Prognostic Role of Muscle Depletion in Palliative Care Patients With Incurable Cancer: A Retrospective Study

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Abstract

Background: Depletion of muscle mass and strength has been proven to be a negative prognostic indicator for patients with cancer receiving anticancer treatment. However, little is known about its role in palliative care patients. The objective of this study was to evaluate the prognostic significance of muscle depletion in predicting survival among patients in palliative care.

Methods: We retrospectively examined the association between muscle mass and strength and prognosis in patients with incurable solid cancer who are supported by a palliative care team at a university hospital. Psoas muscle index (PMI) at the level of the fourth lumbar vertebra was employed as the muscle mass index. Pinch grip strength (PGS) was used as the muscle strength index. Cox proportional hazards analysis was performed to evaluate the factors independently associated with overall survival.

Results: A total of 78 patients were included in this study (35 male, median age 67 years). Median survival was 87.5 (95% confidence interval [CI] 50−124) days. After adjustment for age, sex, albumin, edema, and performance status as potential confounders, loss of PMI (HR=0.998, 95% CI 0.996−0.999; P=0.003) and PGS (HR=0.73, 95% CI 0.55−0.97; P=0.030) independently predicted the overall survival.

Conclusion: Depletion of muscle mass and strength is an independent predictor of survival in patients with incurable solid cancer receiving palliative care. PMI and PGS may help to better assess the prognosis of patients in palliative care.

Background

Muscle depletion is a hallmark of cancer cachexia [1] and affects the majority of patients with cancer in palliative care [2]. Previous studies showed that sarcopenia [3] greatly affects patient outcomes [4] and is a strong negative prognostic indicator for survival across various stages and cancer types [5-7]. However, most of the reports have been conducted in patients undergoing cancer treatment with a prognosis of more than several months. Studies on muscle depletion in palliative care patients are few, and no studies on patients with a prognosis of less than several months have been conducted.

For patients receiving palliative care and their families, lack of precise information about the prognosis could negatively affect treatment outcomes, result in poor symptom management, and deny the opportunity to prepare for death [8]. Thus, more accurate prognostic predictions are crucial in patients receiving palliative care [9]. Several prognostic tools have been developed to predict the prognosis of palliative care patients [10-13]; however, muscle depletion is not adopted in these tools [9]. The diagnostic criteria for sarcopenia primarily include muscle mass and strength [3], which are now included in the criteria for cancer cachexia [1]. The skeletal muscle is a major storage of body proteins that play a central role in vital activities and has various endocrine and paracrine functions [14, 15]; moreover, the skeletal muscle is now considered a vital organ in homeostasis. Hence, muscle depletion is considered a potential prognostic parameter.

In this study, we aimed to report the effect of muscle depletion on survival among palliative care patients. We retrospectively examined the association between muscle depletion and prognosis in patients with incurable solid cancer who are supported by a palliative care team.

Methods

Study design and participants

In this single-center, retrospective, and observational study, we examined data of consecutive patients with cancer who are treated at the Palliative Care Center of Aichi Medical University Hospital, Japan, from July 2017 to April 2018. A palliative care team visited the hospitalized patient who needed palliative care based on consultation from the attending physician. The Ethics Committee of Aichi Medical University Hospital approved the study on October 29, 2019 (reference no: 2019-104) , and the need for written informed consent was waived owing to the retrospective nature of the study. Participants were guaranteed the right to withdraw from the study using an opt-out procedure according to the ethics committee guidelines. The research was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. Overall survival (OS) was the main endpoint. The main inclusion criteria were incurable solid cancer and age ≥18 years. The exclusion criteria included the following: no appropriate computed tomographic (CT) image obtained within 30 days before the first consultation and no pinch grip strength (PGS) data. OS was defined as the time between the first consultation and death. Patients who were still alive at the time of analysis were censored at a fixed date.

Demographic factors and physical status

Demographic factors, including age, sex, primary tumor site, and clinically relevant data (such as body weight, height, serum albumin level, and status of chemotherapy) were obtained. Body mass index (BMI) was calculated using the following formula: BMI = actual body weight (kg)/squared body height (m^2). Edema was assessed and categorized as follows: 0, no edema; 1, partial; 2, half body; and 3 full body (anasarca). Physical function was evaluated using the Eastern Cooperative Oncology Group performance status (ECOG PS).

Muscle mass and radiodensity assessment

The psoas muscle area of the patients referred to the palliative care team was routinely measured using the most recent CT image obtained within 30 days before consultation. CT was performed using a 128-slice CT scanner (SOMATOM Definition AS+; Siemens AG, Munich, Germany) or a 64-slice CT scanner (SOMATOM Definition AS; Siemens AG, Munich, Germany). The region of interest was drawn manually on the plain CT image at the fourth lumbar level [16, 17] using a commercially available image software (ShadeQuest/ViewR version 1.22.008; Yokogawa Medical Solutions Corporation, Suginami, Tokyo, Japan), and the area and average density were calculated automatically. The muscle area was the total area of the bilateral psoas muscles, which was normalized for patient height (m^2) to calculate the psoas

muscle index (PMI; in mm^2/m^2). Psoas muscle radiodensity (PMD) was calculated as the average radiodensity value of the bilateral psoas muscles.

Muscle strength assessment

In the hospital, standard muscle strength is typically assessed in patients at risk of malnutrition by hand grip strength measurement. However, palliative care patients often could not maintain an optimal posture for hand grip measurement. Thus, the palliative care team adopted the pulp PGS measurement, which allows for muscle strength assessment even in patients with reduced physical ability [18], as the standard muscle strength evaluation method. PGS of the dominant hand was measured [19] with the patents in the sitting position using a digital pinch gauge (Jamar Digital Plus, Lafayette Instrument, Lafayette, USA) during the initial visit of the palliative care team.

Statistical analyses

Continuous variables were presented as medians with interquartile ranges (IQR); categorical variables, as counts and percentages. Continuous variables were compared with the Mann-Whitney U test and categorical variables with Fisher's exact test. OS was estimated by the Kaplan-Meier method and compared using the log-rank test. The association between survival and muscle depletion was assessed by a multivariable Cox proportional hazards analysis, with adjustment for several confounding factors. The covariates included in the models were factors affecting muscle status, such as age and sex, and known prognostic parameters, including albumin level [20], edema [12], and ECOG PS [13]. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated. For all statistical tests described, a p-value <0.05 was considered statistically significant. Statistical analyses were performed using EZR, version 1.41 [21], which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Of the 165 patients with incurable solid cancer who were supported by a palliative care team, 104 were eligible and had PGS measurements. Twenty-six patients who lacked an appropriate CT scan were excluded. Thus, a total of 78 consecutive patients with available CT scans and PGS measurement were included in the final analysis (**Fig. 1**). The baseline characteristics of the patients are presented in **Table 1**. Median age of the 78 cases was 67.0 years, and 35 (44.9%) were men. Median PMD was 45.0 (IQR, 40.8–48.5) HU in males and 44.0 (IQR, 37.3–47.3) HU in females. Median PMI was 559 (IQR, 469–677) mm^2/m^2 in males and 452 (IQR, 411–519) mm^2/m^2 in females. Median PGS was 3.5 (IQR, 2.6–4.3) kg in males and 2.4 (IQR, 2.0–2.9) kg in females. During the study period, 74 (94.5%) deaths were recorded. Median follow-up for survivors was 865 (IQR, 847–889) days. Median OS was 87.5 (95% CI 50–124) days.

Moreover, patients were divided into two groups according to the median of PMI or PGS, and Kaplan-Meier curves of PMI and PGS were examined by sex (**Fig. 2**). Patients with a low PMI showed a significantly shorter OS than those with a high PMI among males (P=0.049), but not in females

(P=0.066). Patients with a low PGS showed a significantly shorter OS than those with a high PGS in both males (P=0.003) and females (P=0.032). Univariate analysis showed that albumin levels (HR 0.5, 95% CI 0.35−0.72), edema (HR 1.81, 95% CI 1.35−2.43), performance status (PS) (HR1.38, 95% CI 1.11−1.73), PMI (HR 0.99, 95% CI 0.99−0.99), and PGS (HR 0.63, 95% CI 0.49−0.81) were associated with survival (Table 2), whereas PMD (HR 0.98, 95% CI 0.96−1.01) was not. Both PMI (HR 0.99, 95% CI 0.99−0.99) and PGS (HR 0.73, 95% CI 0.55−0.97) were independently associated with OS in the multivariate analysis adjusted for age, sex, albumin levels, edema, and ECOG PS.

Discussion

In this study, we examined whether muscle depletion, i.e., loss of muscle mass or muscle strength, in patients receiving palliative care is related to prognosis. We retrospectively examined the data obtained in daily clinical practice among patients with various types of cancer who were supported by a palliative care team at a university hospital. A significant association between PMI, which was employed as an indicator of muscle mass, and survival was found. PGS, which was used as a muscle strength index, also was significantly associated with survival. These results suggest that muscle mass and strength in palliative care patients decline as their status deteriorates and that muscle depletion is associated with prognosis. Hence, our study shows that muscle depletion is a potential prognostic parameter.

PMI, which is a measure of muscle mass, was an independent prognostic factor in palliative care patients. PMI measurement has been widely used as an alternative method for evaluating all major skeletal muscles at the lumbar level, and PMI has been associated with prognosis in patients with cancer [22, 23] and with surgical outcomes [24]. However, the previous studies have examined patients receiving anticancer therapy with a prognosis of more than several months. In a recent systematic review, Wiegert et al. [25] reported the association between low muscle mass and survival in patients with incurable cancer and identified that only two [26, 27] of 13 studies had shown low muscle mass as a significant independent predictor of survival in a multivariable analysis; they concluded that the evidence of the association between low muscle mass and survival in patients with incurable cancer is insufficient. Moreover, in the review, the methods for muscle mass evaluation, patient age, type of cancer, and definition of low muscle mass varied across the studies. Thus, further studies may be needed to clarify these factors. In addition, previously reported median OS for incurable cancer ranged from 130 days [28] to 32.3 months [29]. In our study, the median OS was 78.5 days, suggesting that more terminally ill patients are included in our investigation, which in turn had a significant effect on our results. No other study that examined the association between muscle mass and prognosis in a cohort with a high proportion of terminally ill patients has been conducted.

PGS was also an independent prognostic factor in palliative care patients. In the evaluation of muscle strength in patients with cancer, hand grip strength measurement has been widely used as a standard approach [30]. Previous studies showed that reduced hand grip strength is associated with worse prognosis [31, 32] and poor treatment outcome [33, 34]. However, these studies involved patients with cancer with a longer prognosis who are receiving anticancer treatment. Thus, the relationship between

muscular strength and prognosis in palliative care patients whose prognosis is within several months has not been reported. Our study clarified such relationship using PGS as an index of muscle strength. Majority of the patients had PS 3 or 4, with a significantly reduced physical function. PGS is useful in assessing muscle strength in patients with limited physical function [18, 35], and its invasiveness is minimal. Hence, PGS measurement was considered to be a feasible procedure for muscle strength assessment in palliative care patients.

In our study, when comparing sex-stratified survival rates by median PMI and PGS, the differences in prognosis were more pronounced in men than in women. This may reflect sex differences in muscle depletion. Wallengren et al. examined the changes in muscle mass using dual-energy X-ray absorptiometry scans that were performed 2 years before the death of 471 palliative care patients [36] and reported sex differences. In their study, the males had clear muscle mass loss at the end of life, which was not observed in females. Various hormones, cytokines, and the immune system are associated with cachexia progression and muscle depletion [37, 38] and are considered vital factors that cause sex differences. Elucidation of the mechanism of the sex difference is one of the keys to measures for muscle depletion and requires further investigation.

Furthermore, our study suggests that PMI or PGS could be a parameter for prognostic prediction. The parameters used in this study, i.e., edema, albumin levels, and PS, have also been adopted in several prognostic tools [9]. Although PS, which reflects physical functions, has been employed as a parameter [13], no tool included muscle depletion [9]. PMI and PGS may be promising parameters for a more accurate prognostic prediction in palliative care patients.

This retrospective study has some limitations. Patients without PGS measurement and CT scans were excluded from the analysis, which in turn possibly resulted in selection bias. Moreover, the PGS values analyzed in this study were obtained from daily clinical practice and thus may not have been measured in a strict manner. Hence, prospective and validation studies involving larger palliative care populations are warranted.

Conclusion

Muscle mass and strength of patients with incurable solid cancer are related to prognosis. Muscle mass (PMI) evaluation using CT and PGS measurement, which can be performed with little burden on patients with a reduced physical function, are useful tools for prognostic prediction in palliative care patients. For a more accurate prognostication, further studies on PMI and PGS as well as on the characteristics of the cancer type, and other prognostic parameters in a larger palliative care population are needed.

Abbreviations

PMI: Psoas muscle index; PMD: Psoas muscle radiodensity; PGS: Pinch grip strength; OS: Overall survival; CT: Computed tomographic; BMI: Body mass index; ECOG PS: Eastern Cooperative Oncology

Group performance status; IQR: Interquartile ranges; CI: Confidence intervals; HR: Hazard ratio

Declarations

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was performed according to the principles set out in the Declaration of Helsinki 1964 and all subsequent revisions and was approved by the Ethics Committee of Aichi Medical University Hospital (reference no: 2019-104). Due to the nature of the retrospective design, the requirement to obtain informed consent was waived by the Ethics Committee.

Consent for publication

Not applicable.

Competing Interest

The authors declare that they have no competing interest.

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Tables

Table 1. Patient characteristics

n=78	
Age (years)	67.0 (55.3−74.0)
Sex, n (%)	
Male	35 (44.9)
Female	43 (55.1)
Body mass index (kg/m^2)	19.6 (17.0−21.5)
Cancer primary site, n (%)	
Esophagus, stomach	18 (23.1)
Colon	12 (15.4)
Hepatobiliary-pancreatic organ	14 (17.9)
Lung	8 (10.3)
Breast	12 (15.4)
Gynecological	11 (14.1)
Other	3 (3.8)
Albumin (g/dL)	2.75 (2.3−3.38)
Edema, n (%)	
0, none	42 (53.8)
1, partial	25 (32.1)
2, half body	9 (11.5)
3, full body	2 (2.6)
ECOG PS, n (%)	
1	11 (14.1)
2	16 (20.5)
3	30 (38.5)
4	21 (26.9)
Palliative chemotherapy, n (%)	19 (24.4)
Psoas muscle density (HU)	
Male	45.0 (40.8−48.5)
Female	44.0 (37.3−47.3)

Psoas muscle index (mm^2/m^2)	
Male	559 (469–677)
Female	452 (411–519)
Pinch grip strength (kg)	
Male	3.5 (2.6–4.3)
Female	2.4 (2.0–2.9)

ECOG PS, Eastern Cooperative Oncology Group performance status

Table 2. Univariate and multivariate Cox regression analyses for mortality in palliative care patients

	Univariate analysis			Multivariate analysis					
				For psoas muscle index			For pinch grip strength		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age	1.01	0.99–1.03	0.219	1.00	0.98–1.02	0.799	1.00	0.98–1.02	0.816
Sex	1.18	0.74–1.89	0.491	0.82	0.48–1.39	0.465	0.86	0.50–1.48	0.581
Albumin	0.50	0.35–0.72	<0.001	0.82	0.51–1.31	0.397	0.75	0.48–1.17	0.206
Edema	1.81	1.35–2.43	<0.001	1.49	1.05–2.13	0.271	1.35	0.95–1.91	0.095
ECOG PS	1.38	1.11–1.73	0.004	1.29	1.01–1.66	0.043	1.26	0.99–1.60	0.063
Psoas muscle density	0.98	0.96–1.01	0.160						
Psoas muscle index	0.997	0.996–0.999	<0.001	0.998	0.996–0.999	0.003			
Pinch grip strength	0.63	0.49–0.81	<0.001				0.73	0.55–0.97	0.030

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status
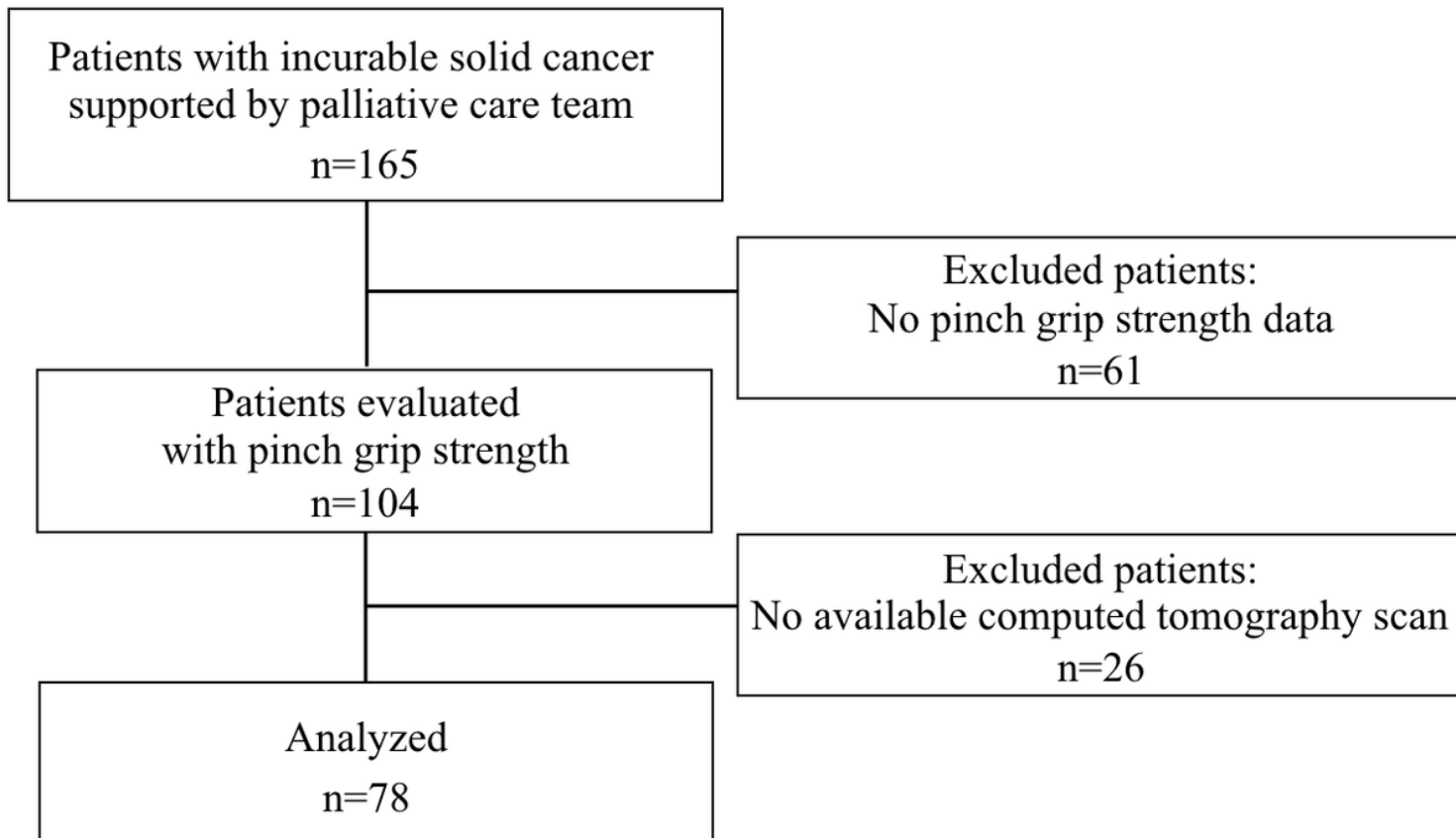
Figures

Figure 1

Flow diagram of the study. Consecutive adult patients with solid cancer (n = 165) were examined for eligibility.
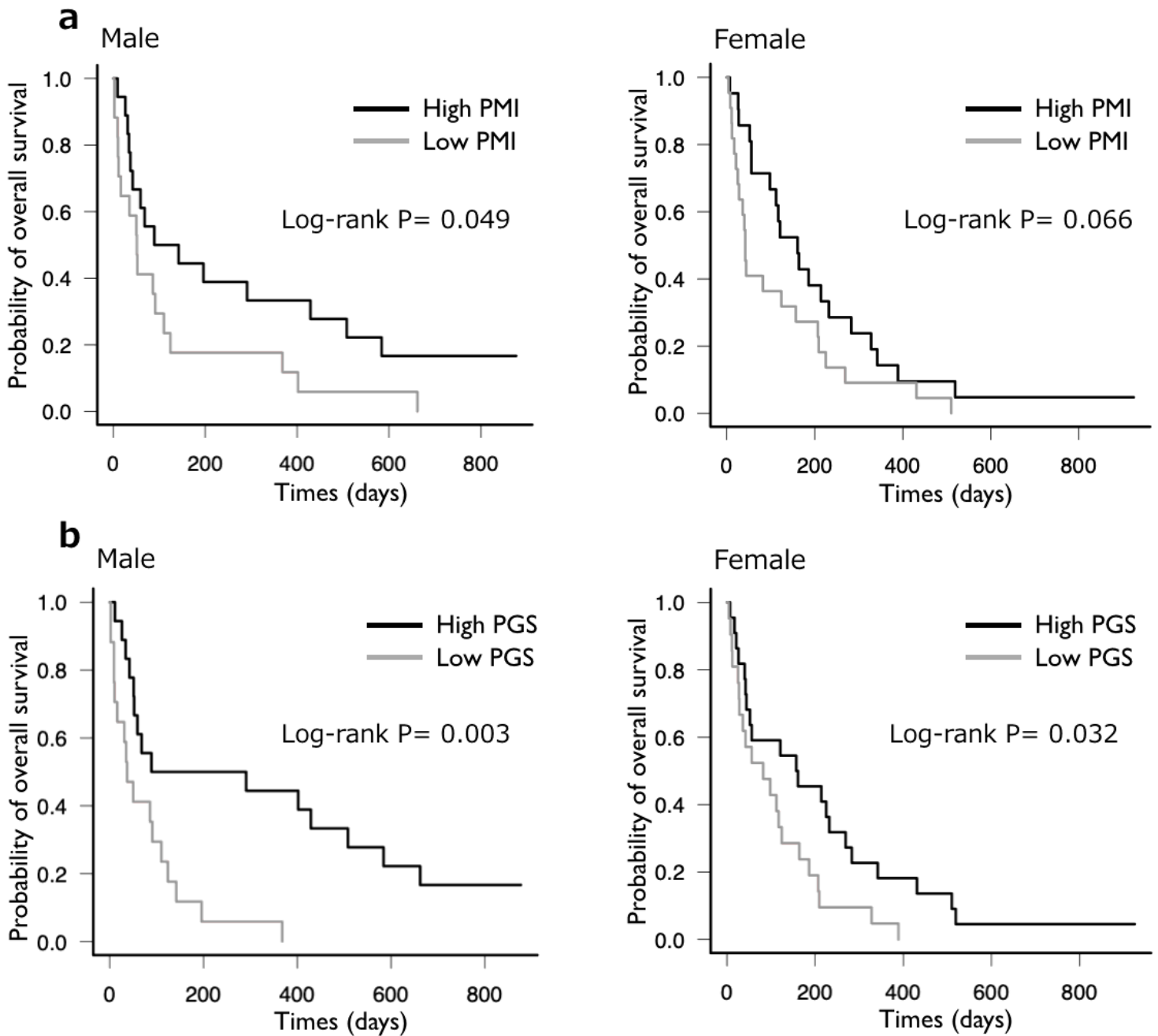
Figure 2

a. Kaplan-Meier survival curves stratified by the median value of psoas muscle index (PMI) in male and female patients. b. Kaplan-Meier survival curves stratified by the median value of pinch grip strength (PGS) in male and female patients.