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Transversal psoas muscle thickness measurement is associated with response and survival in patients with HCC undergoing immunotherapy

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Abstract

Background: Sarcopenia is a common problem in patients with HCC. We aimed to evaluate the prognostic and predictive value of baseline transversal psoas muscle thickness (TPMT) measurement in patients with HCC undergoing immunotherapy.

Methods: HCC patients treated with programmed death ligand 1–based therapies between June 2016 and October 2022 at the Vienna General Hospital (n = 80) and the Hôpital Beaujon Clichy (n = 96) were included and followed until April 2023. TPMT at the level of the third lumbar vertebra was measured independently by 2 radiologists to evaluate interreader

Abbreviations: AFP, alpha-fetoprotein; ALD, alcohol-related liver disease; BCLC, Barcelona-Clinic Liver Cancer; BOR, best overall response; CRP, C-reactive protein; CR, complete response; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICI, immune checkpoint inhibitor; IQR, interquartile range; mRECIST, modified Response Evaluation Criteria In Solid Tumors; NE, not evaluable; OS, overall survival; ORR, objective response rate; PD, progressive disease; PD-(L)1, programmed death ligand 1; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; SIRT, selective internal radiotherapy; SMI, skeletal muscle index; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; TPMT, transversal psoas muscle thickness.

Bernhard Scheiner, Katharina Lampichler, Maxime Ronot, and Matthias Pinter contributed equally.

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reliability. TPMT <12 mm/m in men and <8 mm/m in women indicated sarcopenia.

Results: Overall, 176 patients (age: 66.3 ± 11.7 y; male: n = 143, 81%, Barcelona-Clinic Liver Cancer C: n = 121, 69%) were included, of which 131 (74%) exhibited cirrhosis. Interreader agreement for the diagnosis of sarcopenia based on TPMT was 92.6%, and Cohen κ showed a "strong agreement" [κ = 0.84 (95% CI: 0.75–0.92)]. Sarcopenia, present in 58 patients (33%), was associated with shorter median overall survival [7.2 (95% CI: 5.0–9.5) vs. 22.6 (95% CI: 16.4–28.8 months); $p < 0.001$] and median progression-free survival [3.4 (95% CI: 0.2–6.8) vs. 7.9 (95% CI: 5.8–9.9 months), $p = 0.001$], and an independent predictor of overall [adjusted HR: 1.63 (95% CI: 1.07–2.48)] and progression-free mortality [adjusted HR: 1.54 (95% CI: 1.06–2.23)] in multivariable analyses. The objective response rate [evaluable in 162 subjects (92.0%)] per modified Response Evaluation Criteria In Solid Tumors (mRECIST) in patients with and without sarcopenia was 22% and 39%, respectively ($p = 0.029$). Survival and radiological responses were worse in patients with sarcopenia and systemic inflammation [median overall survival: 6.1 (95% CI: 3.6–8.6) mo; median progression-free survival: 2.8 (95% CI: 2.1–3.4) mo; objective response rate = 16%; disease control rate = 39%].

Conclusions: Evaluation of sarcopenia using TPMT measurement is reliable and identifies HCC patients with a dismal prognosis and response to immunotherapy.

INTRODUCTION

HCC is the most common primary liver cancer and the second most common cause of cancer-related mortality in men and the sixth most common cause in women, respectively.[1] Around 50%–60% of patients will receive systemic therapies during the course of the disease,[2] which is indicated for patients with advanced HCC (ie, macrovascular invasion or extrahepatic metastases) or patients with liver-limited disease not amenable to resection, transplantation, or locoregional therapies.[3] Programmed death ligand 1 [PD-(L)1]-targeted combination therapies have replaced tyrosine kinase inhibitors (TKIs) as a standard of care in systemic front-line treatment.[4] TKIs are now predominantly used in second line or first line if immune checkpoint inhibitors (ICIs) are contraindicated (eg, history of liver transplantation and severe autoimmune disease).[5,6]

PD-(L)1-based therapies can lead to unprecedented survival rates, particularly in patients with durable responses. However, only up to one third of patients shows complete response (CR) or partial response (PR), and around 20%–40% of patients have primary resistance to PD-(L)1-based regimen.[7,8] Furthermore, no validated biomarker exists to predict response or resistance to ICIs in HCC or to guide patient selection for immunotherapy in clinical practice.[9]

Sarcopenia, commonly caused by cancer-associated and treatment-associated anorexia, neuroendocrine changes, and systemic inflammation,[10] is a common problem in patients with advanced cancers, including HCC, and can be diagnosed using clinical or imaging-based methods.[11] In gerontology, sarcopenia is defined by low muscle strength associated with low skeletal muscle quantity or quality and/or low physical performance.[12] Other disciplines, including oncology and hepatology, typically only use skeletal muscle mass to define sarcopenia.[13,14] Sarcopenia is a surrogate marker for an individual's general health[15] and, as such, is associated with worse prognosis in patients with liver cirrhosis[14,16,17] and HCC.[18,19] The loss of skeletal muscle can negatively impact the immune system[20] and may, therefore, impair the efficacy of immunotherapy in cancer patients.[21] Indeed, in a large meta-analysis including 2501 patients with solid cancers treated with PD-(L)1-based regimen from 26

studies, sarcopenia was associated with worse radiological response according to Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1, overall survival (OS), and progression-free survival (PFS).[22]

This study aimed to evaluate the prognostic and predictive value of sarcopenia assessed by CT imaging or MRI–based height-adjusted transversal psoas muscle thickness (TPMT) measurement before treatment initiation in patients with HCC receiving immunotherapy.

METHODS

Patients

Patients with radiologically or histologically diagnosed HCC treated with PD-(L)1-targeted ICI-based monotherapy or combination therapy between June 2016 and October 2022 at the Medical University of Vienna/Vienna General Hospital, Austria (n = 80), and the Hôpital Beaujon Clichy, France (n = 96), were included. PD-(L)1 monotherapies included pembrolizumab (n = 19), nivolumab (n = 16), tislelizumab (n = 3), and atezolizumab (n = 1), while the only combination regimen used was atezolizumab plus bevacizumab (n = 137). We excluded patients without available contrast-enhanced images from CT or MRI before immunotherapy start (Vienna, n = 0; Hôpital Beaujon Clichy, n = 7) and those who received immunotherapy in a (neo)adjuvant setting or in combination with locoregional therapies. This study was performed in accordance with the declarations of Helsinki and Istanbul. The Ethics Committee of the Medical University of Vienna approved the retrospective data analysis (EK 2033/2017) and waived the need for written informed consent due to the retrospective study design.

Radiological evaluation

Routine CT imaging or MRI before the first administration of immunotherapy was used to measure TPMT and skeletal muscle index (SMI). Therefore, the largest transversal diameter of the right psoas muscle was measured in millimeters at the level of the third lumbar vertebral body (where the transverse processes are seen). The results were normalized to the body height in meters (mm/m). TPMT evaluations were performed by 2 independent readers (Vienna cohort: Katharina Lampichler and Lucian Beer and Clichy cohort: Maxime Ronot and Katharina Lampichler). The following previously published height-adjusted TPMT cutoffs for sarcopenia were used: <12 mm/m in men and <8 mm/m in women.[17] The SMI was calculated using OsiriX medical imaging software for iOs (Pixmeo, Version 7.5) and syngo.via software (Siemens Healthcare GmbH, Version VB30). It was defined as the total cross-sectional area of all abdominal muscles (psoas muscle, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis) at the level of the third lumbar vertebrae (L3) on a single scan image. Semiautomated demarcation of the muscle tissue was based on Hounsfield unit thresholds from −29 to +150 with manual correction by the reader (Katharina Lampichler). The calculated area (=total muscle area) was finally corrected by body height [height (m)×height (m)] resulting in the following unit: cm^2/m^2. Cutoffs were chosen according to a recent publication on the use of SMI to detect sarcopenia in patients with liver cancer.[23] While values <40.8 cm^2/m^2 denoted sarcopenia in men, a cutoff of <34.9 cm^2/m^2 was applied in women.

Outcomes and assessment

Interreader reliability of TPMT measurements and clinical outcomes were evaluated in the pooled cohort. These included PFS and OS calculated from the initiation of immunotherapy, as well as best overall response (BOR)—the best radiological response observed during immunotherapy—evaluated according to modified Response Evaluation Criteria In Solid Tumors (mRECIST).[24] The objective response rate (ORR) was defined as the proportion of patients with CR/PR as BOR. The disease control rate (DCR) was defined as the proportion of patients achieving CR/PR or stable disease (SD) as BOR. Systemic inflammation was defined by a C-reactive protein (CRP) level of ≥1 mg/dL.[25–27] The Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) was used to assess the functional status of the included patients.[28]

Statistics

Data on baseline characteristics and radiological tumor evaluation were summarized using descriptive statistics and compared by means of the χ^2 test, Student *t* test, or Mann-Whitney *U* test, as appropriate. A 2-way random-effect intraclass correlation coefficient was used to test the agreement between TPMT measurements (in mm/m), and Cohen κ was calculated to assess the interreader reliability of sarcopenia diagnosis.[29] A κ value of 0.60–0.79 denotes "moderate agreement," while a value of 0.80–0.90 indicates "strong agreement."[30] Median treatment duration was defined as the time from the date of treatment initiation until the date of last administration; patients who were still receiving immunotherapy at data cutoff were censored. Median follow-up time was calculated using the reverse Kaplan-Meier method.[31] Patients with at least 1 follow-up imaging were evaluable for assessment of BOR. PFS

was defined as the time from the date of treatment initiation until the date of the first radiologically confirmed tumor progression or death; patients alive without progression were censored at the date of last contact. OS was defined as the time from treatment start until death; patients still alive were censored at the date of last contact. Survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. Multivariable analyses were performed by Cox regression analysis. Statistical analyses were performed using IBM SPSS Statistics, version 26.0 (SPSS Inc.) and GraphPad Prism 9.1.2 (GraphPad Software).

RESULTS

Patients

In total, 176 patients were included. Most patients were male (n = 143, 81%) with a mean age of 66.3 ± 11.7 years. One hundred thirty-one patients (74%) had liver cirrhosis (Child-Pugh class A: n = 126, 72%). The majority presented with BCLC stage C [n = 121 (69%)]. Immunotherapy was administered as the first line, second line, or further line of systemic treatment in 134 (76%), 25 (14%), and 17 (10%) patients, respectively. One hundred thirty-seven (78%) patients received atezolizumab plus bevacizumab, and 39 patients (22%) underwent PD-(L)1-targeted monotherapy. Detailed baseline characteristics are demonstrated in Table 1. The median estimated follow-up was 21.2 (95% CI: 19.4–22.9) months.

Interreader reliability of height-adjusted TPMT measurements

The median difference in TPMT measurements between the 2 independent readers was 0.8 [interquartile range (IQR): 0.6–1.2] mm/m denoting excellent interreader reliability [intraclass correlation coefficient: 0.97 (95% CI: 0.96–0.98)]. Interreader agreement for the diagnosis of sarcopenia based on TPMT was 92.6%, and Cohen κ showed a "strong agreement" [κ = 0.84 (95% CI: 0.75–0.92)].

Comparison of baseline characteristics between patients with and without sarcopenia

In the pooled cohort, TPMT was assessed at a median of 21 (IQR: 5–37) days before ICI initiation, resulting in a mean value of 13 ± 3 mm/m (Table 1). According to TPMT, sarcopenia was diagnosed in 58 (33%) patients (Supplemental Figure S1, http://links.lww.com/HC9/A523). Patients with sarcopenia were slightly older (68.5 ± 10.9 vs. 65.2 ± 11.9 y, $p = 0.072$), almost exclusively male (n = 55 (95%)), and had a worse ECOG PS compared with those without sarcopenia. Sarcopenic patients had a significantly higher serum CRP value at baseline [median, 1.4 (IQR, 0.7–2.5) vs. 0.7 (IQR, 0.3–1.7) mg/dL, $p = 0.003$]. The percentage of patients with prior surgery for HCC was lower [n = 6 (10%) vs. n = 31 (26%), $p = 0.015$] in patients with sarcopenia. Liver function and BCLC stages were comparable between groups (Table 1). Sarcopenia diagnosis according to SMI cutoffs was present in almost two thirds of patients (n = 106, 60%).

Sarcopenia and survival

Nonsarcopenic patients according to TPMT cutoffs had a significantly longer median OS [22.6 (95% CI: 16.4–28.8) mo] compared with patients with sarcopenia [7.2 (95% CI: 5.0–9.5) mo, $p < 0.001$] (Figure 1 and Table 2). The presence of sarcopenia was significantly associated with higher mortality [HR: 2.20 (95% CI: 1.49–3.25), $p < 0.001$] in univariable analysis, along with ECOG PS, Child-Pugh class, alpha-fetoprotein, and serum CRP, and remained an independent predictor of mortality after adjusting for these factors in multivariable analysis [adjusted HR: 1.63 (95% CI: 1.07–2.48), $p = 0.024$] (Table 3). These results were confirmed in a subgroup analysis only including patients treated with atezolizumab and bevacizumab (Supplemental Table S1, http://links.lww.com/HC9/A523, and Supplemental Table S2, http://links.lww.com/HC9/A523). We also repeated the analyses in patients with Child-Pugh class A liver function treated with atezolizumab and bevacizumab in systemic first line. These results are displayed in Supplemental Tables S3 and S4, (http://links.lww.com/HC9/A523).

In the whole cohort, PFS was also significantly reduced in patients with sarcopenia [3.4 (95% CI: 0.2–6.8) vs. 7.9 (5.8–9.9) mo, $p = 0.001$, Table 2]. In line with the analyses of risk factors for OS, the presence of sarcopenia was significantly associated with PFS in univariable [HR: 1.77 (95% CI: 1.25–2.50), $p = 0.001$] and in multivariable analysis after adjustment for ECOG PS, Child-Pugh class, alpha-fetoprotein, and serum CRP [adjusted HR: 1.54 (95% CI: 1.06–2.23), $p = 0.023$] (Supplemental Table S5, http://links.lww.com/HC9/A523).

While nonsarcopenic patients as diagnosed by SMI tended to have a longer PFS [8.6 (95% CI: 4.8–12.4) vs. 6.2 (95% CI: 4.7–7.7) mo, $p = 0.069$], the presence of sarcopenia was not associated with any of the other outcomes of interest (Supplemental Tables S6 and S7, http://links.lww.com/HC9/A523).

TABLE 1 Patient characteristics

	All patients (N = 176)	n (%) Nonsarcopenic (n = 118)	Sarcopenic (n = 58)	*p*
Age (mean ± SD) (y)	66.3 ± 11.7	65.2 ± 11.9	68.5 ± 10.9	0.072
Sex				
Male	143 (81)	88 (75)	55 (95)	**0.001**
Etiology				
ALD	44 (25)	26 (22)	18 (31)	0.223
Viral	69 (39)	50 (42)	19 (33)	
Other	40 (23)	24 (20)	16 (28)	
Unknown	23 (13)	18 (15)	5 (9)	
Cirrhosis	131 (74)	86 (73)	45 (78)	0.501
Child-Pugh stage				
A	126 (72)	89 (75)	37 (64)	0.228
B	41 (23)	23 (20)	18 (31)	
C	9 (5)	6 (5)	3 (5)	
ECOG PS[a]				
0	120 (69)	91 (77)	29 (51)	**0.001**
1	49 (28)	25 (21)	24 (42)	
2	6 (3)	2 (2)	4 (7)	
Macrovascular invasion[b]	62 (35)	44 (38)	18 (32)	0.390
Extrahepatic metastases[c]	82 (47)	56 (49)	26 (46)	0.703
BCLC stage				
A	2 (1)	1 (1)	1 (2)	0.962
B	44 (25)	30 (25)	14 (24)	
C	121 (69)	81 (69)	40 (69)	
D	9 (5)	6 (5)	3 (5)	
Treatment before ICI				
Surgery	37 (21)	31 (26)	6 (10)	**0.015**
Ablation	23 (13)	19 (16)	4 (7)	0.089
Locoregional (TACE, SIRT, radiation)	98 (56)	70 (59)	28 (48)	0.166
Systemic	42 (24)	26 (22)	16 (28)	0.417
Line of ICI treatment				
First line	134 (76)	92 (78)	42 (72)	0.428
Second line	25 (14)	17 (14)	8 (14)	
Further line	17 (10)	9 (8)	8 (14)	
Type of ICI regimen				
Anti-PD-(L)1 monotherapy	39 (22)	22 (19)	17 (29)	0.109
Atezolizumab/bevacizumab	137 (78)	96 (81)	41 (71)	
CRP [median (IQR)] (mg/dL)[d]	0.9 (0.4-1.9)	0.7 (0.3-1.7)	1.4 (0.7-2.5)	**0.003**
CRP ≥ 1 mg/dL[d]	77 (48)	46 (43)	31 (60)	**0.044**
AFP [median (IQR)] (ng/mL)	54 (5-1266)	39 (5-1211)	131 (7-1321)	0.173
AFP ≥ 100 ng/mL	77 (44)	48 (41)	29 (50)	0.241
Overall TPMT (mean ± SD) (mm/m)	13 ± 3	14 ± 3	10 ± 1	< **0.001**
TPMT in men (mean ± SD) (mm/m)	13 ± 3	15 ± 3	10 ± 1	< **0.001**
TPMT in women (mean ± SD) (mm/m)	12 ± 4	12 ± 4	8 ± 0	**0.027**

Missing values:
[a]sarcopenic: n = 1.
[b]Nonsarcopenic: n = 3; sarcopenic: n = 1.
[c]Nonsarcopenic: n = 3; sarcopenic: n = 1.
[d]Nonsarcopenic: n = 10; sarcopenic: n = 6.
P-values <0.05 denote statistical significance and are printed in bold.
Abbreviations: AFP, alpha-fetoprotein; ALD, alcohol-related liver disease; BCLC, Barcelona-Clinic Liver Cancer; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICI, immune checkpoint inhibitor; IQR, interquartile range; PD-(L)1, programmed death ligand 1; SIRT, selective internal radiotherapy; TACE, transarterial chemoembolization; TPMT, transversal psoas muscle thickness.

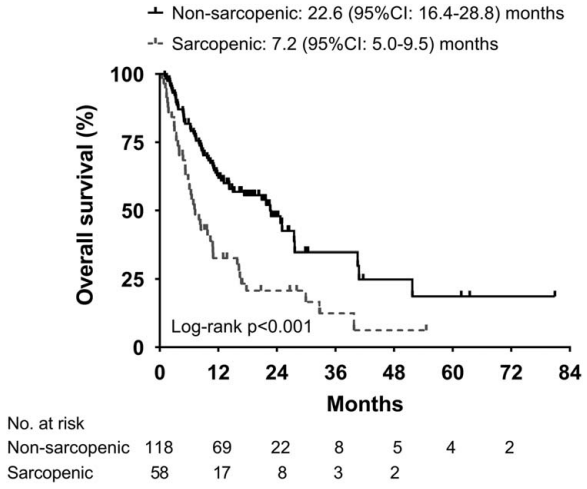

FIGURE 1 Overall survival of patients with HCC treated with immunotherapy according to the presence or absence of sarcopenia.

Sarcopenia and radiological response

The BOR could be evaluated in 113 (96%) sarcopenic and 49 (85%) nonsarcopenic individuals (Table 2). An objective response (CR/PR) was observed in 13 (22%) patients with sarcopenia as diagnosed by TPMT compared with 46 (39%) nonsarcopenic patients (p = 0.029). In line, the DCR (CR/PR/SD) was also significantly worse in sarcopenic (n = 31, 53%) compared with nonsarcopenic patients (n = 84, 71%, p = 0.020) (Table 2).

Outcomes according to the presence of sarcopenia and/or systemic inflammation

Overall, CRP levels before ICI initiation were available in 160 patients (91%), and systemic inflammation (CRP level $\geq$1 mg/dL) was observed in 77 (48%) individuals. Patients were grouped according to the presence or absence of sarcopenia as per TPMT and/or systemic inflammation into 4 prognostic groups. Accordingly, nonsarcopenic patients without systemic inflammation had the most favorable outcome [median OS: 27.5 (95% CI: 22.7–32.3) mo; median PFS: 11.7 (95% CI: 7.5–16.0) mo; ORR = 45%; and DCR = 82%], while sarcopenic patients with systemic inflammation had the worst outcome [median OS: 6.1 (95% CI: 3.6–8.6) mo; median PFS: 2.8 (95% CI: 2.1–3.4) mo; ORR = 16%; and DCR = 39%] (Table 4 and Figure 2).

DISCUSSION

Although, in gerontology, the diagnosis of sarcopenia requires the presence of low muscle strength along with low skeletal muscle quantity or quality,[12] defining sarcopenia by imaging-based assessment of skeletal muscle mass is generally well accepted in patients with cancer and liver cirrhosis.[13,14,32,33]

Indeed, sarcopenia is commonly found in patients with HCC and liver cirrhosis, and multiple factors contribute to the development of sarcopenia, including malnutrition, altered metabolism, catabolic state, hormone deficiency, and changes in cytokine levels.[11,34] In this study, including 176 patients with HCC treated with PD-(L)1-based therapies, sarcopenia determined by TPMT was present in around one third of all patients, in line with a previous meta-analysis reporting a prevalence of sarcopenia of ~39% among patients with HCC.[18] In this very meta-analysis[18] including a total of 8445 patients with HCC from 42 studies, sarcopenia was independently associated with a shorter OS [pooled adjusted HR = 1.84 (95% CI, 1.62–2.09)] and PFS [HR = 1.33 (95% CI, 1.12–1.56)]. Notably, imaging-based sarcopenia assessment varied in the studies included. Six different methods were used, with CT-based TPMT per body height being one of them.[18] This heterogeneity reflects the lack of standardized methodology and cutoffs for diagnosing sarcopenia by imaging even though a recent consensus statement

TABLE 2 Summary of survival outcomes and radiological response for HCC patients with and without sarcopenia treated with immunotherapy

	Nonsarcopenic (N = 118)	Sarcopenic (N = 58)	p
Overall survival [median (95% CI)] (mo)	22.6 (16.4–28.8)	7.2 (5.0–9.5)	< 0.001
Progression-free survival [median (95% CI)] (mo)	7.9 (5.8–9.9)	3.4 (0.2–6.8)	0.001
Best overall response [n (%)]			
CR/PR	46 (39)	13 (22)	0.018
SD	38 (32)	18 (31)	
PD	29 (25)	18 (31)	
NE	5 (4)	9 (16)	
ORR (CR+PR)	46 (39)	13 (22)	0.029
DCR (CR+PR+SD)	84 (71)	31 (53)	0.020

Abbreviations: CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

TABLE 3 Univariable and multivariable analyses of prognostic factors for overall survival in patients with HCC treated with immunotherapy

	Univariable		Multivariable	
	HR (95% CI)	***p***	**Adjusted HR (95% CI)**	***p***
Age (/y)	1.00 (0.99-1.02)	0.605	—	—
Sex (male vs. female)	1.58 (0.92–2.69)	0.096	—	—
ECOG PS (≥1 vs. 0)	**2.29 (1.53–3.41)**	**<0.001**	**1.79 (1.16–2.75)**	**0.008**
Child-Pugh class (B/C vs. A)	**2.19 (1.47–3.26)**	**<0.001**	**1.76 (1.16–2.68)**	**0.009**
Macrovascular invasion (present vs. absent)	1.34 (0.90–1.99)	0.146	—	—
Extrahepatic metastases (present vs. absent)	0.91 (0.61–1.35)	0.628	—	—
Line of systemic treatment (further line vs. first line)	1.17 (0.76–1.81)	0.476	—	—
Treatment type (atezolizumab and bevacizumab vs. ICI monotherapy)	0.78 (0.49–1.26)	0.311	—	—
Alpha-fetoprotein (≥100 vs. <100 ng/mL)	**1.78 (1.21–2.61)**	**0.003**	1.40 (0.92–2.11)	0.116
C-reactive protein (≥1 vs. <1 mg/dL)	**2.50 (1.66–3.78)**	**<0.001**	**1.89 (1.24–2.90)**	**0.003**
Presence of sarcopenia (yes vs. no)	**2.20 (1.49–3.25)**	**<0.001**	**1.63 (1.07–2.48)**	**0.024**

P-values <0.05 denote statistical significance and are printed in bold.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICI, immune checkpoint inhibitor.

recommended SMI as the best-studied method to evaluate sarcopenia in patients listed for liver transplantation.[14]

In the current study, we used TPMT at the level of L3 to assess skeletal muscle mass, showing strong interreader reliability. TPMT is an easy and quick method, widely applicable, and less resource-consuming and infrastructure-consuming than other commonly used methods, such as the SMI, which requires specific software and expertise.[32] In patients with liver cirrhosis, we previously found that sarcopenia measured by TPMT negatively impacted clinical outcomes in compensated and decompensated patients (ie, those who had already experienced portal hypertensive bleeding, developed ascites, or HE) and was independently associated with mortality.[17,35]

Previous studies on the prognostic impact of sarcopenia in HCC patients treated with immunotherapy reported conflicting results, and none of them used TPMT to assess skeletal muscle mass.[36–39] A recently published Chinese study assessed sarcopenia by SMI in 97 HCC patients receiving camrelizumab and only found an association with shorter PFS but not with OS or radiological response.[36] Similarly, a decrease in SMI during treatment with atezolizumab plus bevacizumab was associated with PFS in a small cohort of 32 HCC patients.[37] In contrast, a study including 57 patients with HCC treated with anti-PD-1–based ICIs reported no correlation between sarcopenia measured by SMI and OS or PFS.[38] Another study from China assessed sarcopenia by psoas muscle index in 160 HCC patients treated with TKIs and ICIs; they reported that

TABLE 4 Survival and radiological response according to the presence of sarcopenia and systemic inflammation (defined by CRP ≥1 mg/dL[a]) in patients with HCC treated with immunotherapy

	Nonsarcopenic+CRP <1 mg/dL (n = 62)	**Nonsarcopenic+CRP ≥1 mg/dL (n = 46)**	**Sarcopenic+CRP <1 mg/dL (n = 21)**	**Sarcopenic+CRP ≥1 mg/dL (n = 31)**	***p***
Overall survival [median (95% CI)] (mo)	27.5 (22.7–32.3)	8.9 (6.6–11.2)	15.9 (5.2–26.5)	6.1 (3.6–8.6)	<0.001
Progression-free survival [median (95% CI)] (mo)	11.7 (7.5–16.0)	5.8 (3.7–7.8)	6.9 (2.0–11.7)	2.8 (2.1–3.4)	<0.001
Best overall response					
CR/PR	28 (45)	15 (33)	7 (33)	5 (16)	0.012
SD	23 (37)	13 (28)	7 (33)	7 (23)	
PD	10 (16)	14 (30)	4 (19)	13 (42)	
NE	1 (2)	4 (9)	3 (14)	6 (19)	
ORR (CR+PR)	28 (45)	15 (33)	7 (33)	5 (16)	0.049
DCR (CR+PR+SD)	51 (82)	28 (61)	14 (67)	12 (39)	<0.001

[a]CRP missing in n = 16/176.
Abbreviations: CR, complete response; CRP, C-reactive protein; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

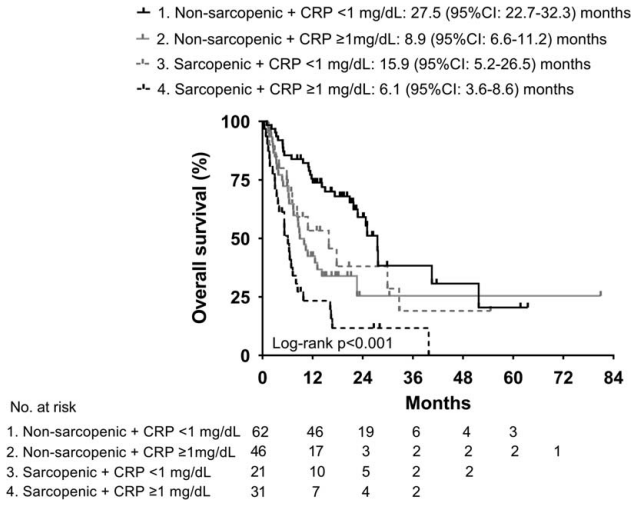

FIGURE 2 Overall survival of patients with HCC treated with immunotherapy according to the presence of sarcopenia and systemic inflammation (defined by CRP ≥ 1 mg/dL). Abbreviation: CRP, C-reactive protein.

sarcopenia and systemic inflammation (as measured by the systemic inflammation response index) were independently associated with OS and PFS.[39] Similar to our findings, patients with sarcopenia and systemic inflammation had the worst survival.[39]

An easy, quick, and reliable method to identify HCC patients with sarcopenia based on routine imaging might help to optimize patient management. TPMT facilitates the identification of at-risk patients within <2 minutes and allows the identification of patients that may particularly benefit from nutritional and psychological support, sports programs, and potentially also pharmacological therapies.[10]

Mechanistically, both sarcopenia and inflammation can promote immunosuppression and, thus, may impair the efficacy of immune-based therapies. Skeletal muscle can regulate immune system functions via the release of myokines (eg, IL-15), including activation and proliferation of natural killer cells and promoting lymphocyte and neutrophil functions.[20] Thus, loss of skeletal muscle accompanied by a decline in myokine secretion may impact immune cell functions and quantities. Indeed, HCC patients with sarcopenia had reduced peripheral blood $CD3^+$ and $CD4^+$ T-cell counts.[39]

Inflammation is a hallmark of cancer[40] and promotes several protumorigenic processes, including tumor cell proliferation and spreading, angiogenesis, and inhibition of adaptive immunity.[41] CRP—a well-recognized inflammatory marker[42]—directly promotes immunosuppression. It can suppress effector T-cell functions, inhibit the expansion of antigen-specific $CD8^+$ T cells, reduce the expression of costimulatory signals on mature dendritic cells, and promote the expansion of myeloid-derived suppressor cells.[43,44] These mechanisms might explain why patients with advanced HCC treated with PD-(L)1-based therapies presenting with elevated serum CRP had a worse radiological response and survival.[27]

There is a link between systemic inflammation and sarcopenia/muscle wasting[20] since inflammation is an underlying mechanism of cancer cachexia[45]—a multifactorial syndrome characterized by an ongoing decrease in skeletal muscle mass and a worse prognosis.[10,46] In our cohort, serum CRP, which is associated with muscle wasting, was significantly higher in patients with sarcopenia, which is well in line with previous reports.[47]

Limitations of our study include the retrospective design, which might be subject to selection and reporting bias and confounding factors. Indeed, the schedule of the radiological follow-up was not preplanned, and PFS data should, therefore, be interpreted with caution. However, all patients were followed up in 2 specialized units following standardized follow-up procedures. In line, the optimal criteria for response evaluation are still a matter of debate. We used mRECIST as it has a higher sensitivity to capture response to treatment compared with conventional RECIST.[3,48,49]

We attempted to control for potential confounding factors, such as liver function or tumor biology through multivariable analysis, but unmeasured or unknown confounders might still have influenced the results. In addition, the height-adjusted TPMT cutoffs for the presence of sarcopenia were set as previously reported for patients with liver cirrhosis.[17] However, they lack external validation in this specific setting. Finally, the lack of an untreated control group represents a limitation, as a worse prognosis does not automatically indicate a lack of treatment efficacy, and thus, treatment should not be withheld in sarcopenic patients. However, these data should stipulate interventions and research to improve sarcopenia.

CONCLUSIONS

TPMT measurement is an easy and quick method with strong interreader reliability. Sarcopenia, as measured by TPMT, was associated with worse survival in patients with HCC treated with PD-(L)1-based therapies, even aggravated when sarcopenia was accompanied by elevated CRP levels indicative of systemic inflammation. Prospective validation of both the TPMT cutoffs and our results is warranted. Whether measures to increase skeletal muscle mass, such as physical exercise and nutritional interventions, can increase immunotherapy efficacy requires further prospective evaluation.

CONFLICTS OF INTEREST

Bernhard Scheiner received travel support from AbbVie, AstraZeneca, Ipsen, and Gilead. Mohamed Bouattour received speaker fees from Bayer, MSD, Sirtex Medical,

and Roche, and advisory board fees from Bayer, MSD, Sirtex Medical, Eisai, AstraZeneca, Ipsen, Servier, Taiho, and BMS. Michael Trauner received speaker fees from Bristol-Myers Squibb (BMS), Falk Foundation, Gilead, Intercept, and Merck Sharp & Dohme (MSD); advisory board fees from Abbvie, Albireo, Boehringer Ingelheim, BiomX, Falk Pharma GmbH, GENFIT, Gilead, Hightide, Intercept, Janssen, MSD, Novartis, Phenex, Pliant, Regulus, and Shire; travel grants from AbbVie, Falk, Gilead, Intercept, and Janssen; and research grants from Albireo, Alnylam, CymaBay, Falk, Gilead, Intercept, MSD, Takeda, and Ultragenyx. He is also a coinventor of patents on the medical use of norUDCA filed by the Medical Universities of Graz and Vienna. Mattias Mandorfer served as a speaker and/or consultant and/or advisory board member for AbbVie, Gilead, Collective Acumen, and W. L. Gore & Associates, Takeda, and received travel support from AbbVie, Bristol-Myers Squibb, and Gilead. Thomas Reiberger served as a speaker and/or consultant and/or advisory board member for AbbVie, Bayer, Boehringer Ingelheim, Gilead, Intercept, MSD, Roche, Siemens, and W. L. Gore & Associates and received grants/research support from AbbVie, Boehringer Ingelheim, Gilead, MSD, Philips, and W. L. Gore & Associates, as well as travel support from Boehringer Ingelheim and Gilead. David J. Pinato received lecture fees from ViiV Healthcare, Bayer Healthcare, BMS, Roche, Eisai, and Falk Foundation; travel expenses from BMS and Bayer Healthcare; consulting fees for Mina Therapeutics, EISAI, Roche, DaVolterra, Mursla, Exact Sciences, and AstraZeneca; and research funding (to institution) from MSD and BMS. Maxime Ronot received educational fees from Ipsen, Servier, Guerbet, Sirtex, Bayer, GE Healthcare, and Canon Medical; he is a consultant for Quantum Surgical (to institution); and he received travel support from Ipsen, Servier, Guerbet, Sirtex, Bayer, GE Healthcare, and Canon Medical. Matthias Pinter is an investigator for Bayer, BMS, Eisai, Ipsen, Lilly, and Roche; he received speaker honoraria from Bayer, BMS, Eisai, Lilly, MSD, and Roche; he is a consultant for AstraZeneca, Bayer, BMS, Eisai, Ipsen, Lilly, MSD, and Roche; and he received travel support from Bayer, BMS, and Roche. The remaining authors have no conflicts to report.

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