumin, and bilirubin at the start date of HCC treatment were obtained from electronic medical records.

Primary endpoint measurement. The primary endpoint was OS of HCC patients receiving HAIC, TACE, SOR, or LEN treatment with varying PMI and NLR status. OS of each group was determined using the Kaplan–Meier method and compared by log-rank test.

Statistical analyses. All values are expressed as mean ± SD or median (first and third quartile). Univariate analyses were performed by chi-square test or Fisher's exact probability test for categorical values and by Student's *t*-test for continuous variables. OS rates were calculated and compared with the Kaplan–Meier method and the log-rank test or Cox regression. To investigate whether PMI and NLR are useful prognostic predictors for patients with HCC, we analyzed OS by Cox regression multivariate analysis. Parameters with a *P*-value <0.1 in the univariate analysis were included in the multivariate analysis. Parameters with a *P*-value <0.05 in the multivariate

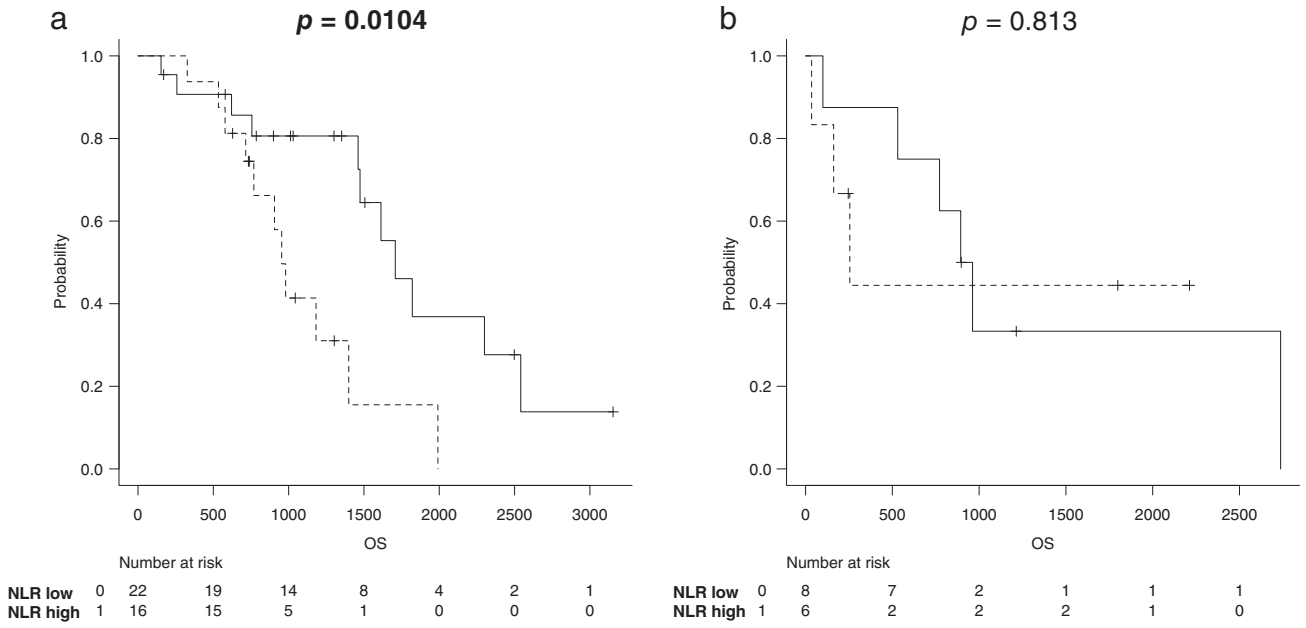

Figure 1 Overall survival (OS) of patients treated with transcatheter arterial chemoembolization (TACE) (a) and hepatic arterial infusion chemotherapy (HAIC) (b) by neutrophil/lymphocyte ratio (NLR) value (cutoff: 2.750). Patients who underwent TACE treatment received intra-arterial injection with a mixture of epirubicin (20–50 mg) and lipiodol followed by gelpart. Patients who underwent HAIC treatment received intra-arterial injection of cisplatin (65 mg/m^2) every 28 days. TACE or HAIC treatment was continued until a complete response, disease progression, or unmanageable adverse events (AEs) occurred, or the patients wished to discontinue treatment at their own discretion. (a) ——, NLR low; - - -, NLR high. (b) ——, NLR low; ----, NLR high.

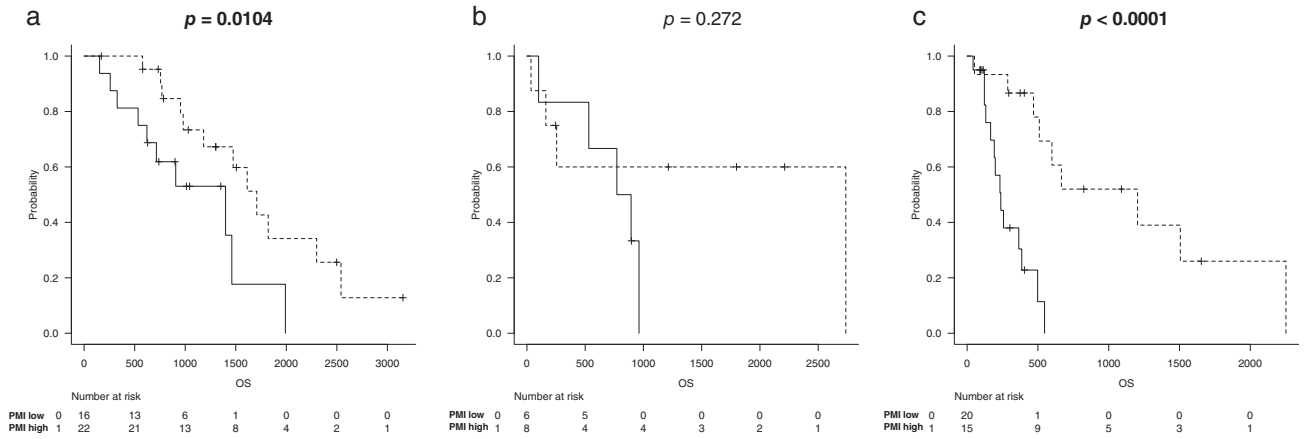

Figure 2 Overall survival (OS) of patients treated with transcatheter arterial chemoembolization (TACE) (a), hepatic arterial infusion chemotherapy (HAIC) (b), sorafenib/lenvatinib (SOR/LEN) (c) according to psoas muscle index (PMI) value (cutoff: 4.98 cm^2/m^2 for males, 3.36 cm^2/m^2 for females for HAIC/TACE or 5.66 cm^2/m^2 for males, 4.61 cm^2/m^2 for females for SOR/LEN). Patients received SOR 400 mg orally twice daily or LEN 12 mg orally once daily for those with a baseline body weight (BW) ≥60 kg and 8 mg with BW <60 kg. If patients had risk factors based on clinical features at baseline, the initial dose administered was reduced from 800 to 400 mg for SOR, or from 12 to 8 mg or from 8 to 4 mg for LEN. During treatment, clinicians could adjust the daily dose of SOR or LEN according to the frequency and severity of adverse events (AEs). SOR/LEN was continued until disease progression or unmanageable AEs occurred, or patients wished to discontinue treatment at their own discretion. (a) ——, PMI low; ----, PMI high. (b) ——, PMI low; ----, PMI high. (c) ——, PMI low; ----, PMI high.

analysis were considered independent prognostic factors. Multivariate analyses were performed using the Cox proportional hazards regression model for OS. The *P*-value threshold for statistical significance was set at <0.025 for the primary endpoint analysis and < 0.05 for other endpoints. All statistical analyses were performed using Easy R (EZR) version 1.42 software (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[23]

Ethics approval. All patient data (including laboratory indicators, imaging data, and pathology data) were obtained from the hospital's electronic information system. The present study was conducted according to Ethical Guidelines for Medical and Realth research Involving Human Subjects by the Japanese Ministry of Health, Labor, and Welfare. The study design was approved by the Institutional Review Board of Sapporo Medical University (approval number 322-147). The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist was used to develop the study.

Results

Clinical features of patients. A total of 87 consecutive patients (61 males and 26 females), with HCC treated with non-surgical treatments such as HAIC, TACE, SOR, or LEN at our department between 1 April 2015 and 31 July 2019 were investigated in this study. The median patient age was 74 years (65–79 years). The BCLC stage distribution was as follows: stage A, 29; stage B, 39; stage C, 18; and stage D, 1 patient. The

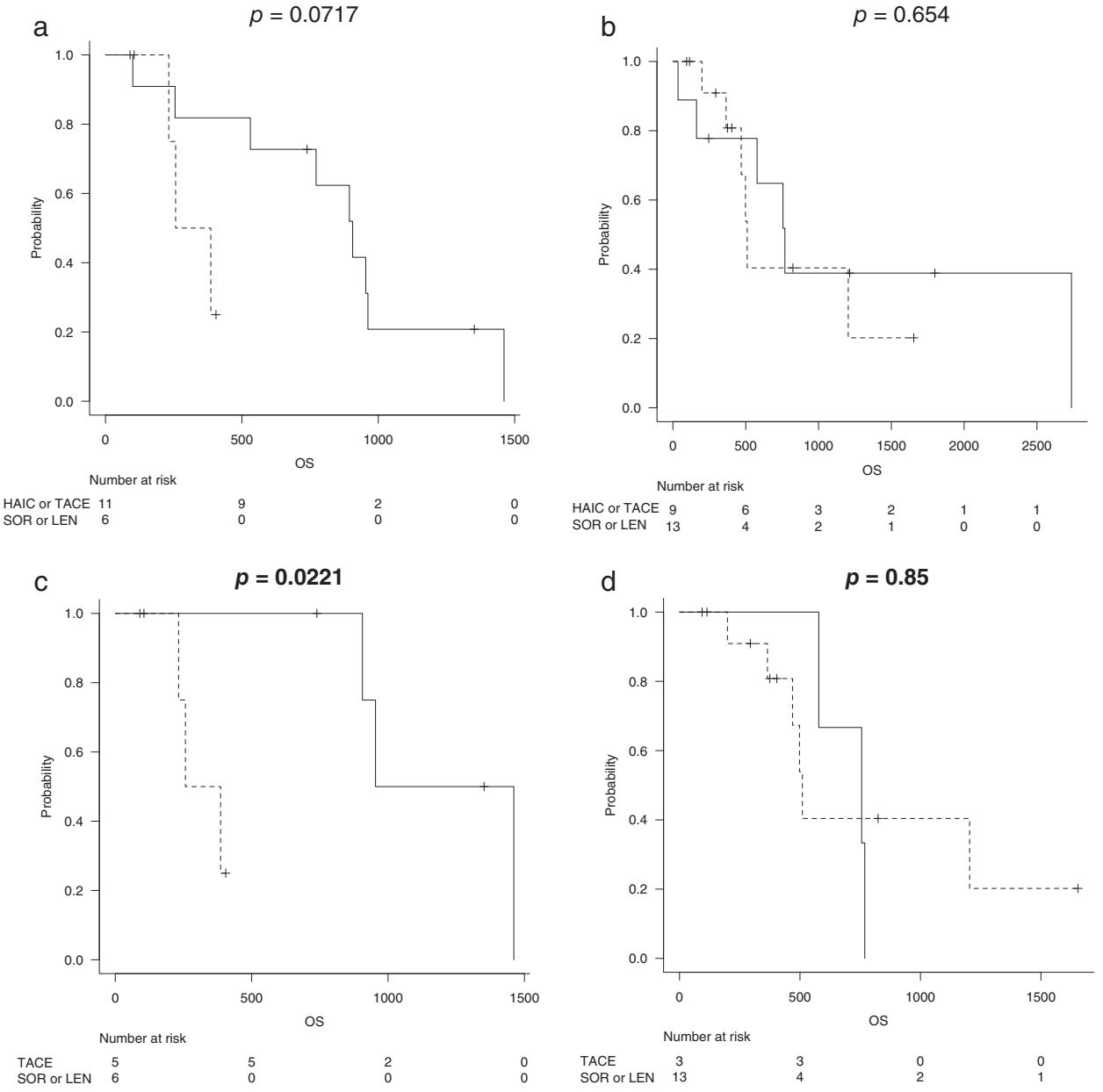

Figure 3 Examination of treatment options for Barcelona Clinic Liver Cancer (BCLC)-B stage hepatocellular carcinoma (HCC). Kaplan–Meier curves show comparisons of overall survival (OS) of patients treated with transcatheter arterial chemoembolization (TACE) or hepatic arterial infusion chemotherapy (HAIC)/TACE and sorafenib/lenvatinib (SOR/LEN) according to psoas muscle index (PMI) value (cutoff: 5.40 cm^2/m^2 for males, 3.81 cm^2/m^2 for females). Patients with low PMI are shown in (a) and (c), high PMI is shown in (b) and (d). (a) ——, HAIC or TACE; ----, SOR or LEN. (b) ——, HAIC or TACE; ----, SOR or LEN. (c) ——, TACE; ----, SOR or LEN. (d) ——, TACE; ----, SOR or LEN.

Table 1 Prognostic analysis of OS among male HCC patients

Characteristic Parameter	Univariate Cox regression		Multivariate Cox regression	
	P-value	Hazard ratio	*P*-value	Hazard ratio
Age (>70 *vs* ≦70)	0.0605	1.905 (0.9719–3.735)	0.2763	1.559 (0.7009–3.468)
BMI (kg/m^2)	0.3900	1.050 (0.94–1.172)		
BCLC (C, D *vs* A, B)	0.0158	2.390 (1.178–4.851)	0.8474	1.100 (0.4180–2.8930)
Up-to-seven criteria (out *vs* in)	0.0489	2.001 (1.003–3.99)	0.0019	3.711 (1.6230–8.4840)
NLR†	0.0199	1.269 (1.038–1.552)	0.0225	1.371 (1.0450–1.7980)
PMI†	0.0635	0.7493 (0.5523–1.017)	0.0130	0.672 (0.4912–0.9196)

†NLR and PMI were based on consecutive numerical values.

Parameters with $P < 0.1$ were included in a subsequent multivariate analysis.

ALBI grade, albumin–bilirubin grade; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; NLR, neutrophil/lymphocyte ratio; PMI, psoas muscle mass index.

Table 2 Multivariate Cox regression analysis to construct the prognostic formula

Characteristic Parameter	Multivariate Cox regression	
	P-value	Hazard ratio
Up-to-seven criteria (out *vs* in)	0.001035	3.5880 (1.6730–7.6960)
NLR†	0.0009557	1.4480 (1.1620–1.8030)
PMI†	0.003565	0.6448 (0.480–0.8662)

†NLR and PMI are investigated with consecutive numerical values.

To construct the prognostic formula, OS rates were analyzed by Cox regression multivariate analysis with three parameters, namely up-to-seven criteria, NLR, and PMI, which had *P*-values <0.05 in the multivariate analysis.

NLR, neutrophil/lymphocyte ratio; PMI, psoas muscle mass index.

treatment for HCC was as follows: TACE, 14; HAIC, 38; SOR, 17; and LEN, 18 patients. Other baseline characteristics are shown in Table S1, Supporting information. It has been previously reported that PMI varies with gender. Similarly, among the patients in this study, the average PMI for males was 5.34 ± 1.30 cm^2/m^2 and that for females was 3.98 ± 0.78 cm^2/m^2, and the difference was statistically significant ($P < 0.0001$). There was no significant difference in NLR between males and females, with an average of 2.85 ± 1.49. The median OS of the HAIC/TACE treatment group and the SOR/LEN treatment group was 1461 and 469 days, respectively.

Setting PMI and NLR cut-off values and assessment of correlation with OS. ROC curves were drawn to determine the cut-off value in this study. The PMI cut-off value was 4.98 cm^2/m^2 for males and 3.36 cm^2/m^2 for females treated with HAIC/TACE, and 5.66 cm^2/m^2 for males and 4.61 cm^2/m^2 for females treated with SOR/LEN. The NLR cut-off value for HAIC/TACE was 2.750 and for SOR/LEN was 2.473. Tables S2 and S3 show the patient backgrounds for the PMI and NLR low and high groups, respectively. There were differences in distant metastasis rate, BCLC stage, and PMI in males in the SOR/LEN treatment group between low and high NLR, but no difference in PMI among females. Other parameters were generally balanced between the groups. OS was examined by grouping into high and low PMI or NLR based on each cut-off value. There was a tendency for OS to differ between low and high NLR in the TACE treatment group (Fig. 1). There was no significant difference in OS between high and low NLR in the SOR/LEN treatment group (Figure S1). There was a tendency for OS to differ between low and high NLR in the HAIC/TACE treatment group, and a significant difference was observed in BCLC-A and BCLC-B patients (Figure S2). There were significant differences in OS between low and high PMI among the TACE treatment group and SOR/LEN treatment group (Fig. 2).

Optimal treatment selection in patients with BCLC-B HCC. Recently, molecular targeted drug therapy has been added to TACE as a treatment option for BCLC-B, making the selection of treatment more difficult. The unified cut-off value, which was calculated from the entire OS rate using the ROC curve and was not related to the treatment type, was 5.40 cm^2/m^2 for males and 3.81 cm^2/m^2 for females. Analysis of BCLC-B patients showed that low PMI tended to be associated with worse treatment outcomes in the SOR/LEN treatment group than in the HAIC/TACE treatment group (Fig. 3a). The outcome of the SOR/LEN group was statistically significantly worse than that of TACE patients (Fig. 3c) However, if PMI was high, the treatment results were equivalent (Fig. 3b,d).

Development of a novel prognostic formula and evaluation of utility. Univariate and multivariate analyses were performed with PMI and NLR as consecutive numerical values. In females, no significant prognostic predictors were detected because of the small number of cases, but in males, univariate analysis identified age (>70 years *vs* ≤70 years), BCLC stage (C, D *vs* A, B), up-to-seven criteria (out *vs* in), NLR, and PMI as significant variables ($P < 0.1$). In multivariate analysis, PMI and NLR were independent prognostic predictors along with up-to-seven criteria ($P < 0.05$) (Table 1). To create a prognostic formula, we then performed multivariate analysis with those three parameters (Table 2). From this result, we created a prognostic formula ($=0.555 \times$ [up-to-seven criteria out:1, in:0] $+ 0.161 \times$ NLR $- 0.191 \times$ PMI). The prognosis was clearly classified by quartile grouping using the values calculated by this prognosis prediction formula (Fig. 4a). A Kaplan–Meier curve was created by setting the low group and high group from the median value calculated by the prognostic formula in the HAIC/TACE treatment group and the SOR/LEN treatment group. As a

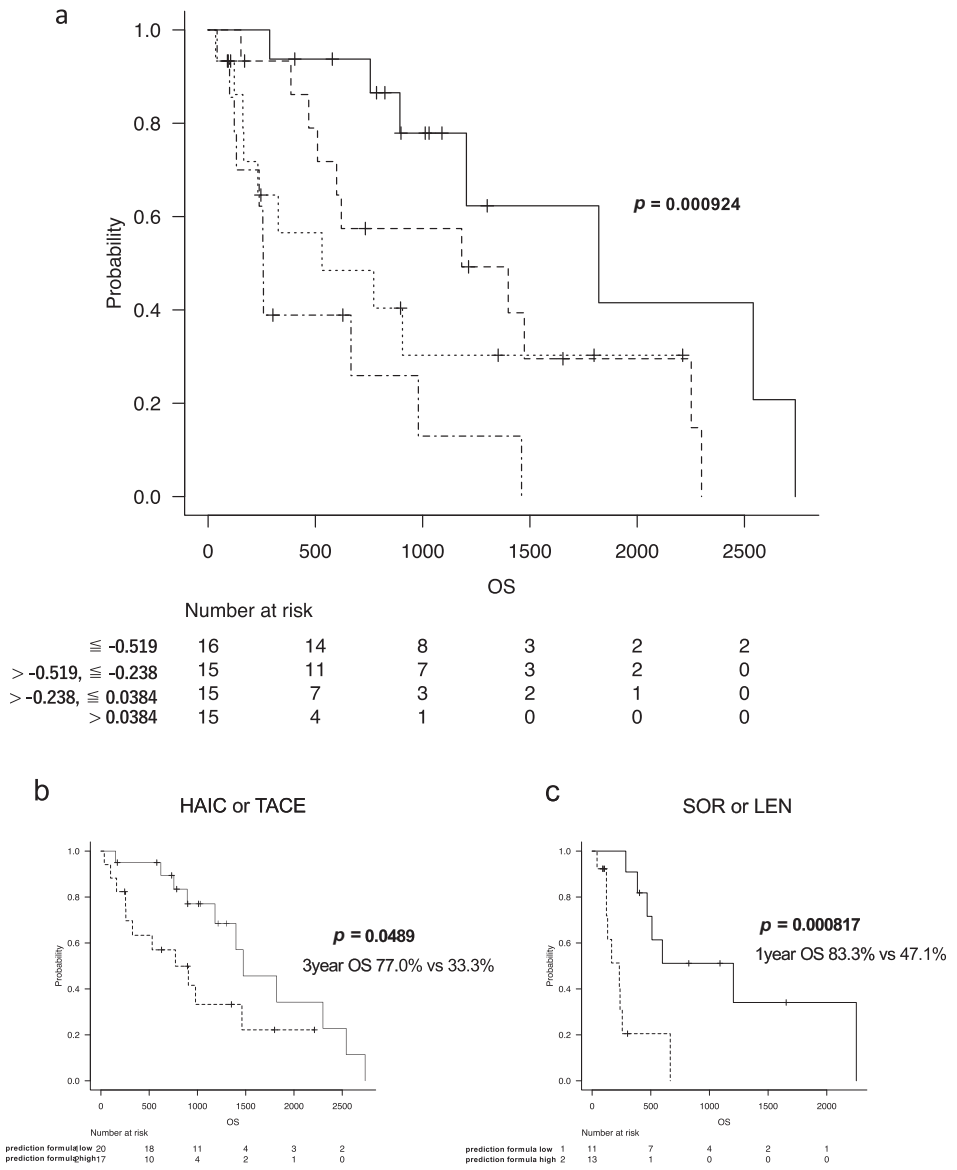

Figure 4 Validity of prediction formula (= 0.555 × [up-to-seven criteria out:1, in:0] + 0.161 × NLR − 0.191 × PMI). Kaplan–Meier curve for patient groups grouped by quartile of prediction formula (a). Overall survival (OS) grouped by median of the newly developed prediction formula in indicated treatment groups (b, c). (a) ——, ≦−0.519; - - -, >−0.519, ≤−0.238; ·····, >−0.238, ≦−0.0384; ·-·-·, >0.0384. (b) ——, prediction formula low; ----, prediction formula high. (c) ——, prediction formula low; ----, prediction formula high.

result, in the log-rank test, the low group had a significantly better prognosis than the high group of HAIC/TACE (Fig. 4b) and SOR/LEN (Fig. 4c). There was no significant difference between the groups with respect to BCLC stage (Figure S4). The prediction of 3-year survival with HAIC/TACE and 1-year survival with SOR/LEN also tended to be better with the prognostic formula than with BCLC.

Discussion

It has been reported that loss of muscle mass correlates with the prognosis of HCC[13]. A correlation between SMI, which is mainly used to evaluate muscle mass, and the prognosis following treatment for HCC has been reported for surgery,[24–26] TAE,[27] HAIC,[28,29] SOR,[30,31] and LEN.[32] PMI is easier to measure than SMI and can be measured relatively quickly, and thus it is an extremely practical evaluation method that can be used in daily practice, and its correlation with SMI has also been demonstrated.[16] There is abundant evidence showing a correlation between HCC prognosis and SMI,[14] but little evidence regarding the correlation between HCC prognosis and PMI. Prediction of the HCC prognosis using PMI has been approved for surgery,[33] RFA,[34] TACE,[35,36] SOR,[37] and LEN,[17] although supportive evidence for this approach is weaker than with SMI. However, these have all been evaluated in single treatment outcome studies, and there are no reports comparing the prognostic value of PMI for

various treatments. There are various reports on the cut-off value; Hiraoka *et al*. set it at 4.24 for males and 2.50 for females,[37] and Hamaguchi *et al*. set it at to 6.36 for males and 3.92 for females.[22] The cutoffs used in the present study (i.e. HAIC/TACE: 4.98 for males, 3.36 for females; SOR or LEN: 5.66 for males, 4.61 for females; unified cut-off value, 5.40 for males, 3.81 for females) do not seem to differ substantially from the values in previous reports. The reason why the loss of muscle mass correlates with the results of HCC treatment is that patients with HCC originally have liver cirrhosis, the frequency of sarcopenia is high, and the quality of life (QOL) and performance status (PS) are likely to decrease due to sarcopenia itself and because muscle volume depletion might be associated with appetite loss, which has been identified as a significant prognostic factor in patients treated for HCC.[17] It has also been reported that low skeletal muscle mass is associated with the occurrence of severe adverse events (AEs) in patients treated with molecular targeted therapy, and it has been suggested that skeletal muscle mass is more important than body weight (BW) in those patients.[16] With respect to BCLC-B stage HCC, it has been suggested that drug therapy is more effective than TACE in some patients,[6] which complicates the choice of treatment options. While it is important to choose whether to begin with TACE or with drug therapy in BCLC-B, it is noteworthy that in the case of BCLC-B, if the PMI was low, the molecular targeted drug was associated with a significantly poorer prognosis in this study. In other words, if PMI is low, the status of other factors should be considered, but treatment selection should be made after considering the possibility that the effect of the molecular targeted drug will be poor.

It has been pointed out that NLR correlates with prognosis in various cancer types. In particular, the correlation between NLR and prognosis has been pointed out in cases treated with molecular targeted drugs[38] and immune checkpoint inhibitors (ICIs).[39] NLR, which is the ratio of the neutrophil count to lymphocyte count, is a readily available marker for assessing systemic inflammatory changes. NLR reflects the potential balance between neutrophil-associated pro-tumor inflammation and lymphocyte-dependent anti-tumor immune function. It has also been considered for HCC, showing good results in a meta-analysis.[18] In that study, the most frequently reported cut-off value was "≥ 2 to <3", which was consistent with this study (HAIC/TACE, 2.750; SOR/LEN, 2.473).

This is the first report to simultaneously evaluate both PMI and NLR in the nonsurgical treatment of multiple HCC. While both HAIC/TACE and SOR/LEN showed a significant OS rate difference between low and high PMI, a significant difference in OS was observed between low and high NLR only among patients treated with TACE or with HAIC/TACE in the BCLC-A or -B groups. Based on these results, it was deduced that PMI may be more useful than NLR for prognosis prediction, especially in the case of molecular targeted drugs. In the analysis of continuous values of PMI and NLR, the standard values of PMI differ between males and females, so the analysis was performed by gender. Among females, the number of cases was small and the tendency was unknown, but for males PMI and NLR were independent prognostic factors in the multivariate analysis. The final model of prognostic factors was obtained with three types of explanatory variables: PMI, NLR, and up-to-seven criteria out/in. Based on these results, a prognosis prediction model was formulated and evaluated. The prognosis can be predicted with greater sensitively using this formula *versus* the BCLC stage,[40] which has an established correlation with the prognosis. A prognostic formula combining PMI and NLR has not yet been reported. NLR, which reflects the condition of the tumor, and PMI, which reflects the condition of the patient, were considered to complementarily improve the accuracy of prognosis prediction.

There are several limitations in this study. These include (i) the study was retrospective, (ii) the number of cases was small, and (iii) the external validity of the prognosis prediction formula using PMI and NLR is unknown. However, such use of PMI and NLR seems to be promising because good results were obtained in the comparison of multiple treatments. For future study, we plan to prospectively investigate additional cases. We also plan to assess the external validity of the prognosis prediction formula after accumulating more cases.

Conclusion

PMI was found to be an independent predictor of OS for all nonsurgical HCC treatments. In contrast, NLR was not a significant predictor for SOR/LEN but was a significant predictor for TACE. In BCLC-B, if the PMI was low, SOR or LEN was associated with a poor prognosis, and thus PMI might be useful for guiding the choice of treatment. The formula combining PMI and NLR appears to be useful for predicting the prognosis of HCC. Because there are several limitations in this study, further studies are warranted.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1. OS of patients treated with SOR/LEN according to NLR value (cut off: 2.473).

Figure S2. OS of patients treated with HAIC/TACE (a, b), TACE (c) and HAIC (d) by NLR value (cutoff: 2.750). Patients at any BCLC stage are shown in panel (a) and BCLC-A or -B in panels (b−d).

Figure S3. OS of patients treated with HAIC/TACE (a, b), TACE (c), HAIC (d), and SOR/LEN (e, f) according to PMI value (cutoff:

4.98 cm^2/m^2 for males, 3.36 cm^2/m^2 for females for HAIC/TACE, or 5.66 cm^2/m^2 for males, 4.61 cm^2/m^2 for females for SOR/LEN). Patients at any BCLC stage are shown in panel (a), BCLC-A or B in panels (b−e), and BCLC-C or D in panel (f).

Figure S4. OS grouped by median of other known prognostic factors. Kaplan–Meier curve in indicated patient groups by BCLC-A or B and C or D (a, b).

Table S1. Baseline characteristics of 87 patients with HCC undergoing medical treatment.

Table S2. Baseline characteristics of HCC patients treated with HAIC or TACE.

Table S3. Baseline characteristics of HCC patients treated with SOR or LEN.