

## Article

# Association between Computed Tomography-Determined Loss of Muscle Mass and Impaired Three-Month Survival in Frail Older Adults with Cancer

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**Simple Summary:** A large proportion of older adults are not fit for oncological treatments due to frailty and comorbidities. To aid in the decision-making of whom to provide active oncological treatment to, we used G8-screening and comprehensive geriatric assessment in patients at risk of frailty. We studied the added value of muscle measurement with computed tomography (CT) at the third lumbar vertebra level in these potentially frail  $\geq 75$ -year-olds. In 58 patients with advanced or metastatic solid tumors, a higher 3-month mortality rate and poorer nutritional status and functioning were noted among those with low muscle mass, independent of other predictive factors. Most patients with low muscle mass were allocated to best supportive care only. A poorer 2-year survival among 21 patients treated with curative intent was noted in those with low muscle mass. Muscle mass assessment alongside geriatric assessment can thus help oncologists identify patients at increased risk of severe toxicities and with little benefit from oncological treatments.

**Abstract:** As patients with solid (non-hematological) cancers and a life expectancy of  $<3$  months rarely benefit from oncological treatment, we examined whether the CT-determined loss of muscle mass is associated with an impaired 3-month overall survival (OS) in frail  $\geq 75$ -year-old patients with cancer. Frailty was assessed with G8-screening and comprehensive geriatric assessment in older adults at risk of frailty. The L3-level skeletal (SMI) and psoas (PMI) muscle indexes were determined from routine CT scans. Established and optimized SMI and PMI cut-offs were used. In the non-curative treatment group ( $n = 58$ ), 3-month OS rates for normal and low SMI were 95% and 64% (HR 9.28; 95% CI 1.2–71) and for PMI 88%, and 60%, respectively (HR 4.10; 1.3–13). A Cox multivariable 3-month OS model showed an HR of 10.7 (1.0–110) for low SMI, 2.34 (0.6–9.8) for ECOG performance status 3–4, 2.11 (0.5–8.6) for clinical frailty scale 5–9, and 0.57 (0.1–2.8) for males. The 24-month OS rates in the curative intent group ( $n = 21$ ) were 91% and 38% for the normal and low SMI groups, respectively. In conclusion, CT-determined low muscle mass is independently associated with an impaired 3-month OS and, alongside geriatric assessment, could aid in oncological versus best supportive care decision-making in frail patients with non-curable cancers.

**Keywords:** computed tomography; loss of muscle mass; sarcopenia; cancer; frailty; older adults



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## 1. Introduction

As the population ages, the number of older adults with cancer increases [1]. Older adults with cancer present unique challenges to cancer care providers, such as an increased number of comorbidities, frailty, loss of physical and mental function, malnutrition, and muscle-wasting conditions (e.g., sarcopenia and cachexia) [2]. To achieve optimal treatment outcomes and adherence, the oncologist should take into account patients' physical, mental, and sociopsychological resources, as well as tumor-related factors and treatment intent. Indeed, patients with a solid tumor and a short life expectancy (i.e., less than 3-month overall survival (OS)) probably do not benefit from oncological treatments and are often excluded from oncological studies [3,4].

Comprehensive geriatric assessment (CGA) for older adults with cancer is regarded as the gold standard in the identification of frailty and other vulnerability-associated conditions [5]. Indeed, compared to usual care, CGA-guided oncological treatment has been shown to reduce treatment-related toxicities [6,7] and treatment discontinuations [8]. However, CGA does not directly determine which patients could undergo oncological treatment, and there is heterogeneous evidence that CGA's implementation improves survival outcomes [5–7,9]. Further tools are needed to supplement CGA to enable a better characterization of the phenomena underlying frailty and augment the assessment of treatability.

Sarcopenia is a syndrome often seen in older adults with cancer and in patients with other serious debilitating diseases. The syndrome is characterized by the progressive and generalized loss of skeletal muscle mass and strength [10]. Cachexia is a more complex condition with both "objective" components (e.g., inadequate food intake, weight loss, inactivity, loss of muscle mass, and metabolic derangements that induce catabolism) and "subjective" components (e.g., anorexia, early satiety, taste alterations, chronic nausea, distress, fatigue, and loss of concentration) and affects approximately half of patients with advanced cancers [11]. The diagnosis of sarcopenia requires low muscle strength combined with low muscle mass or quality [11], whereas the diagnosis of cachexia requires that phenotypical criteria (weight or muscle loss) and etiological criteria (systemic inflammation, reduced food intake) are met [11]. Sarcopenia (with skeletal muscle loss as a surrogate endpoint) in patients with cancer is associated with a decreased survival rate [12–20], an increased risk of oncological treatment toxicities [14,20–22], and an impaired health-related quality of life [23]. As diagnosing muscle-wasting conditions early is important for optimized treatment planning, complementary means to detect these conditions are of great interest.

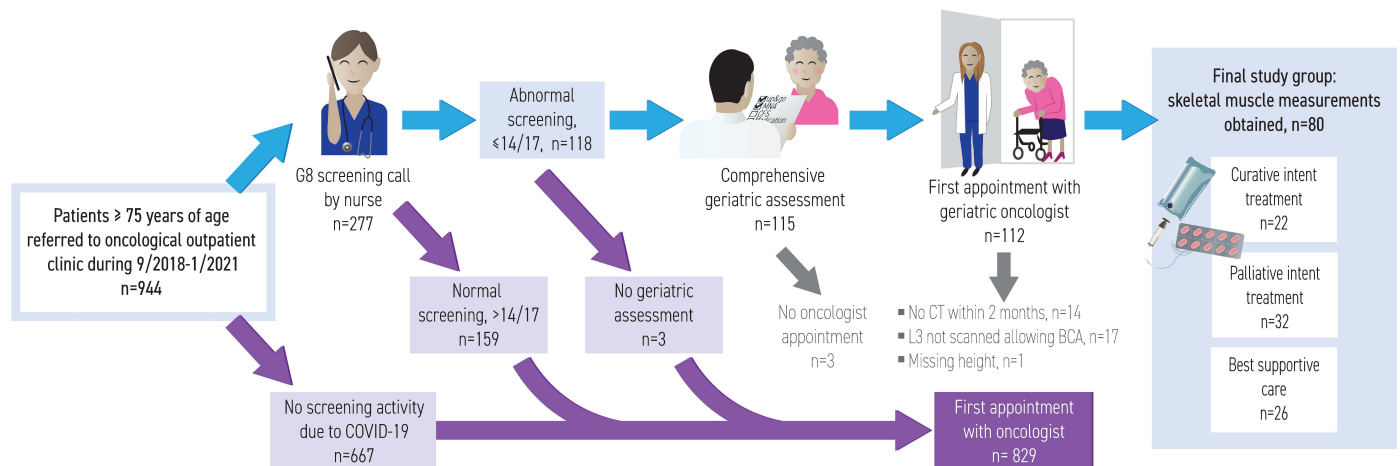
Computed tomography (CT) is an accurate imaging modality for body composition analysis and enables the identification of skeletal muscle-wasting conditions [24]. The opportunistic use of CT scans to quantify the amount of muscle tissue based on Hounsfield units is often possible because patients with cancer are imaged with CT as part of their diagnostic work-up and during treatment to assess treatment response [24]. The most used level in body composition analysis is the third lumbar vertebra, from where the area of all the axially visible muscles or individual muscles (e.g., the psoas muscles) are measured [24]. Analogously to the body mass index (BMI), muscle areas are often normalized by the patient's squared height resulting in muscle indexes, such as the skeletal and psoas muscle indexes (SMI and PMI, respectively). However, the role of these parameters remains poorly studied in older adult patients with cancer, especially those who are frail, for whom there are no established SMI or PMI cut-off values.

The primary aim of this study was to examine the association between CT-determined low muscle mass with published and optimized cut-offs and 3-month OS rates. The secondary aim was to investigate whether low muscle mass offers additional predictive value for treatment decisions in combination with oncological and geriatric evaluations in frail older adults with cancer.

## 2. Materials and Methods

### 2.1. Study Cohort

The study cohort was collected retrospectively among patients referred to an oncology outpatient clinic for consideration of oncological treatment at the Cancer Center at Tampere University Hospital, Finland, from September 2018 to January 2021. According to protocol, an oncology nurse called the referred patients aged  $\geq 75$  years or their relatives to conduct G8-screening to identify patients at risk of frailty. The G8-screening tool consists of eight questions with a maximum of 17 points, with at-risk patients having  $\leq 14$  points [25]. Patients at risk of frailty were referred to a geriatrician for CGA before their appointment with an oncologist. Patients who received more than 14 points in the G8-screening underwent routine treatment without CGA and were not included in this study (flowchart in Figure 1).



**Figure 1.** Flowchart for geriatric oncological patients at the Comprehensive Cancer Center of Tampere University Hospital.

The inclusion criteria for the patients were as follows: the patient had an abnormal G8-screening result and underwent geriatric and oncological evaluation at the Geriatric Oncological Unit; the patient's clinical information was available; and the patient had an appropriate CT scan. The scan had to fulfill the following criteria: the midpoint of the third lumbar vertebra was scanned in a manner that allowed body composition analysis; the scan was performed no more than 2 months prior to CGA according to local standard practice [26] (whereas a maximum of 1 month is frequently used in study populations [27]); and the scan was performed before starting any systemic oncological treatment.

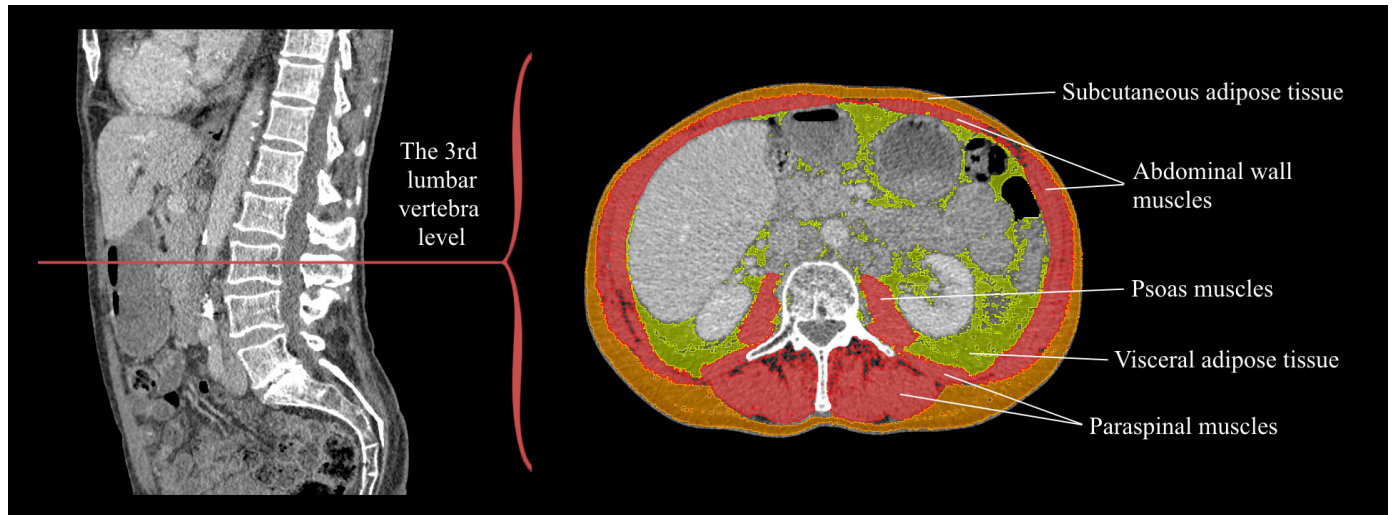
### 2.2. Ethics Statement

The study was approved by the local institutional review board at Tampere University Hospital (study numbers R19628S and R20503S). Ethics Committee approval and written informed consent are not needed in single-institution register-based studies in Finland.

### 2.3. Body Composition Analysis

Appropriate CT studies were collected from the hospital's Picture Archiving and Communication Systems (Commit; RIS IDS7 Radiology Desktop, Sectra AB, Linköping, Sweden). One reader (A.T.) performed body composition analysis with the 3D Slicer software (version 4.11) [28]. A single axial slice was used from the midpoint of the third lumbar vertebra level, determined using the sagittal and coronal images. One patient with incomplete abdominal muscle scanning was excluded from SMI analysis. Slice volumes were divided by slice thicknesses (0.45–3.00 mm) to calculate areas. The Hounsfield unit range for skeletal muscle tissue was set to  $-29$  to  $150$  [29] and used irrespective of contrast agent use and scan phase. Manual correction of the tissues was performed according to

morphology and/or Hounsfield unit variability. SMI and PMI values were calculated by dividing the whole skeletal muscle and psoas areas, respectively, with the patient's squared height (Figure 2).



**Figure 2.** Body composition analysis is performed from an axial slice at the midpoint of the third lumbar vertebral level. The patient had a low optimized skeletal muscle index (SMI) value of  $45.7 \text{ cm}^2/\text{m}^2$  and an optimized psoas muscle index (PMI) of  $5.06 \text{ cm}^2/\text{m}^2$ .

#### 2.4. Clinical Data Acquisition

Patients' age, sex, dates for the CT scan, visits to the geriatrician and the oncologist, and date of death if deceased were collected from the hospital's electronic patient records. The primary tumor site and extent (local vs. locally advanced/metastatic) were recorded. The Eastern cooperative oncology group performance status (ECOG PS) was recorded at the oncologist's appointment [30]; the FRAIL scale [31], clinical frailty scale [32], activities of daily living, instrumental activities of daily living [33], hand-grip strength, and sit-to-stand tests [34] were recorded by the geriatrician at the CGA. Nutritional status was assessed with the mini nutritional assessment-short form [35] and with the Global Leadership Initiative on Malnutrition (GLIM) classification [36]. For GLIM, phenotypic criteria included weight loss of  $>5\%$  per 6 months,  $\text{BMI} < 22 \text{ kg}/\text{m}^2$ , or impaired hand-grip strength with cut-offs as in [34]; we excluded reduced muscle mass as a criterion because there were no quantitative muscle mass records in the patient database. Etiologic criteria were serum albumin  $< 35 \text{ g}/\text{L}$  or C-reactive protein  $> 10 \text{ mg}/\text{L}$  [37]. Hemoglobin  $< 110 \text{ g}/\text{L}$ , creatinine  $> 100 \text{ }\mu\text{mol}/\text{L}$  for men and  $>90 \text{ }\mu\text{mol}/\text{L}$  for women, and albumin  $< 30 \text{ g}/\text{L}$  were also recorded [38].

The patients were categorized into curative and non-curative intent treatment groups. Patients in the non-curative treatment group were further subdivided into the palliative chemotherapy group and the best supportive care only group (BSC).

#### 2.5. Statistical Analyses

The association between CT-determined low muscle mass and 3-month OS was studied with Kaplan–Meier estimation and Cox regression models. The 3-month OS was calculated from the oncologist's visit until the end of the 3-month follow-up or death. The cut-offs for low muscle mass were optimized stepwise. We first used SMI [12,39–42] and PMI [43,44] cut-off values from the literature to examine their performance in our study cohort. As these cut-offs were not optimized for frail older adults with cancer, we also tested sex-specific medians and receiver operating characteristic (ROC)-determined optimized cut-offs. To optimize the SMI and PMI cut-off values, Youden's indexes (sensitivity + specificity – 1) were calculated, and the highest Youden's index was chosen, giving sensitivity and specificity equal weight.

Patient demographics are presented as absolute values and percentages and as medians with ranges or interquartile ranges (IQRs), and muscle index parameters are presented as means with standard deviations. Logistic regression and odds ratios (ORs) with 95% confidence intervals (CIs) were used to examine differences between the muscle indexes and patient characteristics. The OS for the whole follow-up period was calculated from the oncologist's visit until the end of January 2022 or death. Established factors that predict OS (ECOG PS, clinical frailty scale) and sex due to the difference in muscle mass distributions were included in multivariable analyses.

All *p*-values were two-sided and considered significant when  $p \leq 0.05$ , without adjustment for multiple analyses. Data were analyzed with SPSS (IBM SPSS Statistics for Windows, 2020, Version 27.0.0.1, IBM Corporation, Armonk, NY, USA).

### 3. Results

#### 3.1. Patient Demographics

A total of 80 patients (43 men and 37 women) were included with a median age of 80 (range 75–91) years (Figure 1). The median time between the CT scan and the oncologist visit was 21 (range 0–61) days. The cohort consisted of patients with upper GI, lower GI, and other cancers (Table 1, with details in Table S1).

**Table 1.** Patient characteristics for non-curative and curative treatment intent groups.

|                            |                                | All    |    | Non-Curative |     | Curative |    | OR (95% CI)     |
|----------------------------|--------------------------------|--------|----|--------------|-----|----------|----|-----------------|
|                            |                                | N = 80 | %  | n = 58       | %   | n = 22   | %  |                 |
| Age                        | 75–80 years                    | 39     | 49 | 28           | 48  | 11       | 50 | 1               |
|                            | ≥80 years                      | 41     | 51 | 30           | 52  | 11       | 50 | 0.93 (0.4–2.5)  |
| Sex                        | Female                         | 37     | 46 | 28           | 48  | 9        | 41 | 1               |
|                            | Male                           | 43     | 54 | 30           | 52  | 13       | 59 | 1.35 (0.5–3.6)  |
| Tumor site                 | Upper GI                       | 37     | 46 | 30           | 52  | 7        | 32 | 1               |
|                            | Lower GI                       | 26     | 33 | 12           | 21  | 14       | 64 | 5.00 (1.6–15) * |
|                            | Other <sup>a</sup>             | 17     | 21 | 16           | 28  | 1        | 5  | 0.27 (0.0–2.4)  |
| Tumor stage                | Local                          | 13     | 16 | 0            | 0   | 13       | 59 | 1               |
|                            | Metastatic or locally advanced | 67     | 84 | 58           | 100 | 9        | 41 | N/A             |
| ECOG performance status    | 0 to 2                         | 52     | 65 | 37           | 64  | 15       | 68 | 1               |
|                            | 3 to 4                         | 22     | 28 | 15           | 26  | 7        | 32 | 1.15 (0.4–3.4)  |
|                            | Not available                  | 6      | 8  | 6            | 10  | 0        | 0  |                 |
| Activities of daily living | Normal                         | 52     | 65 | 35           | 60  | 17       | 77 | 1               |
|                            | Impaired                       | 24     | 30 | 19           | 33  | 5        | 23 | 0.54 (0.2–1.7)  |
|                            | Not available                  | 4      | 5  | 4            | 7   | 0        | 0  |                 |
| Clinical frailty scale     | 1 to 4                         | 48     | 60 | 35           | 60  | 13       | 59 | 1               |
|                            | 5 to 9                         | 26     | 33 | 20           | 35  | 6        | 27 | 0.81 (0.3–2.5)  |
|                            | Not available                  | 6      | 8  | 3            | 5   | 3        | 14 |                 |
| BMI                        | ≥22 kg/m <sup>2</sup>          | 61     | 76 | 42           | 72  | 19       | 86 | 1               |
|                            | <22 kg/m <sup>2</sup>          | 19     | 24 | 16           | 28  | 3        | 14 | 0.41 (0.1–1.6)  |
| GLIM <sup>b</sup>          | Normal                         | 31     | 39 | 19           | 33  | 12       | 55 | 1               |
|                            | Malnourishment                 | 44     | 55 | 34           | 59  | 10       | 46 | 0.47 (0.2–1.39) |
|                            | Not available                  | 5      | 6  | 5            | 9   | 0        | 0  |                 |
| Hand-grip strength test    | Normal                         | 48     | 60 | 36           | 62  | 12       | 55 | 1               |
|                            | Impaired                       | 22     | 28 | 13           | 22  | 9        | 41 | 2.08 (0.7–6.1)  |
|                            | Not available                  | 10     | 13 | 9            | 16  | 1        | 5  |                 |
| Albumin                    | ≥30 g/L                        | 41     | 51 | 28           | 48  | 13       | 59 | 1               |
|                            | <30 g/L                        | 17     | 21 | 14           | 24  | 3        | 14 | 0.46 (0.1–1.9)  |
|                            | Not available                  | 22     | 28 | 16           | 28  | 6        | 27 |                 |
| SMI <sup>c</sup>           | Normal                         | 33     | 42 | 22           | 38  | 11       | 52 | 1               |
|                            | Low                            | 46     | 58 | 36           | 62  | 10       | 48 | 0.56 (0.2–1.5)  |



Table 1. Cont.

|                      |                               | All    |    | Non-Curative |    | Curative |     | OR (95% CI)    |
|----------------------|-------------------------------|--------|----|--------------|----|----------|-----|----------------|
|                      |                               | N = 80 | %  | n = 58       | %  | n = 22   | %   |                |
| PMI <sup>c</sup>     | Normal                        | 43     | 54 | 33           | 57 | 10       | 46  | 1              |
|                      | Low                           | 37     | 46 | 25           | 43 | 12       | 55  | 1.58 (0.6–4.3) |
| Treatment decision   | Oncological treatments        | 41     | 51 | 31           | 53 | 10       | 46  | 1              |
|                      | Follow-up or BSC <sup>d</sup> | 39     | 49 | 27           | 47 | 12       | 55  | 1.38 (0.5–3.7) |
| Survival at 3 months | Alive                         | 66     | 83 | 44           | 76 | 22       | 100 | 1              |
|                      | Deceased                      | 14     | 18 | 14           | 24 | 0        | 0   | N/A            |

<sup>a</sup> Other cancers included 7 genitourinary cancers, 4 breast cancers, 4 lung cancers, 1 sarcoma of the lower limb, and 1 thymus carcinoma; <sup>b</sup> Global Leadership Initiative on Malnutrition classification; <sup>c</sup> patients were divided into normal and low SMI/PMI categories using our cut-offs obtained by maximizing the Youden's index on the receiver operator characteristic curve; <sup>d</sup> best supportive care; \* indicates statistical significance ( $p \leq 0.05$ ).

### 3.2. Initiated Treatments

All patients treated with curative intent ( $n = 22$ ; 28%) underwent surgical resection. At the time of the oncologist's appointment 20/22 (91%) had been operated and were considered for adjuvant chemotherapy and 2/22 (9%) were considered for neoadjuvant treatment. All patients in the curative intent treatment group receiving curative oncological treatments ( $n = 10$ ) were given chemotherapy.

Treatment intent was non-curative in 58 (73%) patients; 31 received palliative oncological treatment and 27 BSC only. Of the 58 patients in non-curative care, 45 had metastatic disease and 13 had locally advanced disease ineligible for curative surgery because of disease extent, frailty, or poor functional status. The palliative oncological treatments ( $n = 31$ ) that were given were chemotherapy ( $n = 18$ ), chemotherapy and bevacizumab ( $n = 3$ ), hormonal treatment ( $n = 2$ ), hormonal treatment with denosumab or radionucleotides ( $n = 4$ ), tyrosine kinase inhibitors ( $n = 3$ ), and immuno-oncologic treatment ( $n = 1$ ). Six patients were given radiotherapy in combination with other treatments.

Having a lower GI cancer was associated with curative treatment intent but there were no other statistically significant differences in baseline characteristics between the curative and non-curative treatment groups (Tables 1 and S1).

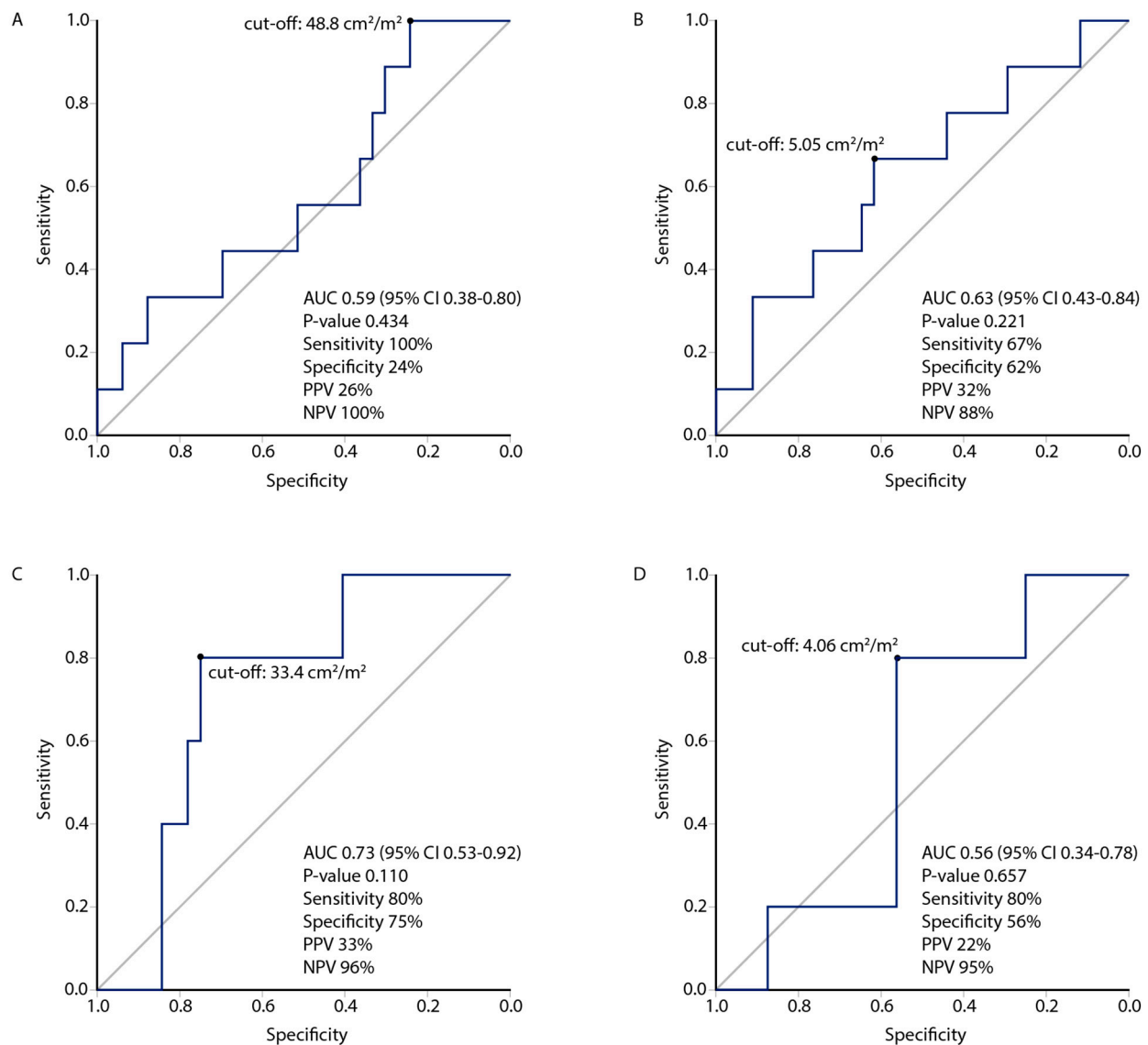
### 3.3. Muscle Index Cut-Offs

The mean SMI values for men and women were  $43.3 \pm 6.1 \text{ cm}^2/\text{m}^2$  and  $35.7 \pm 4.6 \text{ cm}^2/\text{m}^2$ , and mean PMI values were  $5.30 \pm 1.04 \text{ cm}^2/\text{m}^2$  and  $4.34 \pm 1.04 \text{ cm}^2/\text{m}^2$ , respectively.

ROC analyses were performed for SMI ( $n = 79$ ) and PMI ( $n = 80$ ) to predict 3-month OS rates (Figure 3). The optimized ROC cut-off values for SMI were  $48.8 \text{ cm}^2/\text{m}^2$  and  $33.4 \text{ cm}^2/\text{m}^2$ , and for PMI  $5.05 \text{ cm}^2/\text{m}^2$  and  $4.06 \text{ cm}^2/\text{m}^2$  for men and women, respectively, as obtained by maximizing Youden's indexes.

Median SMI cut-offs for men and women were  $42.4 \text{ cm}^2/\text{m}^2$  and  $35.0 \text{ cm}^2/\text{m}^2$ , respectively; median PMI cut-offs were  $5.06 \text{ cm}^2/\text{m}^2$  and  $4.15 \text{ cm}^2/\text{m}^2$ , respectively.

The optimized, median, and literature-referred SMI and PMI cut-offs and their univariate and multivariable associations with 3-month OS are presented in Table 2 [12,39–44] and demographic comparisons of the studies in Table S2.



**Figure 3.** Optimized skeletal muscle index (SMI) and psoas muscle index (PMI) cut-offs to predict 3-month overall survival were determined by maximizing Youden's indexes on the receiver operating characteristic curve. For men, the cut-offs were  $48.8 \text{ cm}^2/\text{m}^2$  for SMI (A) and  $5.05 \text{ cm}^2/\text{m}^2$  for PMI (B); for women  $33.4 \text{ cm}^2/\text{m}^2$  for SMI (C) and  $4.06 \text{ cm}^2/\text{m}^2$  for PMI (D).

**Table 2.** Univariate and multivariable Cox regression analyses between different muscle index cut-offs and 3-month OS in the non-curative intent group.

|                                     |         | All Patients | Non-Curative Patients        | Univariate         | Multivariable <sup>a</sup> |
|-------------------------------------|---------|--------------|------------------------------|--------------------|----------------------------|
|                                     | Cut-Off | N            | n Univariate/n Multivariable | HR 95% CI          | HR 95% CI                  |
| Study SMI (Youden) <sup>b</sup>     | Normal  | 33           | 22/22                        | 1                  | 1                          |
|                                     | Low     | 46           | 36/29                        | 9.28 (1.2–71) *    | 10.65 (1.0–110) *          |
| Study SMI (median) <sup>c</sup>     | Normal  | 40           | 29/28                        | 1                  | 1                          |
|                                     | Low     | 39           | 29/23                        | 2.06 (0.7–6.2)     | 2.21 (0.6–8.4)             |
| Prado et al. SMI <sup>d</sup> [12]  | Normal  | 10           | 7/7                          | 1                  | 1                          |
|                                     | Low     | 69           | 51/44                        | 25.21 (0.0–19,000) | N/A                        |
| Martin et al. SMI <sup>e</sup> [39] | Normal  | 13           | 9/8                          | 1                  | 1                          |
|                                     | Low     | 66           | 49/43                        | 1.19 (0.3–5.3)     | 1.00 (0.1–8.8)             |

Table 2. Cont.

|  | Cut-Off | All Patients | Non-Curative Patients        | Univariate         | Multivariable <sup>a</sup> |
|--|---------|--------------|------------------------------|--------------------|----------------------------|
|  |         | N            | n Univariate/n Multivariable | HR 95% CI          | HR 95% CI                  |
| Baracos et al. SMI <sup>f</sup> [40]     | Normal  | 10           | 7/7                          | 1                  | 1                          |
|  | Low     | 69           | 51/44                        | 25.21 (0.0–19,400) | N/A                        |
| van Vledder et al. SMI <sup>g</sup> [41] | Normal  | 21           | 14/13                        | 1                  | 1                          |
|  | Low     | 58           | 44/38                        | 0.86 (0.3–2.7)     | 1.01 (0.3–4.5)             |
| Camus et al. SMI <sup>h</sup> [42]       | Normal  | 9            | 7/7                          | 1                  | 1                          |
|  | Low     | 70           | 51/44                        | 25.21 (0.3–19,000) | N/A                        |
| Study PMI (Youden) <sup>i</sup>          | Normal  | 43           | 33/32                        | 1                  | 1                          |
|  | Low     | 37           | 25/18                        | 4.10 (1.3–13) *    | 2.23 (0.6–8.9)             |
| Study PMI (median) <sup>j</sup>          | Normal  | 41           | 31/30                        | 1                  | 1                          |
|  | Low     | 39           | 27/21                        | 4.48 (1.1–11) *    | 1.56 (0.4–6.5)             |
| Amini et al. PMI <sup>k</sup> [43]       | Normal  | 34           | 26/26                        | 1                  | 1                          |
|  | Low     | 46           | 32/25                        | 3.46 (1.0–12)      | 1.84 (0.4–7.7)             |
| Joglekar et al. PMI <sup>l</sup> [44]    | Normal  | 37           | 28/28                        | 1                  | 1                          |
|  | Low     | 43           | 30/23                        | 2.74 (0.9–8.7)     | 1.31 (0.3–5.2)             |

<sup>a</sup> Adjusted for sex (female vs. male), ECOG performance status (0–2 vs. 3–4), clinical frailty scale (1–4 vs. 5–9); <sup>b</sup> cut-offs for SMI by Youden method were 48.8 cm<sup>2</sup>/m<sup>2</sup> for men and 33.4 cm<sup>2</sup>/m<sup>2</sup> for women; <sup>c</sup> median cut-offs for SMI were 42.4 cm<sup>2</sup>/m<sup>2</sup> for men and 35.0 cm<sup>2</sup>/m<sup>2</sup> for women; <sup>d</sup> cut-offs for SMI by Prado et al. [12], 52.4 cm<sup>2</sup>/m<sup>2</sup> for men and 38.5 cm<sup>2</sup>/m<sup>2</sup> for women; <sup>e</sup> cut-offs for SMI by Martin et al. [39] 43 cm<sup>2</sup>/m<sup>2</sup> for men with BMI < 25 kg/m<sup>2</sup>, 53 cm<sup>2</sup>/m<sup>2</sup> for men with BMI ≥ 25 kg/m<sup>2</sup>, and 41 cm<sup>2</sup>/m<sup>2</sup> for women regardless of BMI; <sup>f</sup> cut-offs for SMI by Baracos et al. [40], 55.4 cm<sup>2</sup>/m<sup>2</sup> for men and 38.9 cm<sup>2</sup>/m<sup>2</sup> for women; <sup>g</sup> cut-offs for SMI by van Vledder et al. [41], 43.8 cm<sup>2</sup>/m<sup>2</sup> for men and 38.9 cm<sup>2</sup>/m<sup>2</sup> for women; <sup>h</sup> cut-offs for SMI by Camus et al. [42], 55.8 cm<sup>2</sup>/m<sup>2</sup> for men and 38.9 cm<sup>2</sup>/m<sup>2</sup> for women; <sup>i</sup> cut-offs for PMI by Youden method were 5.05 cm<sup>2</sup>/m<sup>2</sup> for men and 4.06 cm<sup>2</sup>/m<sup>2</sup> for women; <sup>j</sup> median cut-offs for PMI were 5.06 cm<sup>2</sup>/m<sup>2</sup> for men and 4.15 cm<sup>2</sup>/m<sup>2</sup> for women; <sup>k</sup> cut-offs for PMI by Amini et al. [43], 5.642 cm<sup>2</sup>/m<sup>2</sup> for men and 4.145 cm<sup>2</sup>/m<sup>2</sup> for women; <sup>l</sup> cut-offs for PMI by Joglekar et al. [44], 5.2 cm<sup>2</sup>/m<sup>2</sup> for men and 4.0 cm<sup>2</sup>/m<sup>2</sup> for women; N/A = not applicable; \* indicates statistical significance ( $p \leq 0.05$ ).

### 3.4. Associations between Low Muscle Mass, Oncological Treatments, and Patient Characteristics

The associations between oncological treatments, clinical characteristics, and low muscle mass based on optimized SMI and PMI cut-offs are presented in Tables 3 and 4, respectively, and further details are presented in Tables S3 and S4, respectively.

A low SMI did not associate with ECOG PS, FRAIL scale, clinical frailty scale, or other measures of functional status, whereas low PMI was associated with ECOG PS 3–4 ( $p = 0.047$ ), clinical frailty scale 5–9 ( $p = 0.006$ ), and an impaired hand-grip strength ( $p = 0.012$ ).

Significant differences were noted in the measures of malnutrition. In the non-curative group, malnutrition according to GLIM was noted in 76% and 45% of patients with low and normal SMI, respectively ( $p = 0.027$ ), and in the curative intent group according to the mini nutritional assessment-short form in 78% and 20%, respectively ( $p = 0.019$ ). In the non-curative group, malnourishment according to GLIM was present in 82% and 52% of patients in the low and normal PMI groups, respectively ( $p = 0.029$ ).

Table 3. Associations between optimized low skeletal muscle index (SMI) and patient characteristics.

|     |             | Non-Curative Treatment |                      |                  | Curative Treatment |                      |                  |
|-----|-------------|------------------------|----------------------|------------------|--------------------|----------------------|------------------|
|     |             | Normal SMI             | Low SMI <sup>a</sup> | OR (95% CI)      | Normal SMI         | Low SMI <sup>a</sup> | OR (95% CI)      |
|     |             | n = 22<br>n (%)        | n = 36<br>n (%)      |                  | n = 11<br>n (%)    | n = 10<br>n (%)      |                  |
| Age | 75–80 years | 8 (29)                 | 20 (71)              | 1                | 8 (80)             | 2 (20)               | 1                |
|     | ≥80 years   | 14 (47)                | 16 (53)              | 0.46 (0.2–1.4)   | 3 (27)             | 8 (73)               | 10.67 (1.4–82) * |
| Sex | Female      | 19 (68)                | 9 (32)               | 1                | 6 (67)             | 3 (33)               | 1                |
|     | Male        | 3 (10)                 | 27 (90)              | 19.00 (4.5–80) * | 5 (42)             | 7 (58)               | 2.80 (0.5–17)    |



Table 3. Cont.

|                            |                                | Non-Curative Treatment |                      |                  | Curative Treatment |                      |                |
|----------------------------|--------------------------------|------------------------|----------------------|------------------|--------------------|----------------------|----------------|
|                            |                                | Normal SMI             | Low SMI <sup>a</sup> | OR (95% CI)      | Normal SMI         | Low SMI <sup>a</sup> | OR (95% CI)    |
|                            |                                | n = 22<br>n (%)        | n = 36<br>n (%)      |                  | n = 11<br>n (%)    | n = 10<br>n (%)      |                |
| Tumor site                 | Upper GI                       | 8 (27)                 | 22 (73)              | 1                | 4 (57)             | 3 (43)               | 1              |
|                            | Lower GI                       | 4 (33)                 | 8 (67)               | 0.73 (0.2–3.1)   | 7 (54)             | 6 (46)               | 1.14 (0.2–7.3) |
|                            | Other <sup>b</sup>             | 10 (63)                | 6 (38)               | 0.22 (0.1–0.8)   | 0 (0)              | 1 (100)              | N/A            |
| Tumor stage                | Local                          | 0 (0)                  | 0 (0)                | 1                | 7 (54)             | 6 (46)               | 1              |
|                            | Metastatic or locally advanced | 22 (38)                | 36 (62)              | N/A              | 4 (50)             | 4 (50)               | 1.17 (0.2–6.8) |
| ECOG performance status    | 0 to 2                         | 16 (43)                | 21 (57)              | 1                | 9 (60)             | 6 (40)               | 1              |
|                            | 3 to 4                         | 6 (40)                 | 9 (60)               | 1.14 (0.3–3.9)   | 2 (33)             | 4 (67)               | 3.00 (0.4–22)  |
|                            | Not available                  | 0 (0)                  | 6 (100)              |                  | 0 (0)              | 0 (0)                |                |
| Activities of daily living | Normal                         | 14 (40)                | 21 (60)              | 1                | 8 (50)             | 8 (50)               | 1              |
|                            | Impaired                       | 7 (37)                 | 12 (63)              | 1.14 (0.4–3.6)   | 3 (60)             | 2 (40)               | 0.67 (0.1–5.1) |
|                            | Not available                  | 1 (25)                 | 3 (75)               |                  | 0 (0)              | 0 (0)                |                |
| Clinical frailty scale     | 1 to 4                         | 15 (43)                | 20 (57)              | 1                | 8 (62)             | 5 (39)               | 1              |
|                            | 5 to 9                         | 7 (35)                 | 13 (65)              | 1.39 (0.4–4.3)   | 2 (40)             | 3 (60)               | 2.40 (0.3–20)  |
|                            | Not available                  | 0 (0)                  | 3 (100)              |                  | 1 (33)             | 2 (67)               |                |
| BMI                        | ≥22 kg/m <sup>2</sup>          | 17 (41)                | 25 (60)              | 1                | 10 (56)            | 8 (44)               | 1              |
|                            | <22 kg/m <sup>2</sup>          | 5 (31)                 | 11 (69)              | 1.50 (0.4–5.1)   | 1 (33)             | 2 (67)               | 2.50 (0.2–33)  |
| GLIM <sup>c</sup>          | Normal                         | 11 (58)                | 8 (42)               | 1                | 6 (55)             | 5 (46)               | 1              |
|                            | Malnourishment                 | 9 (27)                 | 25 (74)              | 3.82 (1.2–13) *  | 5 (50)             | 5 (50)               | 1.20 (0.2–6.7) |
|                            | Not available                  | 2 (40)                 | 3 (60)               |                  | 0 (0)              | 0 (0)                |                |
| Hand-grip strength test    | Normal                         | 16 (44)                | 20 (56)              | 1                | 6 (50)             | 6 (50)               | 1              |
|                            | Impaired                       | 3 (23)                 | 10 (77)              | 2.67 (0.6–11)    | 4 (50)             | 4 (50)               | 1.00 (0.2–6.0) |
|                            | Not available                  | 3 (33)                 | 6 (67)               |                  | 1 (100)            | 0 (0)                |                |
| Albumin                    | ≥30 g/L                        | 12 (43)                | 16 (57)              | 1                | 8 (67)             | 4 (33)               | 1              |
|                            | <30 g/L                        | 2 (14)                 | 12 (86)              | 4.50 (0.8–24)    | 1 (33)             | 2 (67)               | 4.00 (0.3–59)  |
|                            | Not available                  | 8 (50)                 | 8 (50)               |                  | 2 (33)             | 4 (67)               |                |
| Treatment decision         | Oncological treatment          | 16 (52)                | 15 (48)              | 1                | 6 (60)             | 4 (40)               | 1              |
|                            | Follow-up or BSC <sup>d</sup>  | 6 (22)                 | 21 (78)              | 3.73 (1.2–12) *  | 5 (46)             | 6 (55)               | 1.80 (0.3–10)  |
| Survival at 3 months       | Alive                          | 21 (48)                | 23 (52)              | 1                | 11 (52)            | 10 (48)              | 1              |
|                            | Deceased                       | 1 (7)                  | 13 (93)              | 11.87 (1.4–99) * | 0 (0)              | 0 (0)                | N/A            |

<sup>a</sup> Patients with normal and low SMI according to our cut-offs obtained by maximizing the Youden's index on the receiver operator characteristic curve. <sup>b</sup> Other cancers included 7 genitourinary cancers, 4 breast cancers, 4 lung cancers, 1 sarcoma of the lower limb, and 1 thymus carcinoma. <sup>c</sup> Global Leadership Initiative on Malnutrition classification. <sup>d</sup> Best supportive care. \* indicates statistical significance ( $p \leq 0.05$ ).

Table 4. Associations between optimized low psoas muscle index (PMI) and patient characteristics.

|                         |                                | Non-Curative Treatment |                      |                 | Curative Treatment |                      |                |
|-------------------------|--------------------------------|------------------------|----------------------|-----------------|--------------------|----------------------|----------------|
|                         |                                | Normal PMI             | Low PMI <sup>a</sup> | OR (95% CI)     | Normal PMI         | Low PMI <sup>a</sup> | OR (95% CI)    |
|                         |                                | n = 33<br>n (%)        | n = 25<br>n (%)      |                 | n = 10<br>n (%)    | n = 12<br>n (%)      |                |
| Age                     | 75–80 years                    | 16 (57)                | 12 (43)              | 1               | 5 (46)             | 6 (55)               | 1              |
|                         | ≥80 years                      | 17 (57)                | 13 (43)              | 1.02 (0.4–2.9)  | 5 (46)             | 6 (55)               | 1.00 (0.2–5.4) |
| Sex                     | Female                         | 16 (57)                | 12 (43)              | 1               | 3 (33)             | 6 (67)               | 1              |
|                         | Male                           | 17 (57)                | 13 (43)              | 1.02 (0.4–2.9)  | 7 (54)             | 6 (46)               | 0.43 (0.1–2.5) |
| Tumor site              | Upper GI                       | 18 (60)                | 12 (40)              | 1               | 1 (14)             | 6 (86)               | 1              |
|                         | Lower GI                       | 5 (42)                 | 7 (58)               | 2.10 (0.5–8.2)  | 8 (57)             | 6 (43)               | 0.13 (0.0–1.3) |
|                         | Other <sup>b</sup>             | 10 (63)                | 6 (38)               | 0.9 (0.3–3.1)   | 1 (100)            | 0 (0)                | N/A            |
| Tumor stage             | Local                          | 0 (0)                  | 0 (0)                | 1               | 7 (54)             | 6 (46)               | 1              |
|                         | Metastatic or locally advanced | 33 (57)                | 25 (43)              | N/A             | 3 (33)             | 6 (67)               | 2.33 (0.4–14)  |
| ECOG performance status | 0 to 2                         | 26 (70)                | 11 (30)              | 1               | 8(53)              | 7 (47)               | 1              |
|                         | 3 to 4                         | 6 (40)                 | 9 (60)               | 3.55 (1.0–12) * | 2 (29)             | 5 (71)               | 2.86 (0.4–20)  |
|                         | Not available                  | 1 (17)                 | 5 (83)               |                 | 0 (0)              | 0 (0)                |                |

Table 4. Cont.

|                            |                               | Non-Curative Treatment |                      |                 | Curative Treatment |                      |                |
|----------------------------|-------------------------------|------------------------|----------------------|-----------------|--------------------|----------------------|----------------|
|                            |                               | Normal PMI             | Low PMI <sup>a</sup> | OR (95% CI)     | Normal PMI         | Low PMI <sup>a</sup> | OR (95% CI)    |
|                            |                               | n = 33<br>n (%)        | n = 25<br>n (%)      |                 | n = 10<br>n (%)    | n = 12<br>n (%)      |                |
| Activities of daily living | Normal                        | 22 (63)                | 13 (37)              | 1               | 9 (53)             | 8 (47)               | 1              |
|                            | Impaired                      | 10 (53)                | 9 (47)               | 1.52 (0.5–4.7)  | 1 (20)             | 4 (80)               | 4.50 (0.4–49)  |
|                            | Not available                 | 1 (25)                 | 3 (75)               |                 | 0 (0)              | 0 (0)                |                |
| Clinical frailty scale     | 1 to 4                        | 26 (74)                | 9 (26)               | 1               | 6 (46)             | 7 (54)               | 1              |
|                            | 5 to 9                        | 7 (35)                 | 13 (65)              | 5.37 (1.6–18) * | 1 (17)             | 5 (83)               | 4.29 (0.4–48)  |
|                            | Not available                 | 0 (0)                  | 3 (100)              |                 | 3 (100)            | 0 (0)                |                |
|                            |                               |                        |                      |                 |                    |                      |                |
| BMI                        | ≥22 kg/m <sup>2</sup>         | 25 (60)                | 17 (41)              | 1               | 10 (53)            | 9 (47)               | 1              |
|                            | <22 kg/m <sup>2</sup>         | 8 (50)                 | 8 (50)               | 1.47 (0.5–4.7)  | 0 (0)              | 3 (100)              | N/A            |
| GLIM <sup>c</sup>          | Normal                        | 15 (79)                | 4 (21)               | 1               | 6 (50)             | 6 (50)               | 1              |
|                            | Malnourishment                | 16 (47)                | 18 (53)              | 4.22 (1.2–15) * | 4 (40)             | 6 (60)               | 1.50 (0.3–8.2) |
|                            | Not available                 | 2 (40)                 | 3 (60)               |                 | 0 (0)              | 0 (0)                |                |
| Hand-grip strength         | Normal                        | 26 (72)                | 10 (28)              | 1               | 4 (33)             | 8 (67)               | 1              |
|                            | Impaired                      | 4 (31)                 | 9 (69)               | 5.85 (1.5–23) * | 5 (56)             | 4 (44)               | 0.40 (0.1–2.4) |
|                            | Not available                 | 3 (33)                 | 6 (67)               |                 | 1 (100)            | 0 (0)                |                |
| Albumin                    | ≥30                           | 19 (68)                | 9 (32)               | 1               | 7 (54)             | 6 (46)               | 1              |
|                            | <30                           | 6 (43)                 | 8 (57)               | 2.82 (0.8–11)   | 0 (0)              | 3 (100)              | N/A            |
|                            | Not available                 | 8 (50)                 | 8 (50)               |                 | 3 (50)             | 3 (50)               |                |
| Treatment decision         | Oncological treatment         | 23 (74)                | 8 (26)               | 1               | 3 (30)             | 7 (70)               | 1              |
|                            | Follow-up or BSC <sup>d</sup> | 10 (37)                | 17 (63)              | 4.89 (1.6–15) * | 7 (58)             | 5 (42)               | 0.31 (0.1–1.8) |
| Survival at 3 months       | Alive                         | 29 (66)                | 15 (34)              | 1               | 10 (46)            | 12 (55)              | 1              |
|                            | Deceased                      | 4 (29)                 | 10 (71)              | 4.83 (1.3–18) * | 0 (0)              | 0 (0)                | N/A            |

<sup>a</sup> Patients with normal and low PMI categories according to our cut-offs obtained by maximizing the Youden’s index on the receiver operator characteristic curve. <sup>b</sup> Other cancers included 7 genitourinary cancers, 4 breast cancers, 4 lung cancers, 1 sarcoma of the lower limb, and 1 thymus carcinoma. <sup>c</sup> Global Leadership Initiative on Malnutrition classification. <sup>d</sup> Best supportive care. \* indicates statistical significance ( $p \leq 0.05$ ).

### 3.5. Three-Month Survival Analyses

The 3-month OS rates were 64% and 95% in the low and normal SMI groups, respectively, among the non-curatively treated patients with an HR of 9.28 (95% CI 1.2–71.0; Figure 4A). Respective 3-month OS rates were 60% and 88% in the low and normal PMI groups with an HR of 4.10 (95% CI 1.3–13.1; Figure 4B). Most deaths (13/14, 93%) occurred in the BSC group, with one death (due to stroke) out of 31 (3%) among oncologically treated patients. No patients in the curative treatment intent group died within 3 months.

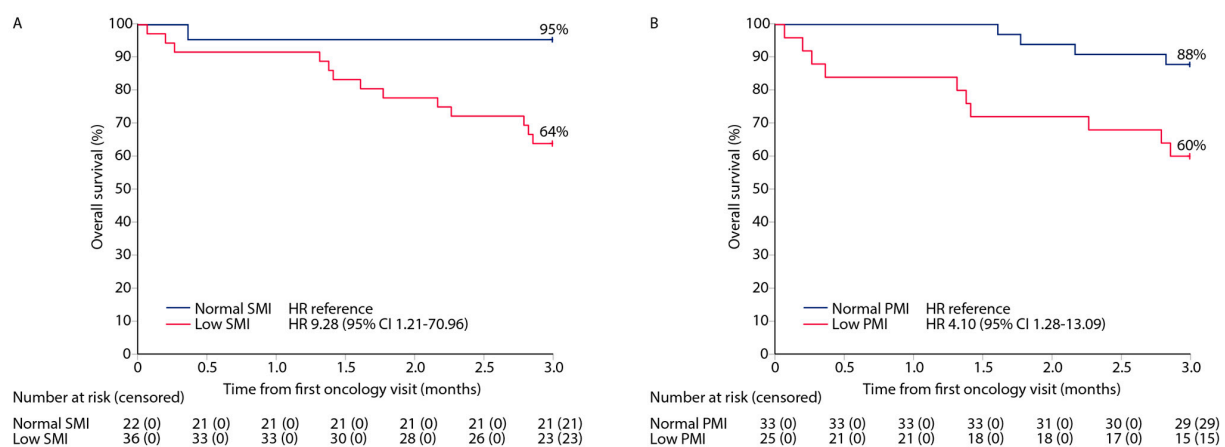


Figure 4. The Kaplan–Meier plots for 3-month OS rates in non-curative treatment intent patients based on optimized skeletal muscle index (SMI; (A)) and psoas muscle index (PMI; (B)) cut-offs determined with the Youden’s index method for patients in the non-curative intent treatment group.

### 3.6. Univariate and Multivariable Analyses for 3-Month Overall Survival in the Non-Curative Treatment Group

In the univariate analyses, low SMI, low PMI, and clinical frailty scale 5–9 were associated with impaired 3-month OS, whereas sex and ECOG PS 3–4 were not (Table 5).

**Table 5.** Univariate and multivariable Cox regression analyses between 3-month OS and optimized muscle indexes (SMI/PMI), sex, ECOG performance status and clinical frailty scale in the non-curative intent treatment group.

|                        | Patient n<br>Univariate/Multivariable | SMI                       |                              | PMI                       |                              |
|------------------------|---------------------------------------|---------------------------|------------------------------|---------------------------|------------------------------|
|                        |                                       | Univariate<br>HR (95% CI) | Multivariable<br>HR (95% CI) | Univariate<br>HR (95% CI) | Multivariable<br>HR (95% CI) |
| Muscle mass            |                                       |                           |                              |                           |                              |
| Normal                 | SMI 22/22; PMI 33/32                  | 1                         | 1                            | 1                         | 1                            |
| Low <sup>a</sup>       | SMI 36/29; PMI 25/18                  | 9.28 (1.2–71) *           | 10.65 (1.0–110) *            | 4.10 (1.3–13) *           | 2.23 (0.6–8.9)               |
| Sex                    |                                       |                           |                              |                           |                              |
| Women                  | 28/25                                 | 1                         | 1                            | 1                         | 1                            |
| Men                    | 30/26                                 | 1.68 (0.6–5.0)            | 0.57 (0.1–2.8)               | 1.68 (0.6–5.0)            | 2.1 (0.5–8.1)                |
| ECOG PS                |                                       |                           |                              |                           |                              |
| 0 to 2                 | 37/36                                 | 1                         | 1                            | 1                         | 1                            |
| 3 to 4                 | 15/15                                 | 3.01 (0.9–10)             | 2.34 (0.6–9.8)               | 3.01 (0.9–10)             | 1.80 (0.4–7.2)               |
| Clinical frailty scale |                                       |                           |                              |                           |                              |
| 1 to 4                 | 35/33                                 | 1                         | 1                            | 1                         | 1                            |
| 5 to 9                 | 20/18                                 | 3.35 (1.1–10) *           | 2.11 (0.5–8.6)               | 3.35 (1.1–10) *           | 1.66 (0.4–7.6)               |

<sup>a</sup> Patients were divided into normal and low SMI/PMI categories using our SMI/PMI cut-offs obtained by maximizing Youden's indexes on the receiver operating characteristic curve; \* indicates statistical significance ( $p \leq 0.05$ ).

The 3-month OS models included predefined predictors for cancer treatment outcome (low muscle mass, ECOG PS, and clinical frailty scale) and sex due to differences in muscle mass distributions. There were no significant interactions between SMI and ECOG PS ( $p = 0.954$ ), SMI and clinical frailty scale ( $p = 0.929$ ), or ECOG and clinical frailty scale ( $p = 0.947$ ). Low SMI (HR 10.65 (95% CI 1.0–110)) remained statistically significant in the multivariable model (Table 5). None of the factors in the PMI model remained significant after the adjustment (Table 5).

The SMI [12,39–42] and PMI cut-offs [43,44] from the literature, in addition to our own median cut-offs, were included separately in the multivariable models that included low muscle mass, sex, ECOG PS, and clinical frailty scale. Of these, only the study median PMI cut-off was significant in the univariate analysis; however, none were independently associated with an impaired 3-month OS in multivariable analysis (Table 2).

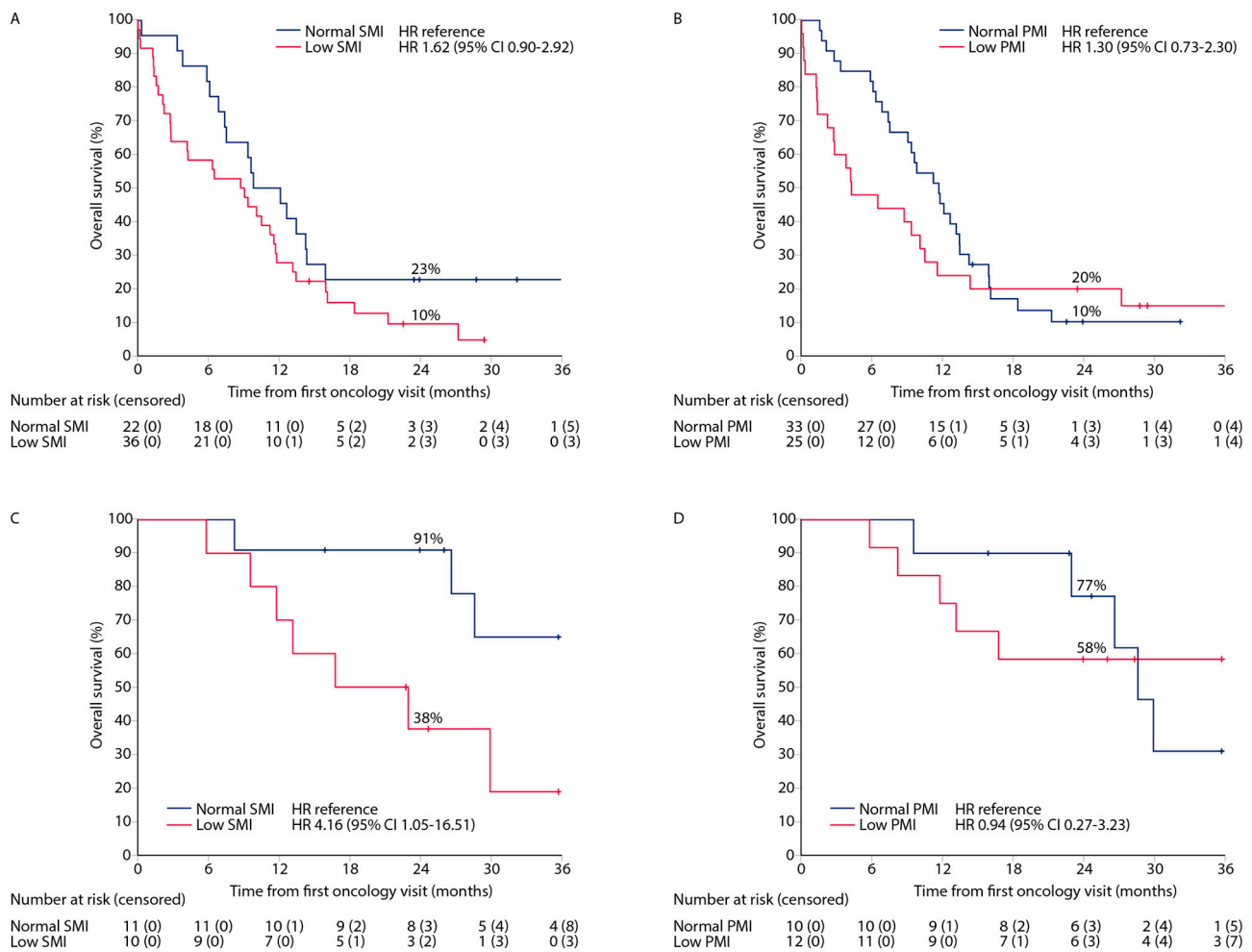
### 3.7. Long-Term Overall Survival

The median reverse Kaplan–Meier follow-up was 29 months (IQR 24–38) with no patients lost to follow-up.

Patients in the non-curative group showed no statistically significant long-term OS associations between the low and normal SMI groups (HR 1.62 (95% CI 0.9–2.9)) with 24-month OS rates of 10% and 23%, respectively (Figure 5A). Low and normal PMI showed crossing of the curves after 12 months in the non-curative group ( $n = 58$ ) (Figure 5B).

The 24-month OS rates in the palliative chemotherapy group ( $n = 31$ ) were 23% and 31% in the low and normal SMI groups, respectively, with an HR of 1.19 (95% CI 0.53–2.7). Respective 24-month OS rates were 63% and 15% in the low and normal PMI groups.

Patients in the curative treatment group with low SMI had an impaired long-term survival (HR 4.16 (95% CI 1.1–17)) with 24-month OS rates of 38% and 91% in the low and normal SMI groups, respectively (Figure 5C), whereas PMI curves crossed after 24 months (Figure 5D).



**Figure 5.** The Kaplan–Meier plots for long-term OS for patients in non-curative treatment intent group based on optimized skeletal muscle index (SMI; **A**) and psoas muscle index (PMI; **B**) and for patients in curative treatment intent group based on SMI (**C**) and PMI (**D**).

#### 4. Discussion

Our study suggests that low SMI is a predictor of worse 3-month OS independent of oncological and geriatric performance scores (ECOG PS and clinical frailty scale, respectively) in frail older adults with cancer. The study enrolled only patients at risk of frailty based on G8-screening ( $\leq 14/17$  points) who underwent full CGA; fit older adults not at risk of frailty ( $>14/17$  points) were excluded. Low PMI was predictive of 3-month survival in the univariate analysis but did not retain its statistical significance in the multivariable model. Low SMI was also associated with impaired long-term OS in the curative intent treatment group. Most patients allocated to BSC or follow-up (i.e., did not receive active oncological treatment) had low SMI. CT-determined low muscle mass could thus aid in the assessment of the treatability of these patients.

Several SMI and PMI cut-offs for low muscle mass in different patient populations have been proposed in the literature (Table 2). We noted that previously published SMI cut-offs by Prado et al. [12], Martin et al. [39], Baracos et al. [40], van Vledder et al. [41], and Camus et al. [42] classified most of our cohort's older frail patients as having low muscle mass, and these classifications did not predict 3-month OS. In the studies by Prado et al. and Martin et al., the patients were significantly younger and had higher mean BMI values and notably higher SMI values than the patients in the current study. Patients in these two studies had a variety of primary tumors with stage IV disease in 38 and 52% of patients, respectively. The lower cut-off values by van Vledder et al. did not predict 3-month OS,

probably due to the selection of fit patients undergoing liver resection for colorectal liver metastases, unlike our patient material, which excluded the fit. In the study by Camus et al., the patients' ages were closer to the current cohort but with higher mean SMI values, probably reflecting the study population consisting of patients with lymphoma that mostly did not affect the gastrointestinal canal and thus their nutritional status. Similarly, the PMI cut-offs from surgical scenarios by Amini et al. [43] and Joglekar et al. [44] did not predict survival, but they classified patients into low and normal muscle mass groups more evenly than the cited SMI cut-offs from the literature. Indeed, PMI has been used mostly in surgical scenarios rather than oncological ones, and the cut-offs may not be applicable due to the differences in patient cohorts. In all the abovementioned studies, patients' median ages were lower, and frailty was not reported (Table S2). Similar to this study, two of five studies assessing SMI included patients with a variety of solid tumors. Oncological therapy was assessed in five of the seven studies, as in our study, and surgical treatment in three studies. We clearly had the highest proportion of patients with locally advanced non-resectable, or metastatic tumors. To our knowledge, there are no frail older adult patient cohorts in the literature with which to compare our cut-offs. Larger cohorts are needed to validate our proposed cut-off values.

Our findings align with previous research showing that CT-based body composition analysis is a promising method for identifying patients with muscle-wasting conditions and impaired OS in many cancers [16,24,45–50]. Our results showed a non-significant association between low SMI and impaired long-term survival in the non-curative intent group. The association was statistically significant only in the curative intent treatment group that underwent surgical resection with or without neo-/adjuvant treatment. However, the baseline measurement of PMI seemed to lose its predictive value after 1 year in both instances.

BMI as a measure of body composition was not associated with OS or muscle mass in the current cohort. High BMI may be linked with worse cancer survival outcomes, as shown in two large meta-analyses [51,52], and in a large meta-analysis of early-stage breast cancer, obesity (BMI > 30) was found to be associated with a 75% and 34% mortality increase in premenopausal and postmenopausal women, respectively [53]. However, in a study of 41,015 patients with colorectal cancer, BMI values from 25 to 29 and from 30 to 35 were associated with better OS rates than normal BMI in adults  $\geq 70$  years of age (HRs of 0.77 (0.73–0.81) and 0.77 (0.69–0.87), respectively) with similar HRs for cancer-specific survival [54]. Similarly, in 471 adults  $\geq 80$  years of age undergoing a curative resection of stage I–III colorectal cancer, BMI  $\geq 23$  was found to be associated with better cancer-specific survival (0.54 (0.29–0.94) and OS (0.45 (0.30–0.65)) than BMI < 23 in multivariable analysis [55]. In addition, high BMI and better survival outcomes were reported in a meta-analysis of patients receiving immuno-oncological treatment [56]. The mechanism for the association between BMI and cancer mortality is unclear, but it has been suggested that a higher BMI may interfere with the effective delivery of oncological treatments [57] and contribute to the development of fatal comorbidities [58,59]. However, it is feasible that a higher BMI is reflective of higher energy and nutrient reserves [60] and is thus protective against cancer cachexia and mortality. The use of BMI alone to assess body composition in older adults is not advisable, considering the conflicting evidence, as it does not measure the highly variable proportions of lean or adipose tissue mass.

In line with our results, low muscle mass has previously been shown to be associated with a higher 3-month mortality in patients undergoing cancer surgery (e.g., for bladder cancer [61], abdominal emergencies in older adults [62], glioblastoma [63], liver metastases [64], and hepatocellular carcinoma [65]).

In the current study, only low PMI was associated with frailty as defined by clinical frailty scale points ranging between 5 and 9, ECOG PS 3 and 4, and impaired hand-grip strength. The psoas muscles are important in maintaining posture and are probably preserved in physically active patients (ECOG PS 0–2 and clinical frailty scale 0–4). It is unclear whether inactivity is reflected equally in reduced psoas or total muscle mass, but



SMI is regarded as the gold standard surrogate for whole body muscle mass [20,24]. The finding regarding the SMI's association with OS, but not with these measures of functional status, suggests that SMI probably reflects some aspects of fitness not readily detected at the geriatrician's or oncologist's appointment.

Low muscle mass with both muscle indexes was associated with impaired nutritional status, according to the GLIM classification. Many patients suffered from advanced diseases with inflammatory components (elevated CRP in 36% and hypoalbuminemia in 21%), which contribute to cachexia-related muscle loss (such as in pancreatic cancer). In addition, aging-related sarcopenia and frailty can cause malnutrition through several other mechanisms, including less activity, lower energy needs, food intake, and appetite, impaired cognition, and disrupted social functioning [66]. Previous surgery and fasting can also cause low muscle mass. The etiology of low muscle mass in this cohort remains unclear and is probably multifactorial.

The opportunistic use of CT-based body composition analysis is feasible and can complement geriatricians and oncologists in treatment decision-making. Our results suggest that low SMI is associated with treatment allocation to BSC, as 78% of these patients had low SMI. Based on our results, SMI would be preferred over PMI for the assessment of muscle mass in frail older adults, as only SMI remained significant in the multivariable 3-month OS model. We hypothesize that psoas measurements may be more susceptible to inter-reader and inter-study variability due to the smaller muscle area than the whole muscle area; hypothetically, small measurement errors could result in a comparatively large variability in PMI values.

The major limitation of this study is the small patient sample with varying types of cancer, stages, and treatment intents. There is thus a clear need for validation of the results in larger, homogenous patient cohorts. Another limitation (or strength) is the exclusion of fit older adults and the inclusion of only at-risk-of-frailty and CGA-assessed older adults. This affects long-term OS estimates, as these frail patients have a relatively short life expectancy, even without cancer [67,68]; patients in non-curative treatment have a less-than-12-month life expectancy due to a high unmet need in most cases, and the treatment intent necessitates the separation of the treatment intent groups. The exclusion of fit older adult patients (G8-screening > 14 points) suggests that our cut-off values are probably not applicable to these patients, warranting further research in this group. Furthermore, a time delay of 2 months between the CT scan and CGA was accepted, in which time the muscle mass may have changed, and we excluded newer scans taken after treatment initiation. Modest area-under-the-curve values, positive and negative predictive values, and broad CIs also indicate the need for further research in larger patient cohorts. The major strengths of the study are the primary endpoint and the patient population, where treatment decisions are extremely challenging. The 3-month OS, commonly used in oncological studies [64,69,70], was chosen to control the heterogeneity of the patient material and to serve as a surrogate for treatability decisions. The study is also a real-life application of body composition analysis, where all consecutive frail older adults were enrolled, and it reflects the current clinical practice of a modern geriatric oncological unit.

## 5. Conclusions

CT-determined low SMI is independently associated with impaired 3-month OS in frail older adults with cancer treated with non-curative intent. In addition, low PMI was associated with impaired functional status, and both muscle indexes were associated with malnutrition. Low SMI could thus be used as an indicator of treatability alongside oncologic and geriatric assessments and can help in the treatment decision between active oncological treatment and best supportive care or follow-up.

**Supplementary Materials:** The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/cancers15133398/s1>, Table S1: Extended patient characteristics for non-curative and curative treatment intent groups; Table S2: Extended associations between optimized low skeletal muscle index (SMI) and patient characteristics; Table S3: Extended associations between optimized low psoas muscle index (PMI) and patient characteristics; Table S4: Demographic comparisons of the referred SMI/PMI cut-off studies in the literature.

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**Data Availability Statement:** All the relevant data are presented in the article.

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