Predictive impact of sarcopenia in solid cancers treated with immune checkpoint inhibitors: a meta-analysis

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Abstract

Sarcopenia, which is characterized by a decrease in muscle quantity or quality, is commonly observed in patients with cancer. Recent research has reported contradictory results on the association between sarcopenia and the efficacy of immune checkpoint inhibitors (ICIs). We conducted a systematic review and meta-analysis to investigate this discrepancy. We systematically searched three electronic databases to identify articles reporting on the association between sarcopenia and treatment outcomes in patients with solid cancers who received ICIs. The outcomes assessed were hazard ratios (HRs) for overall survival (OS) and progression-free survival (PFS), and odds ratios (ORs) for objective response rate (ORR), disease control rate (DCR), and toxicity. Pooled estimates and their 95% confidence intervals (CIs) were calculated. A total of 2501 patients from 26 studies were analysed. Sarcopenia was observed in 44.7% (95% CI: 38.2–51.3) of the patients and was significantly associated with poor survival (HR = 1.55, 95% CI = 1.32–1.82 for OS and HR = 1.61, 95% CI = 1.35 to 1.93 for PFS). The HRs (95% CIs) for OS according to the diagnostic measures used were 1.97 (0.88–4.41) for psoas muscle index (PMI), 1.41 (0.87–2.28) for skeletal muscle density (SMD), and 1.43 (1.23–1.67) for skeletal mass index (SMI). The HRs (95% CIs) for PFS were 1.86 (1.08–3.21) for PMI, 1.27 (0.94–1.71) for SMD, and 1.38 (1.11–1.71) for SMI. Poor radiological response to ICI therapy was observed in patients with sarcopenia (OR = 0.52, 95% CI = 0.34–0.80 for ORR and OR = 0.45, 95% CI = 0.30–0.67 for DCR). The ORs for ORR (95% CIs) were 0.56 (0.15–2.05) for PMI and 0.78 (0.56–1.09) for SMI. The oncologic outcomes associated with melanoma and non-small cell lung cancer (NSCLC) were comparable with those observed overall (HR for OS = 2.02, 95% CI = 1.26–3.24 for melanoma and HR for OS = 1.61, 95% CI = 1.19–2.18 for NSCLC). In contrast, the occurrence of severe toxicity was not associated with sarcopenia (OR = 1.13, 95% CI = 0.51–2.52). Poor survival and poor response in patients with sarcopenia indicate a negative association between sarcopenia and efficacy of ICIs. Sarcopenia’s predictive ability is consistent across various tumour types. For the selection of patients who may respond to ICIs pre-therapeutically, the presence of sarcopenia should be assessed in clinical practice.

Keywords Immune checkpoint inhibitor; Sarcopenia; Solid cancer; Non-small cell lung cancer; Melanoma
Background

Surgery, radiation, and chemotherapy have been the three main pillars of cancer treatment for decades. However, recent rapid progress in immunotherapy has changed this paradigm. Immune checkpoint inhibitor (ICI) therapy is the most frequently used immunotherapy against various cancer types. ICIs are predominantly used for the treatment of recurrent and metastatic diseases that cannot be cured with conventional therapy; however, the indications for their use have been expanding. The use of ICIs can significantly lengthen survival and sometimes result in a long duration of disease control even in patients with advanced disease and disease progression. So far, seven drugs—a tezolizumab, avelumab, cemiplimab, durvalumab, ipilimumab, nivolumab, and pembrolizumab—have been approved for use in clinical practice. Although their clinical benefit is apparent, the use of ICIs is limited owing to the associated cost. To identify patients who may benefit the most from ICIs, companion and complementary diagnostics have been developed. All ICIs, except ipilimumab, inhibit the binding between programmed death protein 1 (PD-1) and programmed death ligand 1 (PD-L1). Therefore, the immunohistochemical measurement of PD-L1 expression is employed as a tool for companion diagnostics. However, partly owing to the heterogeneous PD-L1 expression in tumour tissues, its predictive ability is not satisfactory for use in clinical practice. Other cancer immunity-associated biomarkers used for companion diagnostics include tumour mutation burden and microsatellite instability. However, when used alone, these biomarkers have limited predictive value. Efforts are underway for the identification of other biomarkers.

Sarcopenia is a skeletal muscle disorder characterized by reduced muscle strength and muscle quantity. Recently, a meta-analysis of various types of cancers demonstrated an association between sarcopenia and prognoses. In addition, an increasing number of studies are focusing on the impact of sarcopenia on ICI treatment efficacy. However, most previous studies on the topic had a retrospective design and included a small number of patients in whom various methods were employed for the diagnosis of sarcopenia. Therefore, the predictive value of sarcopenia in ICI therapy requires elucidation.

Methods

Search strategy

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We conducted a search for published studies focusing on the association between sarcopenia and ICI efficacy in the following electronic databases: PubMed, Scopus, and Ichushi-Web, which contains bibliographic information and abstracts of articles in Japanese journals. This study aimed to determine the differences between various tools and tests for sarcopenia in the following electronic databases: PubMed, Scopus, and Ichushi-Web, which contains bibliographic information and abstracts of articles in Japanese journals. This study aimed to determine the differences between various tools and tests for sarcopenia in the following electronic databases: PubMed, Scopus, and Ichushi-Web, which contains bibliographic information and abstracts of articles in Japanese journals. This study aimed to determine the differences between various tools and tests for sarcopenia in the following electronic databases: PubMed, Scopus, and Ichushi-Web, which contains bibliographic information and abstracts of articles in Japanese journals. This study aimed to determine the differences between various tools and tests for sarcopenia in the following electronic databases: PubMed, Scopus, and Ichushi-Web, which contains bibliographic information and abstracts of articles in Japanese journals. This study aimed to determine the differences between various tools and tests for sarcopenia in the following electronic databases: PubMed, Scopus, and Ichushi-Web, which contains bibliographic information and abstracts of articles in Japanese journals. This study aimed to determine the differences between various tools and tests for sarcopenia in the following electronic databases: PubMed, Scopus, and Ichushi-Web, which contains bibliographic information and abstracts of articles in Japanese journals. This study aimed to determine the differences between various tools and tests for sarcopenia in the following electronic databases: PubMed, Scopus, and Ichushi-Web, which contains bibliographic information and abstracts of articles in Japanese journals.
sarcopenia and their cut-off methods and cut-off values, and
HRs and ORs and their 95% confidence intervals (CIs). The
HRs, ORs, and 95% CIs were extracted preferentially from
multivariate or univariate analyses. When HRs were not pro-
vided in the manuscript, survival data were extracted from
Kaplan–Meier curves and estimated using the method pro-
posed by Tierney et al.37 The Newcastle–Ottawa Scale38 was
used to assess the quality of the included studies; those with
a score ≥6 were considered high-quality studies.

Statistical analysis

Pooled HRs, ORs, and their 95% CIs were estimated with both
a random effect model and a fixed effect model using
Comprehensive Meta-Analysis Version 2 (Biostat, Englewood,
NJ, USA). First, we investigated the predictive impact of
sarcopenia on OS, PFS, objective response, disease control,
and toxicity. The mean HR was used as the representative
of the study in a meta-analysis when more than one diagno-
tic procedure for sarcopenia was used.12,16,25,26,29 Second, we
conducted meta-analyses according to each diagnostic proce-
dure. Sensitivity analyses were performed by the sequential
omission of each individual study. Subgroup analyses were
conducted for primary tumour sites and ICIs. Publication bias
was assessed using the funnel plot and tested with Egger’s re-
gression intercept test. Heterogeneity was assessed using
Cochran’s Q test and I² statistics. All statistical tests were
two-sided, and significance was defined by a P-value <0.05.

Results

Literature search results

The electronic database search for articles from the inception
of each database to 4 May 2021 led to the retrieval of 597 re-
cords (Figure 1). We excluded duplicate entries and articles
written in languages other than English and Japanese and
then screened for titles and abstracts. The full texts of the
49 studies selected were then inspected according to the in-
clusion and exclusion criteria; finally, 26 studies9–33 compris-
ing 2501 patients were included in the systematic review.
Two studies by Cortellini et al. contain overlapping data.11,16
Newer and more detailed data were used when the same
outcome data were provided in both studies. All 26 articles
were written in English.

Diagnosis and prevalence of sarcopenia

Table 1 shows the characteristics of the included studies.
Nine studies each were conducted in Europe and Japan,
and three were performed in the USA. All the studies used
computed tomography (CT) as a modality to diagnose
sarcopenia. None of the included studies used question-
naires, dual-energy X-ray absorptiometry (DXA), or bioelec-
trical impedance assay (BIA). Of the diagnostic methods,
the skeletal mass index (SMI) was the most commonly
used,9–11,16,18,19,22,23,25–27,29–31,33 followed by the psoas
muscle index (PMI)14,17,20,21,24,26,28 and skeletal muscle density
(SMD).15,16,29 Of the 15 articles that employed SMI,
five10,11,18,19,29 used the cut-off value described by Martin
et al.,39 while of the seven that employed PMI, four14,24,26,28
used the cut-off value for Asian adults.40 The prevalence of
sarcopenia ranged from 21.9% to 75.0%, and the pooled

Figure 1 Flow diagram of article selection.
| Year  | Author     | Country | Site                          | Treatment                                                                 | Diagnostic method                                           |
|-------|------------|---------|-------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------|
| 2015  | Sabel      | USA     | Melanoma                      | Ipilimumab                                                                | Psoas density                                               |
| 2016  | Dercle     | France  | Melanoma, lung cancer, bladder cancer, RCC | Anti-PD1 and anti-PDL1                                                    | SMI                                                         |
| 2017  | Daly       | Ireland | Melanoma                      | Ipilimumab                                                                | Muscle loss at L3                                           |
| 2019  | Cortellini | Italy   | NSCLC                         | Nivolumab                                                                 | SMI                                                         |
| 2019  | Deike-Hofmann | Germany | Melanoma                      | Ipilimumab                                                                | Mean psoas density                                          |
| 2019  | Nishioka   | Japan   | NSCLC                         | Nivolumab and pembrolizumab                                              | Decrease of the psoas major muscle area                     |
| 2019  | Shiroyama  | Japan   | NSCLC                         | Nivolumab and pembrolizumab                                              | PMI                                                         |
| 2020  | Chu        | Canada  | Melanoma                      | Ipilimumab                                                                | SMI                                                         |
| 2020  | Cortellini | Italy   | NSCLC, melanoma, RCC, and others | Atezolizumab, nivolumab, pembrolizum, and others | SMI                                                         |
| 2020  | Crombe     | France  | Metastatic solid cancers      | Anti-PD1, anti-PDL1, and anti-PDL1/CTLA4                                  | PMI decrease                                               |
| 2020  | Fukushima  | Japan   | Urothelial carcinoma          | Pembrolizumab                                                            | SMI                                                         |
| 2020  | Hirsch     | France  | Solid cancer                  | Nivolumab                                                                 | SMI                                                         |
| 2020  | Hu         | USA     | Melanoma                      | Pembrolizumab                                                            | SMI                                                         |
| 2020  | Kim N      | Korea   | HCC                           | Nivolumab and pembrolizumab                                              | SMI                                                         |
| 2020  | Kim Y      | Korea   | Gastric cancer                | Pembrolizumab and nivolumab                                              | SMI                                                         |
| 2020  | Minami     | Japan   | NSCLC                         | Nivolumab, pembrolizumab, and atezolizumab                               | SMI                                                         |
| 2020  | Roch       | France  | NSCLC                         | Nivolumab and pembrolizumab                                              | SMI decrease                                               |
| 2020  | Shimizu    | Japan   | Urothelial carcinoma          | Pembrolizumab                                                            | SMI                                                         |
| 2020  | Takada     | Japan   | NSCLC                         | Nivolumab and pembrolizumab                                              | SMI decrease                                               |
| 2020  | Tsukagoshi | Japan   | NSCLC                         | Nivolumab and pembrolizumab                                              | SMI decrease                                               |
| 2020  | Young      | USA     | Melanoma                      | Nivolumab and pembrolizumab, nivolumab, pembrolizumab, and atezolizumab  | SMI                                                         |
| 2021  | Akce       | Canada  | HCC                           | Anti-PD-1 antibody                                                       | SMG                                                         |
| 2021  | Loosen     | Germany | NSCLC, melanoma, urothelial cancer, GI cancer, head and neck cancer, and others | Nivolumab, pembrolizumab, nivolumab + ipilimumab, and others | SMI                                                         |
| 2021  | Nishioka   | Japan   | NSCLC                         | Nivolumab, pembrolizumab, and atezolizumab                               | SMI decrease                                               |
| 2021  | Youn       | Canada  | Melanoma                      | Nivolumab or nivolumab + ipilimumab                                      | SMI                                                         |

DCR, disease control rate; GI, gastrointestinal; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; N/A, not available; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PMI, psoas muscle index; SMD, skeletal muscle density; SMG, skeletal muscle gauge; SMI, skeletal muscle index.
| Year | Cut-off value | Outcome | No. of patients | Age median [range] (interquartile range) | Gender (male/female) | Newcastle–Ottawa scale |
|------|---------------|---------|----------------|----------------------------------------|---------------------|------------------------|
| 2015 | Highest quartile | DCR, ORR, and OS | 44 | 55.1 [15–90] | 84/49 | 4 |
| 2016 | 53 | OS | 251 | 56 ± 13 | 131/120 | 7 |
| 2017 | 7.5% (lowest quartile) | Male, 43 for BMI < 25, 53 for BMI ≥ 25; Female, 41 | Toxicity | 84 | 54 [22–85] | 52/32 | 7 |
| 2019 | Male, 43 for BMI < 25, 53 for BMI ≥ 25; Female, 41 | ORR and toxicity | 22 | 67 [41–82] | 18/5 | 4 |
| 2019 | 10% | PFS | 147 | 60 {49.5–66.5} | 90/57 | 7 |
| 2019 | Male, 6.36; Female, 3.92 | DCR, ORR, and PFS | 38 | 68.7 [46–85] | 26/12 | 4 |
| 2020 | Male, 6.36; Female, 3.92 | DCR, ORR, OS, PFS, and toxicity | 97 | 56 [25–91] | 58/39 | 6 |
| 2020 | BMI > 25; 20 HU; BMI < 25; 42 | ORR, OS, and PFS | 100 | 66 [25–88] | 67/33 | 6 |
| 2020 | 5% | DCR, PFS, and OS | 142 | 63.54 ± 10.58 | 93/49 | 5 |
| 2020 | Male, 52.4; Female, 38.5 | DCR, PFS, and OS | 142 | 63.54 ± 10.58 | 93/49 | 5 |
| 2020 | Male, 6.36; Female, 3.92 | OS and PFS | 27 | 73 [52–82] | 23/4 | 5 |
| 2020 | Male, 6.36; Female, 3.92 | OS and PFS | 27 | 73 [52–82] | 23/4 | 5 |
| 2020 | Male, 25.63; Female, 21.73 | DCR, ORR, OS, and PFS | 103 | 67 [36–88] | 84/19 | 5 |
| 2020 | Male, 6.36; Female, 3.92 | DCR, ORR, OS, and PFS | 103 | 67 [36–88] | 84/19 | 5 |
| 2020 | Male, 3 for BMI < 25, 33 for BMI ≥ 25 | DCR, ORR, OS, and PFS | 287 | 63 [20–89]; 61 ± 14.4 | 184/103 | 7 |
| 2020 | Male, 43; Female, 39 | OS and PFS | 57 | Median 66 | 44/13 | 5 |
| 2020 | Male, 43; Female, 39 | OS and PFS | 57 | Median 66 | 44/13 | 5 |
| 2020 | Male, 43; Female, 39 | OS and PFS | 57 | Median 66 | 44/13 | 5 |
| 2020 | Male, 0.4 | OS | 88 | 67 [34–87] | 58/30 | 6 |
| 2020 | Male, 43; Female, 39 | OS and PFS | 57 | Median 66 | 44/13 | 5 |
| 2020 | Male, 43; Female, 39 | OS and PFS | 57 | Median 66 | 44/13 | 5 |
| 2020 | Male, 0.4 | OS | 88 | 67 [34–87] | 58/30 | 6 |
| 2020 | Male, 0.4 | OS | 88 | 67 [34–87] | 58/30 | 6 |
prevalence of sarcopenia was 44.7% (95% CI: 38.2–51.3) (Supporting Information, Figure S1).

**Overall survival and sarcopenia**

Eighteen studies investigated the association between sarcopenia and OS. The HRs for OS ranged from 0.76 to 6.21. Multivariate analyses were performed in 13 studies. HRs were estimated using the Kaplan–Meier curve in three studies. The meta-analysis demonstrated the significant predictive ability of sarcopenia for OS (HR [95% CI] 1.55 [1.32–1.82]) (Figure 2A). The results of the sensitivity analysis are shown in the Supporting Information, Table S1.

The HRs for OS according to the diagnostic measures used are shown in the Supporting Information, Table S2. PMI, SMD, and SMI were employed for dichotomization in five, four, and 10 studies, respectively. The HRs (95% CIs) were 1.97 (0.88–4.41) for PMI, 1.41 (0.87–2.28) for SMD, and 1.43 (1.23–1.67) for SMI. There were no significant differences among the different diagnostic measures (P = 0.507).

**Progression-free survival and sarcopenia**

Eighteen studies investigated the association between sarcopenia and PFS. Multivariate analysis was performed in 14 studies. The HRs for PFS were estimated using the Kaplan–Meier curve analysis in two studies. Sarcopenia was significantly associated with worse PFS values (random effect model, HR [95% CI] 1.61 [1.35–1.93]) (Figure 2B). The results of the sensitivity analysis are shown in the Supporting Information, Table S3. The result was similar when any individual study was removed from the analysis.

The HRs for PFS according to the diagnostic measures employed are shown in the Supporting Information, Table S4. PMI, SMD, and SMI were employed for dichotomization in five, four, and nine studies, respectively. SMI and PMI were predictors of PFS (HR = 1.38, 95% CI = 1.11–1.71; and HR = 1.86, 95% CI = 1.08–3.21, respectively). In contrast, SMD was not associated with PFS (HR = 1.27, 95% CI = 0.94–1.71). There were no significant differences among the different diagnostic measures (P = 0.207).

**Objective response and sarcopenia**

Objective response rate was investigated in 15 studies. Only one study used multivariate analyses. The ORs for ORR ranged from 0.03 to 5.26.
Sarcopenia was significantly associated with worse response (OR = 0.52, 95% CI = 0.34–0.80) (Figure 3A). The results of the sensitivity analysis are shown in the Supporting Information, Table S5. The result was similar when any individual study was removed from the analysis.

PMI, SMD, and SMI were employed for dichotomization in five,14,20,24,28 four,15,16,29,31 and seven studies,16,18,22,23,27,29,31 respectively. The ORs for each procedure showed a tendency for worse response in sarcopenia patients. The pooled ORs (95% CIs) were 0.56 (0.15–2.05) for PMI, 0.51 (0.22–1.71) for SMD, and 0.78 (0.56–1.09) for SMI (Supporting Information, Table S6). There were no significant differences among the different diagnostic measures (P = 0.153). The ORs and 95% CIs for other diagnostic procedures are also shown in the Supporting Information, Table S6.

**Disease control and sarcopenia**

Disease control rate was investigated in 10 studies.8,13–15,22–25,27,28 None of the 10 studies performed multivariate analyses for DCR. The ORs for DCR ranged

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**Figure 2** Forest plot showing the hazard ratios for overall survival (A) and progression-free survival (B) between the sarcopenia and non-sarcopenia patients. The squares represent the hazard ratios for each study. The sizes of the squares and the horizontal lines crossing the squares represent the weight of the study in the random effect model and the 95% confidence intervals, respectively.
from 0.07 to 1.79. The pooled OR (95% CI) in the 10 studies was 0.45 (0.30–0.67) (Figure 3B). Although the studies by Minami and Tsukagoshi seemed to be outliers, the exclusion of either study did not change the results significantly (Supporting Information, Table S7).

Pssoas muscle index and SMI were employed for dichotomization in three studies each14,24,28.22,25,27 The pooled ORs (95% CIs) were 0.47 (0.09–2.52) for PMI and 0.51 (0.34–0.78) for SMI (Supporting Information, Table S8). There were no significant differences among the different diagnostic measures (P = 0.754).

**Subgroup analysis**

Subgroup analyses using a random effect model were performed according to the primary tumour site (Table 2). Melanoma and non-small cell lung cancer (NSCLC) were the most commonly investigated tumours; other tumours were included only in two or fewer studies. The pooled HRs and ORs for melanoma and NSCLC showed a statistically significant association between sarcopenia and worse OS, worse PFS, and worse DCR. Similar results were obtained with other types of tumours, although some failed to show a significant result.

Next, we conducted a subgroup analysis for the ICI drugs (Table 3). Data on ICI monotherapy were investigated in four studies on Ipilimumab,8,10,12,15 five on Nivolumab,11,19,21,23,28 and three on pembrolizumab.18,20,26 HR for OS and PFS, OR for ORR, and DCR favoured non-sarcopenia in all drugs. The difference among the drugs was not significant with respect to any outcomes (P = 0.670 for OS, P = 0.291 for PFS, P = 0.107 for ORR, and P = 0.876 for DCR).

**Figure 3** Forest plot showing the odds ratios for objective response rate (A) and disease control rate (B) between the sarcopenia and non-sarcopenia patients. The squares represent the hazard ratios for each study. The sizes of the squares and the horizontal lines crossing the squares represent the weight of the study in the random effect model and the 95% confidence intervals, respectively.
Severe toxicity and sarcopenia

The incidence of severe toxicity was assessed in seven studies.\textsuperscript{8,11,15,17,19,23,26} Of them, two performed multivariate analyses\textsuperscript{17,19}. The ORs for severe toxicity ranged from 0.26 to 5.34. The pooled OR (95% CI), irrespective of the diagnostic procedure, was 1.13 (0.51–2.52) (Figure 4).

Publication bias

Figure 5 shows funnel plots of the HRs and ORs for the relationship between sarcopenia and OS, PFS, DCR, ORR, and toxicity. These funnel plots showed apparent asymmetry towards higher HRs and asymmetry towards lower ORs. The P values derived from the Egger’s test of the intercept were 0.006 for OS, 0.013 for PFS, 0.008 for ORR, 0.263 for DCR, and 0.592 for severe toxicity.

Discussion

In the present study, we found that sarcopenia could predict the response to ICIs and survival after ICI treatment for solid cancers and that its presence was not associated with severe toxicity.

| Table 2 | Hazard ratios and odds ratios according to the primary tumour site |
|---------|-------------------------------------------------------------------|
|         | No. of studies | No. of patients | Estimates | Lower limit | Upper limit | P-value |
| OS      |               |                 |          |            |            |         |
| Gastric cancer | 1  | 149             | 1.01     | 0.58       | 1.75       | 0.972   |
| HCC     | 2            | 159             | 1.40     | 0.91       | 2.14       | 0.121   |
| Melanoma | 6  | 583             | 2.02     | 1.26       | 3.24       | 0.003   |
| NSCLC   | 6            | 551             | 1.61     | 1.19       | 2.18       | 0.002   |
| Urothelial cancer | 2  | 55              | 2.49     | 1.00       | 6.20       | 0.051   |
| PFS     |               |                 |          |            |            |         |
| Gastric cancer | 2  | 180             | 1.86     | 1.20       | 2.87       | 0.005   |
| HCC     | 2            | 159             | 1.05     | 0.69       | 1.60       | 0.813   |
| Melanoma | 4  | 558             | 1.53     | 1.13       | 2.07       | 0.006   |
| NSCLC   | 8            | 631             | 1.69     | 1.24       | 2.31       | 0.001   |
| Urothelial cancer | 2  | 55              | 3.32     | 1.55       | 7.11       | 0.002   |
| ORR     |               |                 |          |            |            |         |
| Gastric cancer | 2  | 178             | 0.68     | 0.27       | 1.69       | 0.406   |
| HCC     | 1            | 102             | 0.31     | 0.04       | 2.59       | 0.282   |
| Melanoma | 4  | 584             | 0.63     | 0.30       | 1.31       | 0.295   |
| NSCLC   | 7            | 465             | 0.49     | 0.20       | 1.22       | 0.127   |
| Urothelial cancer | 1  | 28              | 0.13     | 0.02       | 0.78       | 0.026   |
| DCR     |               |                 |          |            |            |         |
| Gastric cancer | 1  | 147             | 0.48     | 0.24       | 0.94       | 0.032   |
| HCC     | 1            | 102             | 0.80     | 0.29       | 2.17       | 0.657   |
| Melanoma | 2  | 141             | 0.28     | 0.12       | 0.66       | 0.003   |
| NSCLC   | 6            | 429             | 0.43     | 0.22       | 0.87       | 0.019   |

CI, confidence interval; DCR, disease control rate; HCC, hepatocellular carcinoma; HR, hazard ratio; NSCLC, non-small cell lung cancer; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS; progression-free survival.

| Table 3 | Hazard ratios and odds ratios according to immune checkpoint inhibitors |
|---------|-------------------------------------------------------------------------|
|         | No. of studies | No. of patients | Estimates | 95% CI | P-value |
| OS      |               |                 |          |       |         |
| Ipilimumab | 3  | 225             | 2.20     | 1.44   | 3.35   | 0.000   |
| Nivolumab | 2  | 132             | 1.63     | 0.88   | 3.03   | 0.121   |
| Pembrolizumab | 2  | 55              | 2.49     | 1.00   | 6.20   | 0.051   |
| PFS     |               |                 |          |       |         |
| Ipilimumab | 2  | 244             | 1.73     | 1.25   | 2.38   | 0.001   |
| Nivolumab | 3  | 163             | 1.74     | 0.95   | 3.20   | 0.072   |
| Pembrolizumab | 2  | 55              | 3.32     | 1.55   | 7.11   | 0.002   |
| ORR     |               |                 |          |       |         |
| Ipilimumab | 2  | 141             | 0.16     | 0.04   | 0.62   | 0.008   |
| Nivolumab | 4  | 185             | 0.44     | 0.11   | 1.72   | 0.239   |
| Pembrolizumab | 2  | 184             | 0.43     | 0.06   | 2.82   | 0.375   |
| DCR     |               |                 |          |       |         |
| Ipilimumab | 2  | 141             | 0.28     | 0.12   | 0.66   | 0.003   |
| Nivolumab | 2  | 132             | 0.34     | 0.03   | 3.48   | 0.367   |

CI, confidence interval; DCR, disease control rate; HR, hazard ratio; OR, odds ratio; ORR, objective response rate.
Immune checkpoint inhibitors and sarcopenia

The increased mortality observed in the sarcopenia patients was consistent across various cancer types. Immune checkpoint inhibitors exhibit dramatic and long-term effects in some patients, while imposing immune-related adverse events (irAEs) without survival benefits in others. To personalize treatment, facilitate the cost-effective use of ICIs, and avoid unnecessary irAEs, predictive and prognostic biomarkers have been sought. Some predictive factors for ICI treatment include PDL-1 expression, haematologic markers, tissue infiltration lymphocytes, metastatic site, inflammatory cytokines, T cell markers, and irAEs. Sarcopenia has been shown to be a prognostic marker of cancer and a predictive marker of toxicity during chemotherapy. A recent meta-analysis on NSCLC showed that the loss of CT-defined skeletal muscle mass affected the efficacy of ICIs. However, the predictive role of sarcopenia in other types of cancer remains to be elucidated. 

Figure 4 Forest plot showing the odds ratios for severe toxicity between the sarcopenia and non-sarcopenia patients. The squares represent the hazard ratios for each study. The sizes of the squares and the horizontal lines crossing the squares represent the weight of the study in the random effect model and the 95% confidence intervals, respectively.

Figure 5 Funnel plot of the hazard ratios for overall survival (A) and progression-free survival (B), and funnel plot of the odds ratio for objective response rate (C), disease control rate (D), and severe toxicity (E).
Moreover, although several diagnostic procedures for sarcopenia have been used in the oncologic field, it remains to be elucidated which procedure best predicts the efficacy of ICIs.

Sarcopenia is a muscle disease defined by muscle quantity or quality. A variety of diagnostic tests and tools are used to detect and diagnose sarcopenia. These include the SARC-F questionnaire, physical performance tests, muscle strength tests, anthropometric measures, and skeletal muscle measurements. Among them, muscle measurements using CT, dual-energy X-ray, and BIA are popular in the oncology research field. DXA requires special equipment, and the accuracy of BIA is affected by dehydration, which is commonly observed in patients with advanced cancer. In contrast, patients with cancer routinely undergo CT for tumour assessment. Thus, CT is the modality of choice for the diagnosis of sarcopenia in the oncologic field. SMI is the most commonly used index in the literature and is calculated as the total skeletal muscle area at the third lumbar vertebra level divided by the height squared. This index has been shown to be closely correlated with whole body muscle and is associated with various health-related outcomes. PMI is frequently used in research from Japan, it uses the psoas major muscle area instead of the total skeletal muscle area. PMI is easier to calculate, and a cut-off value has been proposed for Asian adults. However, some argue that PMI is not a good indicator of sarcopenia. When PMI and SMI as continuous variables were applied to the same cohort, their HRs for PFS showed comparable values. Similarly, our meta-analysis showed that the HRs for OS and PFS were comparable between the two indices, although statistical significance in OS for PMI was not reached owing to the statistical power. Therefore, both SMI and PMI could be used as predictive factors for ICIs.

Previous meta-analyses on cancer and sarcopenia incorporated only SMI or other muscle mass evaluations as a requirement for inclusion. However, we allowed the inclusion of other methods, such as SMD, muscle mass decrease, and skeletal muscle gauge (SMG). The European consensus statement notes that low muscle quantity or quality is required for the confirmation of sarcopenia diagnoses. On CT images, the muscle mass area represents muscle quantity, while the muscle density reflects muscle quality. The impairment of muscle quality and infiltration of fat into the skeletal muscle can be indicative of muscle density decrease. SMD is a widely used index for muscle quality and has been shown to be a prognosticator in cancer. Moreover, SMD, but not SMI, was shown to be associated with physical function, indicating that it may be a better marker for severe sarcopenia. However, the results of the present meta-analysis demonstrated that SMD could not predict the survival in patients treated with ICIs. In addition, SMG, an index in which the quantity and quality of skeletal muscle are integrated, was not a predictor of ICI therapy. Patients with cancer lose weight due to decreased food intake, a catabolic state induced by cancer, and anti-cancer treatment. Weight loss is a well-established prognostic factor in patients with cancer. Similarly, patients with cancer experience loss of skeletal muscle after diagnosis and a decline in gait speed even before diagnosis. Owing to the small number of studies and differences in the diagnostic procedures, we did not synthesize HRs pertaining to the progression of sarcopenia in the present meta-analysis. Collectively, of the various sarcopenia measures, muscle mass or its change can be a predictive factor for the efficacy of ICIs.

It may be argued that sarcopenia is reflective of a person’s advanced disease status and deteriorated physical condition, resulting in a worse survival. However, our ORR and DCR results suggest that sarcopenia is not a mere prognostic factor but also a predictive factor. Skeletal muscle is known to release myokines, which are muscle-derived cytokines that exert their effects through the autocrine, paracrine, and endocrine routes. Among the myokines, interleukin (IL)-15 increases the proportion of circulating natural killer cells and CD8+ T cells. More importantly, the administration of IL-15 in combination with ICIs prolonged the survival of tumour-bearing mice. Thus, changes in the myokine levels as a result of sarcopenia may affect the efficacy of ICI treatment, indicating the predictive value of sarcopenia in this therapy.

Skeletal muscle decrease after the initiation of ICIs treatment; that is, PMI and SMI decrease showed higher HRs than pretreatment sarcopenia did (Supporting Information, Tables S2 and S4). There are several causes for sarcopenia associated with cancer treatment, which include impaired food intake, reduced activity secondary to fatigue, and a direct effect of drugs on muscle. Cytotoxic anti-cancer drugs, including cisplatin, irinotecan, doxorubicin, and etoposide, increase proteinolysis through NF-κB and inflammatory cytokines, resulting in sarcopenia. Mammalian target of rapamycin (mTOR) is one of the key enzymes involved in the maintenance of skeletal muscle. Activation of mTOR pathway induces muscle hypertrophy, while blockade of the pathway leads to muscle atrophy. Everolimus and temsirolimus, mTOR inhibitors used for renal cancer, induced a marked loss of muscle mass in clinical settings. In vitro experiments demonstrated that pembrolizumab activated mTOR pathway. Therefore, ICIs could affect skeletal muscle directly. Several studies have reported change in skeletal mass after ICIs therapy. Supporting Information, Table S9 summarises the results of these studies. Six out of seven studies assessed skeletal muscle change from 3 weeks to 3 months after baseline and showed reduced muscle mass or muscle attenuation. On the contrary, long-term survivors treated with ICIs showed increased SMI.
and SMG. This discrepancy between short-term and long-terms might indicate that the direct effect of ICIs on skeletal muscle is minimal and that skeletal muscle loss in short-term reflects cancer progression and resultant cachexia in non-responders. Therefore, higher HRs associated with progressive muscle loss could suggest worse survival in non-responders.

This study has several strengths. First, we investigated a large number of patients using a meta-analysis. The studies included in the present meta-analysis were small-scale retrospective studies. By combining the results, we obtained more reliable estimates of the predictive impact of sarcopenia. Till this date, only one published meta-analysis has focused on the effect of sarcopenia on ICI efficacy. However, while the previous meta-analysis included 576 patients with NSCLC, the present study enrolled 2501 patients with solid cancers, providing a more comprehensive understanding of the predictive ability of sarcopenia. Another strong point is the broad inclusion criteria for muscle measurement. This enabled us to decide which method would be suitable for the prediction of ICI efficacy.

However, our study also has some limitations that must be considered. First, the studies included were of a retrospective nature. A majority of the enrolled studies retrospectively collected patient data. For the precise determination of the response rate and PFS, predefined protocols are mandatory. Second, the methods used for the calculation of the HRs and ORs differed across the studies. Although the use of data from multivariate analyses was desirable, we also included HRs from univariate analyses and estimated HRs from Kaplan–Meier curves. Moreover, the ORs for ORR were adjusted in only one study and those for DCR were not adjusted in any of the studies. Even when the HRs were adjusted for confounders, the adjustment was not sufficient owing to the limited number of events. In the investigation of the factors predictive of ICI efficacy, adjustment with established predictive factors, such as PD-L1 expression or tumour mutation burden, is required. In addition, when investigating the effect of sarcopenia, adjustment with relevant factors, such as body mass index, performance status, and nutritional parameters should be conducted. Third, the cut-off values associated with the same diagnostic measure varied across the studies. Seven and three cut-off values were used for PMI and SMI, respectively. The effect of cut-off values should be investigated using meta-regression analyses in future studies. Finally, there existed significant publication bias, as shown in Figure 5. To reduce the degree of publication bias, we attempted to include non-English articles. Researchers from non-English-speaking countries tend to publish studies of a weaker impact in their local journals and those with positive results in international journals. To retrieve non-English articles and English articles, we searched Ichushi-Web, but no Japanese article pertaining to our study topic was identified.

Conclusions

The number of patients who respond to ICIs is limited. Additionally, ICI treatment imposes a huge financial burden and is associated with irAEs. The identification of responders pre-therapeutically or in the early phase of the treatment course is critically important. Unfortunately, current companion and complementary diagnostics are insufficient. In the present study, we demonstrated the predictive impact of sarcopenia in patients treated with ICIs. However, sarcopenia alone as a predictor would not be sufficiently useful. Indices comprising the combination of predictive factors are warranted. Further research is required to elaborate on the effective use of ICIs.

Ethics approval

The approval of the institutional review board was not required because this study was conducted using only previously published data. The authors certify that they comply with the ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2019.

Conflict of interests

There are no conflicts of interest to declare.

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Author contributions

Y.T. conceived and designed the study and wrote the paper. Y.T. and R.O. collected and analysed the data. N.T., R.O., and H.I. reviewed and revised the manuscript.

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Data availability statement

All the data generated during this study are included in this published article and supporting information. All the original data were obtained from the published articles listed in the references.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. PRISMA Checklist

**Figure S1.** Forest plot showing the prevalence of sarcopenia. The squares represent the hazard ratios for each study.

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