Importance of skeletal muscle mass during chemotherapy in patients with hematological malignancies: A retrospective study

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Abstract

Objective:

This study investigated whether baseline or alteration in muscle mass affects complications during chemotherapy or overall survival (OS) in hematological malignancies.

Methods:

Skeletal muscle index (SMI) was evaluated by bioimpedance analysis before and after chemotherapy in patients with hematological malignancies, and the association between muscle mass and clinical data was retrospectively analyzed.

Results:

Exactly 104 patients were enrolled, with a mean age of 62.2 years. SMI was 7.85 and 6.08 in male and female patients under 65 years and 7.10 and 5.92 over 65 years, before chemotherapy, respectively. Lower baseline SMI was not correlated with worse OS in total patients (p=0.915)**.** After a median measurement interval of 30 days after chemotherapy (n=67), body weight and SMI decreased by 2.73% and 2.87% (mean), respectively. The decrease in body weight correlated with the loss of trunk muscle mass (R^2=0.2107) but was more strongly associated with the loss of lower limbs muscle mass (R^2=0.3985). The muscle mass of lower limbs significantly decreased in lymphoma patients who experienced febrile neutropenia (-0.42% vs -6.04%, p=0.040). OS significantly decreased in lymphoma patients with loss of lower limbs muscle ≥2.8% (p=0.0327).

Conclusions:

Muscle loss occurred following anti-cancer treatments, significantly contributing to worse outcomes. Body composition assessment and relevant multi-modal prevention of

muscle loss may be vital for patients receiving chemotherapy for hematological malignancies.

Keywords: sarcopenia, malignant lymphoma, febrile neutropenia, skeletal muscle index, bioimpedance analysis

What is already known on this topic:

- The prognosis of patients with solid organ cancers receiving systemic chemotherapy was reportedly worsened in patients with sarcopenia.

What this study adds:

- Muscle loss of lower limbs occurred following anti-cancer treatments in patients with hematological malignancies, significantly contributing to worse outcomes.

How this study might affect research, practice, or policy:

- Assessment of body composition and relevant multi-modal prevention of muscle loss may be vital for patients receiving chemotherapies for hematological malignancies.

INTRODUCTION

Sarcopenia refers to age-related loss of muscle mass, with low muscle strength and/or low physical performance [1]. In cancer patients, especially in older patients, muscle mass and/or physical functions tend to decrease before cancer treatment. Furthermore, cancer cachexia may lead to exacerbation of muscle loss in affected patients [2]. We treat such patients with systemic chemotherapy, but the effects of chemotherapy on skeletal muscle are not fully understood.

Bioelectrical impedance analysis (BIA) is a method for estimating muscle mass. This method measures body impedance with a low-level current conducted through the tissues and enables the estimation of skeletal muscle [3]. The prognosis of patients with solid organ cancers receiving systemic chemotherapy was worse in patients with decreased muscle mass in various clinical trials [4]. However, the effects of muscle mass in patients with hematological cancers have not been fully studied. Thus, this study aimed to evaluate whether baseline muscle mass affects complications such as febrile neutropenia (FN) and long-time prognosis in systemic chemotherapy and whether alteration in muscle mass affects prognosis or is affected by complications during chemotherapy in hematological malignancies.

METHODS

We included patients with hematological malignancies treated with systemic chemotherapy and their skeletal muscle measured by BIA, excluding hematopoietic stem cell transplantation from January 2016 to November 2021. Their skeletal muscle mass was examined after breakfast with a portable direct segmental multifrequency BIA device (InBody 770®, InBody S10®, InBody Japan, Tokyo, Japan) before and after systemic

chemotherapy. Clinical parameters were extracted from medical charts. The episode of FN was collected during the subsequent cycle of chemotherapy immediately after the evaluation of BIA. The significance of differences was evaluated by the Student's t-test using Excel (Microsoft Office 365; Microsoft, Richmond, CA, USA), and Fisher's exact test, log-rank test and Cox regression analyses were done using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [5]. Statistical significance was set at $p < 0.05$.

RESULTS

Patient characteristics

We enrolled 59 males and 45 females, and about two-thirds of patients had lymphomas (supple Table1). The mean age was 63.4 and 60.6 years in males and females, respectively. Exactly 73 patients were enrolled with newly diagnosed hematological malignancies at initial chemotherapy. Exactly 42 (40%) patients developed FN. The mean interval between tests was 30 days, and 67 (64.4%) patients were able to assess both before and after chemotherapy.

Skeletal muscle mass at baseline

SMI was in males under 65 years, with 7.85±0.68 kg/m^2, in males over 65 years, with 7.10±0.70, in females under 65 years, with 6.08±1.47, and in females over 65 years, with 5.92±0.90. We defined low SMI as <7.0 kg/m^2 in males and 5.7 kg/m^2 in females based on the consensus by the Asian Working Group for Sarcopenia [1]. The number of patients with low SMI accounted for 8.6% of males under 65 years but 44.4% of males over 65 years, 59.0% and 43.5% of females under and over 65 years, respectively.

Impact of muscle mass during pre-chemotherapy with incidence of FN and overall survival

Low muscle mass is associated with overall survival (OS) in patients with cancer [6], and affects the increased risk of FN in esophageal cancer patients treated with systemic chemotherapy [7]. When we analyzed whether SMI before chemotherapy affects the development of FN or clinical outcome, no difference in SMI was observed between patients with or without FN in male (p=0.218) and female (p=0.979) (Supplementary Figure1A), and low SMI before chemotherapy did not affect OS (p=0.915) (Supplementary Figure 1B).

Change in skeletal muscle mass change during chemotherapy

SMI decreased -2.01±9.28 %, in male < 65 years, -2.04±5.89 %, in male > 65 years, -2.59±10.4 %, in female < 65 years, and -4.90±6.31 %, in female >65 years, during chemotherapy, respectively. Though the decrease in skeletal muscle may be associated with body weight, we checked the relationship between weight loss and the decrease in muscle mass. The mean weight change was -2.73% (median -3.09%) and correlated with the change rate of lower limbs muscle mass (R^2=0.3985) and correlated better than the change rate of trunk muscle mass (R^2=0.2107). The absence or presence of low SMI before chemotherapy was not associated with changes in weight or muscle mass (data not shown). These results suggest that the main cause of weight loss can be attributed to lower limbs muscle mass during chemotherapy regardless of pre-chemotherapy muscle mass.

Correlation between change in muscle mass during chemotherapy and FN

Next, we analyzed the influence of FN development on weight loss or change in muscle mass. Even though FN did not affect the degree of change in weight (-2.30±3.96% vs -3.45±4.05%, p=0.270), trunk muscle mass (-2.84±4.79% vs -3.88±5.12%, p=0.42), and SMI (-1.93±7.28% vs -4.48±8.39%, p=0.22), but significantly decreased lower limbs muscle mass (-0.83±9.63% vs -6.29±6.03%, p=0.006) (Figure 1A, 1B, 1C, 1D). Even when the analysis was limited to patients with lymphoma, the muscle mass in lower limbs significantly decreased in the FN group (Supplementary Figure2). The absence or presence of low SMI before chemotherapy did not affect OS analyzed in lymphoma patients (p=0.587) (Figure 1E), but patients whose lower limb muscle mass decreased by ≥2.8% had significantly worse survival rates (p=0.0327) (Figure 1F). Univariate analysis using Cox regression analysis showed that age, sex, body mass index, low SMI before chemotherapy, performance status, development of FN, and B symptoms did not affect OS. However, only muscle mass loss in the lower limbs exceeding 2.8% significantly influenced OS (supple Table2).

DISCUSSION

In this study, we investigated whether baseline muscle mass affects complications such as FN and whether alteration in muscle mass is affected by complications during chemotherapy in hematological malignancies. Skeletal muscle is essential for maintaining activities of daily living. However, until recently, difficulties had been encountered in measuring whole-body skeletal muscle mass. Computed tomography (CT)-based estimation has been tried but is inadequate [8]. The BIA method is relatively inexpensive and can be frequently used clinically. The prevalence of sarcopenia is

approximately 10−16% in healthy people [9] but is reported to be higher in cancer patients at 55.3% [10] and 33% [11]. Sarcopenia reportedly increases toxicity and may induce chemotherapy-induced sarcopenia [12]. However, research on muscle mass during systemic chemotherapy is limited.

Although there is little research examining muscle mass and its therapeutic effects, the occurrence of sarcopenia before treatment in patients with diffuse large B cell lymphoma (DLBCL) was a poor prognostic factor [13]. Due to higher chemosensitivity in hematological malignancies than solid cancers, relatively higher intensity chemotherapy was administered. Therefore, both cancer-related and chemotherapy-related effects induce weight loss. In this study, the rate of weight loss correlated with the loss of lower limbs muscle mass. Further, muscle mass in the lower limbs decreased significantly in patients with FN during chemotherapy. The association between decreased muscle mass and FN is unknown, but inflammatory cytokines and/or appetite loss during FN may play a role. There are few similar studies on this subject, and the ability to measure each area using the BIA method contributed to carrying out our study.

Notably, loss of lower limbs muscle mass during the early phase of treatment is associated with OS in lymphoma. Our findings revealed that OS was associated with a lower limbs muscle mass decrease by ≥ 2.8% after initiation of chemotherapy but not low SMI at pretreatment. The cause of the reduction in lower limbs muscle shortly after initiation of chemotherapy was expected to be the sum of various factors such as severity of disease, metabolic abnormality, corticosteroid, toxicity of chemotherapy, quantity of food intake, and immobility. Decreased lower limbs muscle mass had the highest hazard ratio and statistical significance among existing prognostic factors on lymphoma by univariate Cox proportional hazard model. These data suggest that preserving muscle

mass at the initial phase of systemic chemotherapy is profoundly important. Xiao DY et al. reported that 2.8% of muscle mass area decreased from baseline with 342 patients with DLBCL after completing chemotherapy [14]. Maintaining muscle mass during treatment is essential, but muscle mass during chemotherapy has not been previously discussed. A multidisciplinary approach encompassing nutritional intake and rehabilitation with repeated evaluation of muscle mass using the BIA method is also required.

This study had some limitations. First, the BIA method is simple, quick, and repeatedly conducted without X-ray. However, it has a disadvantage. In this study, measurements of muscle mass were done after breakfast, not before breakfast. In this condition, increased water amount may affect body impedance. However, we measured muscle mass using the same procedure with all patients, therefore, errors between and within the same patients were minimized. Second, muscle mass is thought to be closely related to nutrition, and exercise quality/quantity, but these parameters were not evaluated in this study. Finally, larger studies would be desirable since the study subjects were small and multivariate analysis could not be performed.

In conclusion, muscle wasting and loss during chemotherapy significantly contributes to worse outcomes. Assessment of body composition and relevant multi-modal prevention of muscle mass loss appears vital for patients receiving chemotherapy for hematological malignancies.

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AUTHOR CONTRIBUTIONS

Conceptualization, M.T. , S.K., and S.N.; Data acquisition and processing, M.T., K.K., S.N. and S.K; Clinical work for the patient, M.T., S.N., K.K., M.N., Y.M., R.S., H.Y., M.O., K.S., T.H., S.F., H.M.; Writing—original draft preparation, M.T. and S.N.; Writing—revised draft and editing, I.E. and M.A.; Manuscript supervision, I.E. and M.A.; Project administration, M.T. and S.N. All authors have read and agreed to the published version of the manuscript.

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COMPETING INTERESTS

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ETHICAL DECLARATIONS

Institutional Review Board Statement: This study was conducted per the Declaration of Helsinki and was approved by the review board of the Tokushima University Ethics Committee (Permission number: 2756-2).

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Figure legends

Figure 1. Association between muscle mass and outcome after chemotherapy.

(A, B, C, D) Association between change in weight or muscle mass and febrile neutropenia (FN) . Changes in weight or muscle mass compared between patients with or without FN. Paired t-test was used to analyze statistical significance.

(E, F) Prognosis of lymphoma patients according to muscle mass at baseline or change in muscle mass during chemotherapy. Overall survival of patients with or without low SMI at baseline (E). Overall survival of patients with ≥ 2.8% change in lower limbs muscle mass during chemotherapy (F). Survival analysis in lymphoma patients with or without lower limbs muscle mass during chemotherapy over 2.8 % was conducted by log-rank test.

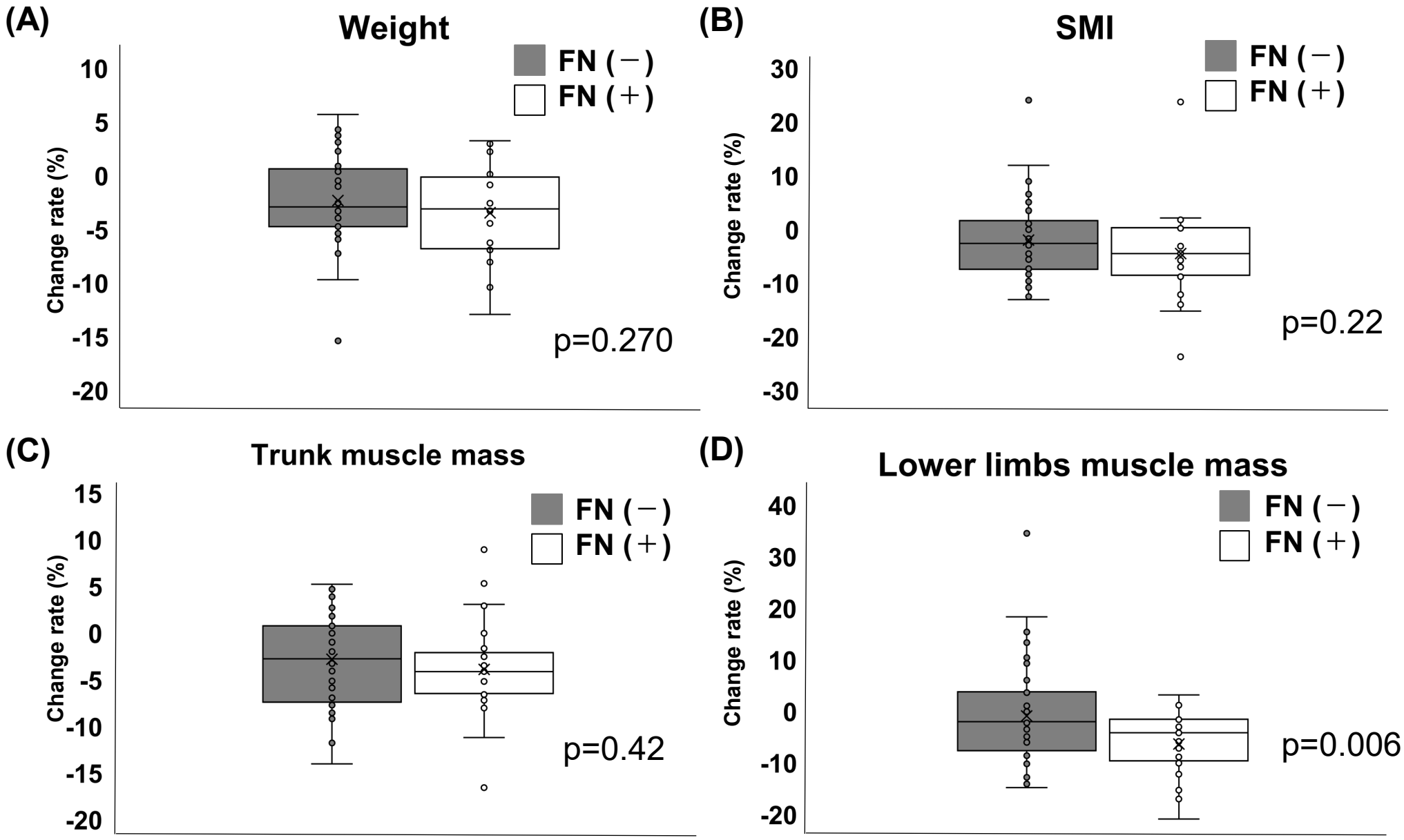
(A)
Weight
FN (−)
FN (+)
Change rate (%)
10
5
0
-5
-10
-15
-20
p=0.270
(B)
SMI
FN (−)
FN (+)
Change rate (%)
30
20
10
0
-10
-20
-30
p=0.22
(C)
Trunk muscle mass
FN (−)
FN (+)
Change rate (%)
15
10
5
0
-5
-10
-15
-20
p=0.42
(D)
Lower limbs muscle mass
FN (−)
FN (+)
Change rate (%)
40
30
20
10
0
-10
-20
p=0.006

Figure1

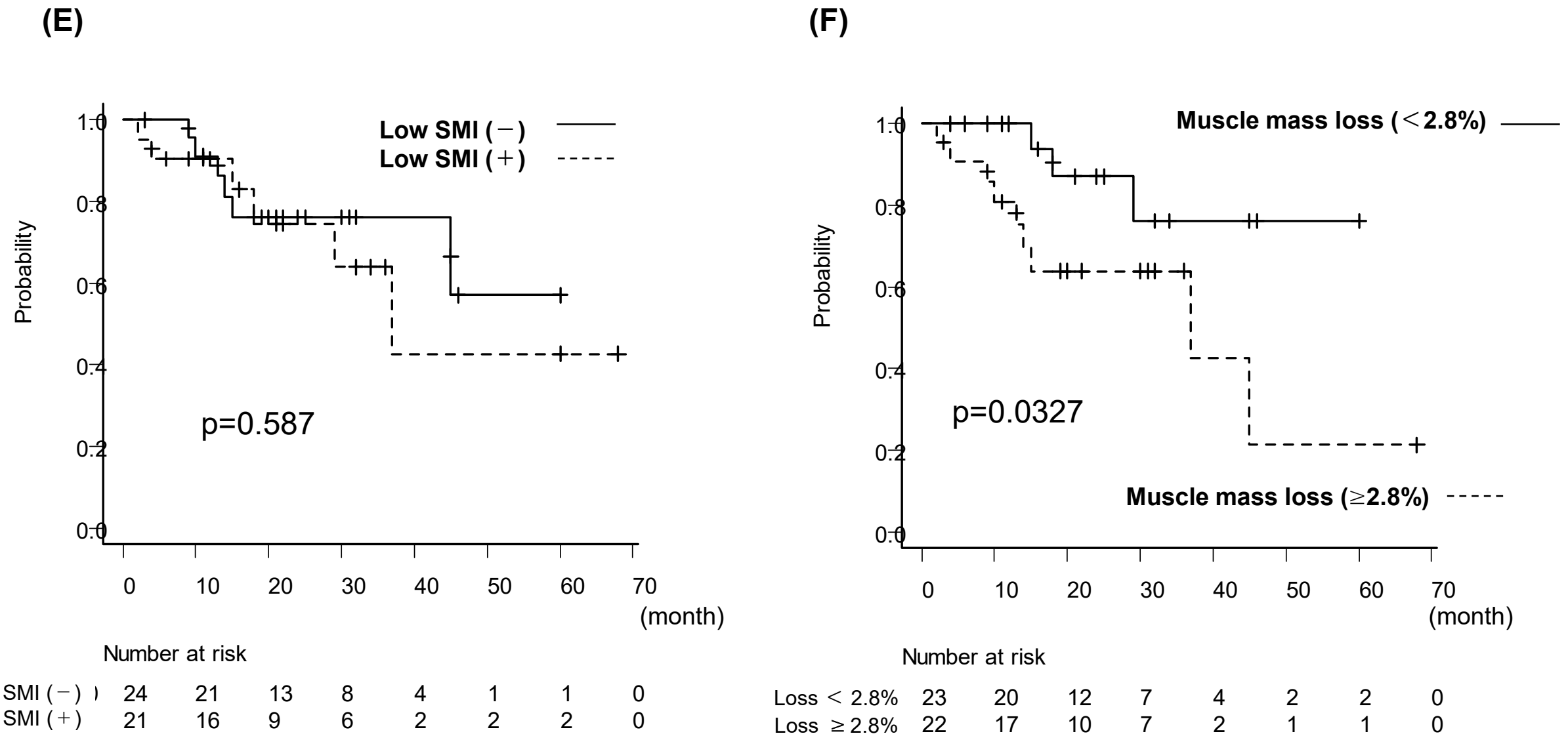
(E)
Low SMI (−)
Low SMI (+)
Probability
1.0
0.8
0.6
0.4
0.2
0.0
p=0.587
0
10
20
30
40
50
60
70
(month)
Number at risk
Low SMI (−) 24 21 13 8 4 1 1 0
Low SMI (+) 21 16 9 6 2 2 2 0
(F)
Muscle mass loss (＜2.8%)
Muscle mass loss (≥2.8%)
Probability
1.0
0.8
0.6
0.4
0.2
0.0
p=0.0327
0
10
20
30
40
50
60
70
(month)
Number at risk
Loss ＜ 2.8% 23 20 12 7 4 2 2 0
Loss ≥ 2.8% 22 17 10 7 2 1 1 0

Figure1