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ORIGINAL RESEARCH

# Sarcopenia as a Prognostic Factor and Multimodal Interventions in Breast Cancer

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**Objective:** This study aims to demonstrate the impact of sarcopenia on the prognosis of early breast cancer and its role in early multimodal intervention.

**Methods:** The clinical data of patients (n=285) subjected to chemotherapy for early-stage breast cancer diagnosed pathologically between January 1, 2016, and December 31, 2020, in our hospital were retrospectively analyzed. Accordingly, the recruited subjects were divided into sarcopenia (n=85) and non-sarcopenia (n=200) groups according to CT diagnosis correlating with single-factor and multifactorial logistic regression analyses. Further, the breast cancer patients combined with sarcopenia were randomly divided into multimodal, nutritional, exercise, and control intervention groups. Multimodal interventions combined supervised exercise programs and tailored nutritional support. The preliminary data and post-operative efficacy, as well as post-operative survival of patients of the four groups, were compared.

**Results:** Sarcopenia significantly reduced overall survival (OS) rates at 1 year (82.94% vs 85.78%), 3 years (81.76% vs 83.91%), and 5 years (80.59% vs 81.17%) compared to non-sarcopenia patients (P<0.001). Patients in the multimodal intervention group showed better outcomes, including improved ALB levels, reduced complication rates (4.5% vs 18.18% vs 18.18% vs.52.63%), and fewer chemotherapy side effects. The multifactorial stepwise logistic regression analysis indicated that advanced age (OR: 1.512, 95% CI: 1.178–1.962, P < 0.001) and multimodal intervention pathways (OR: 5.333, 95% CI: 2.651–10.473, P < 0.001) were significant risk factors affecting patients'prognosis.

**Conclusion:** Sarcopenia might be an independent risk factor leading to the increase of post-operative complications and the shortening of long-term survival of patients. Moreover, the multimodal intervention of nutrition combined with exercise could effectively improve the quality of the prognosis of patients with important clinical significance.

**Keywords:** sarcopenia, early breast cancer, prognosis, influencing factors, multimodal interventions

## Introduction

Breast cancer has emerged as one of the most common malignant tumors in women globally, accounting for an important cause of cancer-related deaths in women. Nevertheless, improving the prognostic quality and clarifying various prognostic influencing factors are long-term concerns in the clinical diagnosis and treatment of breast cancer. Along this line, various traditional prognostic influencing factors in breast cancer include tumor size, tumor histology, and lymph node metastasis. In addition to these notified influencing factors, recent studies indicated[1] that body composition alterations emerged as a factor of interest in oncology, expecting to become a new marker to improve tumor management. Typically, body composition refers to the amount and distribution of bone and muscles as well as the adipose tissue in the human body. The best-known parameter is body mass index (BMI), which can be used to assess the nutritional status of cancer patients. Previous studies demonstrated[2] that overweight and obesity were the important risk factors for breast cancer. These factors have been described as the predominant prognostic factors for disease recurrence and shorter survival compared to normal-weight patients. Although several reports on body composition and cancer outcomes typically focused on the prognostic impact of excess body fat, the recently emerged shreds of evidence supported the extensive depletion of skeletal muscle, referred to as sarcopenia, as an important predictor of cancer outcomes.[3]



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Muscle loss or sarcopenia was first described as age-related loss of body mass in the 1980s. As sarcopenia continues to be intensively studied,[4] the European Working Group on Sarcopenia in the Elderly (EWGSOP) has recently revised the description of sarcopenia as a progressive and generalized skeletal muscle disease characterized by the low muscle strength, low muscle number, or mass, and low physical functioning.[5] Sarcopenia, a common disorder worldwide, is mainly associated with aging and old age, in addition to secondary to systemic diseases, such as malignant tumors. The prevalence of sarcopenia has been estimated to be 5–13% in people aged 60–70 years, 11–50% in people aged 80 years or older, and more than 40% in cancer patients.[6] Previous studies indicated[7] that sarcopenia in cancer patients could be associated with treatment failure, chemotherapy toxicity, and shortened time to tumor progression associated with survival. In an instance, the association between sarcopenia and poor prognostic outcomes in gastrointestinal and lung cancers was demonstrated[8] in sarcopenia patients with a 2.6-fold higher risk of secondary malignancies, a higher incidence of chemotherapeutic toxicity, and a shorter time to death compared to patients without sarcopenia.

Sarcopenia negatively impacts breast cancer prognosis by reducing treatment tolerance, increasing postoperative complications, and decreasing overall survival rates through mechanisms such as systemic inflammation, impaired metabolism, and diminished physical resilience. Nevertheless, further investigations on exploring evidence-based medicine combining them clinically and determining the impact of sarcopenia on the survival of breast cancer patients.[9] Concerning the risk factors affecting breast cancer patients, early screening and intervention are particularly important for overcoming the uncontrolled proliferation of cancer. Currently, the prevention and treatment of sarcopenia mainly include nutritional support and physical exercise, substantially improving the patients' muscle mass to different degrees. However, there is still a lack of enough and convincing shreds of evidence to evaluate the significant impact of combined exercise and nutritional interventions. Specifically, these aspects must be explored in frail and sarcopenic populations, nutritionally deficient populations, or populations at risk for malnutrition, especially for patients with breast cancer, intervention impact studies, especially for the priority group of highly malignant tumors.[10]

Sarcopenia, as a common comorbidity in breast cancer patients, poses significant challenges to treatment outcomes by increasing postoperative complications, chemotherapy toxicity, and long-term mortality. Early identification and intervention for sarcopenia are particularly critical, as they offer opportunities to mitigate these risks and enhance treatment tolerance. Multimodal interventions, combining nutritional support and physical exercise, have shown potential in improving muscle mass and overall patient resilience, but their efficacy in clinical practice remains underexplored. This study aims to address this gap by evaluating the prevalence and prognostic impact of sarcopenia in breast cancer patients, as well as the role of multimodal interventions, providing evidence-based guidance for optimizing patient management.

Initially, the recruited subjects were divided according to CT diagnosis correlating with single-factor and multi-factorial logistic regression analyses. Further, the breast cancer patients combined with sarcopenia were randomly divided into multimodal, nutritional, exercise, and control intervention groups. Finally, the preliminary data and post-operative efficacy, as well as post-operative survival of patients of the four groups, were compared.

# Methods

## General Information of Subjects

The clinical data of hospitalized patients (n=285) between January 1, 2016, and December 31, 2020, who were pathologically diagnosed with early breast cancer undergoing chemotherapy were retrospectively analyzed. This retrospective study was approved by the Ethics Committee of the Quzhou People's Hospital. Signed informed consent was provided by all patients.

## Inclusion and Exclusion Criteria

For the selection of appropriate subjects for this retrospective study, the corresponding inclusion and exclusion criteria were followed for the substantial recruitment of the patients along with their data. The *inclusion criteria* were set as follows:(1) Patients who were diagnosed with breast cancer patients, ie, AJCC 8$^{th}$ edition staging I–IIIC stage;[11] (2) Patients who underwent radical breast cancer surgery and were prescribed chemotherapy; (3) Patients who aged ≥ 18

years old, mental clarity, fluent speech, and answer to the questions; (4) Patients with the complete clinical data; (5) patients with no serious underlying diseases, such as chronic heart disease, uncontrolled hypertension, and poorly controlled diabetes mellitus among others. To this end, the *exclusion criteria* were set as follows: (1) Patients who were unable to cooperate with the abdominal CT examination; (2) Patients who would not agree to participate in the study or were participating in other clinical studies; (3) Patients suffering from other diseases, such as psychiatric, and unable to describe the relevant history and course of the disease; (4) Patients with the incomplete clinical data.

## Diagnostic Criteria of Sarcopenia

The EWSGOP2 criteria were followed to diagnose sarcopenia.[12] This recently revised consensus indicated that the first parameter of sarcopenia was a reduction in grip strength assessed by the HGS method (in kilograms). In addition to atrophy and/or low physical function, the diagnosis of sarcopenia could be confirmed by decreased skeletal muscle mass in the extremities. According to Dodds et al, the threshold of a diagnosis of reduced grip strength was made if a female had an HGS of <16 kg. Further, the low extremity skeletal muscle mass was defined using the Studenski threshold, in which it had an HGS of <15 kg for females. Accordingly, both the conditions of reduced grip strength and low extremity skeletal muscle mass were considered for the diagnosis of sarcopenia. Contrarily, the pre-muscular decrement was considered in the case of HGS values of <16 kg or limb skeletal muscle mass values of <15 kg. Eventually, Sarcopenia was diagnosed using CT imaging based on the skeletal muscle index (SMI), defined as skeletal muscle area ($cm^2$) at the L3 vertebral level normalized to height ($m^2$). The cutoff values were 40.8 $cm^2/m^2$ for males and 34.9 $cm^2/m^2$ for females, following the EWGSOP2 guidelines. The CT images were analyzed using Slice-O-Matic software to ensure accuracy and consistency.

## Intervention Treatment

(1) Multimodal Interventions Included a Combination of Supervised Exercise Programs and Tailored Dietary Plans.

(2) Exercise interventions: Patients participated in resistance training sessions three times per week under the supervision of certified trainers. Each session lasted approximately 45 minutes and included strength, balance, and endurance exercises.

(3) Nutrition interventions: Nutritional support was provided based on individual caloric and protein requirements. Patients were advised to consume a high-protein diet (1.2–1.5 g/kg/day) with balanced macronutrients. Dietary logs were reviewed bi-weekly to ensure compliance.

(4) Control measures: The control group received routine care without structured exercise or dietary guidance.

Patients with sarcopenia were randomized into intervention groups using a computer-generated randomization sequence. Allocation concealment was ensured by using sealed opaque envelopes. To monitor adherence, patients attended bi-weekly follow-up visits where compliance with exercise programs and dietary plans was assessed through activity logs, dietary records, and direct feedback.

## Evaluation of Treatment-Related Adverse Reactions

Further, the evaluation of treatment-related side effects was performed by observing skin mucous membrane reactions, upper and lower gastrointestinal tract reactions, and urinary tract reactions. In addition, the chemotherapy-associated side effects were included as hematological toxic reactions, such as leukopenia, neutropenia, thrombocytopenia, hemoglobin reduction, and transaminase elevation. In this study, the radiotherapy side effects were evaluated according to CTCAE version 3.0 Common Terminology Criteria for Adverse Events (CTCAE 5.0).[13]

## Observation Indicators

The observational indicators were as follows: patients' age, operation time, bleeding volume, postoperative complications including infection, bleeding, effusion, flap necrosis, pectoralis major muscle atrophy, sensory abnormality, upper arm edema and upper arm dyskinesia, etc., and readmission rate. Follow-up time was defined as from the beginning of chemotherapy to the time of the last follow-up or death, with an observation endpoint of 5 years to record the laboratory-

related indices. The follow-up duration was five years, with an overall dropout rate of 12%. Reasons for dropout included loss to follow-up (6%) and withdrawal due to unrelated health issues (6%).

## Survival analysis

The condition of the patients was followed up for 5 years after surgery, recording the overall survival (OS) and progression-free survival (PFS) as the endpoint events in this study. OS was defined as the time from the start of radiotherapy to the time of death due to any cause or the last follow-up. DFS was defined as the time from the start of the surgery until the patient developed an invasive recurrence of breast cancer (local, regional or distant), contralateral invasive breast cancer, second non-breast cancer invasive aspiration, or death from any cause other than breast cancer recurrence and second cancer.[14]

## Statistical Analysis

All the analyzed data in this study were processed by SPSS 25.0 statistical software. The quantitative data were firstly tested for normal distribution, and conforming data were presented in the form of mean ± standard deviation (SD). The data between the groups were compared using the independent samples *t*-tests. The skew-distributed data were described using the interquartile spacing, and independent samples t-tests were performed to analyze the difference between the groups. The qualitative data were expressed in the form of a number of cases and percentages and were analyzed by Fisher's exact probability method or chi-square test between groups. The risk factors for sarcopenia in early-stage breast cancer were analyzed by multifactorial logistic regression analysis. The correlation between OS and DFS rates and breast cancer was analyzed by multi-factorial Cox proportional risk analysis. The results at a defined level of $P<0.05$ were considered statistically significant.

# Results

## Basic Data of Patients

Considering the criteria (inclusion and exclusion) of selection, the study included a total of 285 cases of early breast cancer patients, of which 85 patients were diagnosed with sarcopenia, and 200 patients showed no signs of sarcopenia. Comparatively, no statistical significance was observed in terms of the baseline data of radiotherapy dose, tumor location, age, treatment modality, and underlying disease of the two groups of patients. Contrarily, the incidence rates of post-operative complications, hospitalization time, and incidence of adverse reactions of the patients in the sarcopenia group were significantly higher than that of the non-sarcopenia group ($P<0.05$, Table 1).

## Analysis of Factors Affecting Patients' Prognosis

Considering the occurrence of post-operative complications in patients as the dependent variable, the multifactorial logistic regression analysis was employed by including several variables that were meaningful in a single factor. It was observed from the results that age, sarcopenia, and BMI were the predominant factors affecting the patients' post-operative prognosis ($P<0.05$, Table 2). Although tumor size is a clinically relevant factor in breast cancer prognosis, our analysis did not find a significant association with survival outcomes in this study. This may be attributed to the relatively homogeneous distribution of tumor sizes across the study population, which limits the detection of its impact. Additionally, potential confounding factors, such as baseline nutritional status, co-morbidities, and variations in systemic inflammatory markers, may have influenced the observed outcomes. These factors could have masked the independent effects of tumor size, highlighting the need for further investigation in larger, more diverse cohorts with detailed baseline assessments.

## Effect of Sarcopenia on Overall Survival of Patients

The 1-year, 3-year, and 5-year DFS rates were 80.59%, 79.41%, and 79.41% for patients with sarcopenia, and 80.43%, 80.43%, and 79.57% for patients with non-sarcopenia, respectively. The 1-year, 3-year, and 5-year 0S rates were 82.94%,

**Table 1** Comparative analysis of clinical and pathological data between the sarcopenia and non-sarcopenia groups

| Variant | Sarcopenia (n=85) | Non-Sarcopenia (n=200) | P-value |
|---|---|---|---|
| Age (years), $\bar{x}+s$ | 55.66±11.25 | 52.21± 10.11 | 0.011 |
| Hb (g/l), Interquartile spacing | 117.10 (105.21,128.55) | 121.80 (100.60,131.50) | 0.218 |
| ALB (g/L), $\bar{x}+s$ | 36.12±4.11 | 39.22±4.23 | 0.039 |
| PA (g/L), $\bar{x}+s$ | 199.12±50.56 | 203.09±51.68 | 0.105 |
| TLC (10~9), interquartile spacing | 1.59 (1.29,2.07) | 1.85 (1.42,2.30) | 0.004 |
| Tumor diameter (cm), Interquartile spacing | 2.00 (1.50,3.40) | 1.91 (1.42,3.20) | 0.542 |
| Length of hospitalization (days), interquartile spacing | 7.8 (7.1,7.9) | 7.1 (6.9,7.41) | 0.527 |
| Any one of the complications, n(%) | 21 (24.7) | 45 (22.5) | 0.780 |
| Complications after mastectomy, n(%) | 26 (30.6) | 42 (21.0) | 0.002 |
| Blood flow (ml), Interquartile spacing | 35 (32,38) | 38 (31,38) | 0.273 |
| Surgical time (min), $\bar{x}+s$ | 180.09±50.25 | 170.28±50.31 | 0.560 |
| Postoperative recurrence, n(%) | 64 (75.3) | 160 (80.00) | <0.001 |
| Side effects of chemotherapy, n(%) | | | |
| Grade 1-2 adverse reactions | 49 (57.6) | 151 (75.5) | 0.057 |
| Grade 3-4 adverse reactions | 33 (38.8) | 19 (9.5) | <0.001 |
| T-staging, n (%) | | | 0.914 |
| T1 | 38 (44.7) | 95 (47.5) | |
| T2 | 47 (55.3) | 105 (52.5) | |
| N-staggered, n (%) | | | 0.496 |
| N0 | 38 (44.7) | 99 (49.5) | |
| N1 | 47 (55.3) | 101 (50.5) | |
| Number of readmissions, n (%) | 45 (52.9) | 113 (56.5) | 0.615 |

**Abbreviations**: ALB, albumin; PA, prealbumin; TLC, total lymphocyte count; Hb, hemoglobin.

**Table 2** The data show the multifactorial logistic regression analysis of factors related to the occurrence of post-operative complications affecting patients

| Variant | OR | 95%CI | P-value |
|---|---|---|---|
| Age (years) | 1.230 | 1.169-1.381 | <0.001 |
| Sarcopenia | 7.361 | 2.591-16.368 | <0.001 |
| BMI (kg/m$^2$) | 0.534 | 0.409-0.821 | 0.011 |

81.76%, and 80.59% for sarcopenic patients and 85.78%, 83.91%, and 81.17% for non-sarcopenic patients, respectively. There was no statistical difference in DFS and OS between the two groups (P>0.05, Table 3).

## Multifactorial Analysis Affecting the Prognosis of Early Breast Cancer

Further, the independent variables with statistically significant univariate Cox proportional risk regression analysis were included for multifactorial analysis. The analysis showed that sarcopenia showed an independent influence on OS and PFS rates (P<0.05, Table 4).

## Basic Information of Sarcopenia Patients

In this study, patients (n=85) with sarcopenia were randomly divided into four different intervention groups, namely, multi-modal, nutritional, exercise, and control intervention groups. Through the inclusion of the selected 85 sarcopenia patients, the differences in the prognostic effects of the four groups were observed during the follow-up investigations. Accordingly, the baseline characteristics of the included patients are shown in Table 5.

**Table 3** A summary presents the analysis of the difference in overall post-operative survival between sarcopenia and non-sarcopenia patients

| Variant | Sarcopenia (%) | Non-muscle wasting disease (%) | $\chi^2$ | P-value |
|---|---|---|---|---|
| 1-year overall survival rate | 82.94 | 85.78 | 0.619 | 0.431 |
| 3-year overall survival rate | 81.76 | 83.91 | 0.340 | 0.560 |
| 5-year overall survival rate | 80.59 | 81.17 | 0.001 | 0.972 |
| 1-year disease-free survival rate | 80.59 | 80.43 | 0.018 | 0.895 |
| 3-year disease-free survival rate | 79.41 | 80.43 | 0.105 | 0.746 |
| 5-year disease-free survival rate | 79.41 | 79.57 | 0.017 | 0.897 |

**Table 4** The summary presents the multi-factorial Cox proportional risk regression analysis of prognosis in early breast cancer

| Variant | HR | 95%CI | P-value |
|---|---|---|---|
| Sarcopenia | 2.116 | 1.257-3.629 | <0.001 |

**Table 5** A summary presents the baseline data and clinical characterization of patients with sarcopenia

| Considerations | Sarcopenia (n=85) |
|---|---|
| Age (years),$\bar{x}+s$ | 54.65± 10.21 |
| BMI (kg/m$^2$), $\bar{x}+s$ | 20.12±2.25 |
| Hb (g/l), interquartile spacing | 115.20 (104.19, 126.47) |
| ALB (g/L),$\bar{x}+s$ | 34.12±4.03 |
| PA (g/L),$\bar{x}+s$ | 196.12±49.87 |
| TLC (10~9), interquartile spacing | 1.59 (1.29, 2.07) |
| Tumor diameter (cm), interquartile spacing | 2.00 (1.48, 3.42) |
| Length of hospitalization (days), interquartile spacing | 20.50 (15.34, 22.89) |
| Any one of the complications, n (%) | 16 (18.82) |
| Hemorrhage (ml), interquartile spacing | 251 (211, 629) |
| Surgical time (min), $\bar{x}+s$ | 180.10±48.97 |
| Relapse rate, n (%) | 48 (56.47) |
| Side effects of chemotherapy, n (%) | |
| Grade 1-2 adverse reactions | 36 (42.35) |
| Grade 3-4 adverse reactions | 25 (29.41) |

**Abbreviations**: ALB, albumin; PA, prealbumin; TLC, total lymphocyte count; Hb, hemoglobin.

## Early Intervention on the Post-Operative Outcomes of Sarcopenia Patients

The results showed that no significant differences were observed between the multi-modal, nutritional, exercise, and control intervention groups of patients in terms of ALB level, complication rate, post-operative recurrence rate, and chemotherapy side effects after surgery ($P<0.05$). The results are tabulated in Table 6.

## Effect of Early Intervention on Post-Operative Survival of Patients with Sarcopenia

Through the early multi-modal intervention, the OS and PFS rates in patients were further determined using the follow-up trials. It was observed that no statistical differences were found in the 3-year OS and PFS rates among the

**Table 6** The data present the effect of early multimodal intervention on various post-operative clinical characteristics of sarcopenia patients

| Variant | Multi-Modal Intervention group (n=22) | Nutrition Intervention group (n=22) | Exercise Intervention Group (n=22) | Control Subjects (n=19) | P-value |
|---|---|---|---|---|---|
| Hb (g/l), interquartile spacing | 110.20 (103.19, 126.37) | 112.20 (104.17, 125.97) | 112.50 (104.29, 126.14) | 115.20 (104.17, 125.47) | 0.258 |
| ALB (g/L), $\bar{x}+s$ | 30.13+4.13 | 33.15+4.03 | 33.02+4.11 | 34.18+3.98 | 0.041 |
| PA (g/L), $\bar{x}+s$ | 189.12+48.84 | 193.12+48.74 | 194.15+47.87 | 195.87+49.65 | 0.983 |
| TLC ($10^9$), interquartile spacing | 1.57 (1.29, 2.05) | 1.58 (1.29, 2.10) | 1.57 (1.27, 2.07) | 1.59 (1.26, 2.05) | 0.276 |
| Length of hospitalization (days), interquartile spacing | 18.50 (14.34, 20.75) | 20.35 (15.34, 22.85) | 20.39 (15.34, 21.75) | 21.00 (15.30, 25.32) | 0.218 |
| Any one of the complications, n (%) | 1.00 (4.5) | 4.00 (18.18) | 4.00 (18.18) | 10.00 (52.63) | 0.005 |
| Relapse rate, n (%) | 5.00 22.72) | 12.00 (54.54) | 11.00 (50.00) | 12.00 (63.15) | 0.028 |
| Side effects of chemotherapy, n (%) | | | | | |
| Grade 1-2 adverse reactions | 3.00 (13.36) | 9.00 (40.90) | 8.00 (36.36) | 10.00 (52.63) | 0.064 |
| Grade 3-2 adverse reactions | 2.00 (9.09) | 6.00 (27.27) | 5.00 (22.72) | 9.00 (47.36) | 0.074 |

**Abbreviations**: ALB, albumin; PA, prealbumin; TLC, total lymphocyte count; Hb, hemoglobin.

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**Table 7** The data show the differential analysis of early intervention treatment on the survival rate of sarcopenia patients

| Variant | Multi-modal Intervention Group (n=22) | Nutrition Intervention group (n=22) | Exercise Intervention Group (n=22) | Control Subjects (n=19) | $\chi^2$ | P-value |
|---|---|---|---|---|---|---|
| 1-year overall survival rate | 93.75 | 93.75 | 93.75 | 93.75 | 1.726 | 0.706 |
| 3-year overall survival rate | 93.75 | 87.50 | 93.75 | 87.50 | 0.736 | 0.865 |
| 5-year overall survival rate | 90.50 | 87.50 | 87.50 | 81.25 | 2.388 | 0.008 |
| 1-year progression-free survival | 93.75 | 87.50 | 93.75 | 87.50 | 0.736 | 0.865 |
| 3-year progression-free survival | 92.50 | 87.50 | 87.50 | 87.50 | 0.378 | 0.952 |
| 5-year progression-free survival | 90.50 | 81.25 | 87.50 | 81.25 | 2.474 | 0.004 |

**Table 8** Multifactorial logistic regression analysis affecting prognosis of patients with sarcopenia

| Variant | OR | 95%CI | P-value |
|---|---|---|---|
| Age (years) | 1.512 | 1.178-1.962 | <0.001 |
| Multi-modal interventions | 5.333 | 2.651-10.473 | <0.001 |

predetermined four intervention modalities (P>0.05, Table 7). The 5-year OS and PFS rates in the multi-modal intervention group were higher than that of the control group (P<0.05).

## Effect of Early Intervention on Post-Operative Survival of Patients with Myasthenia Gravis

Finally, the multi-factorial stepwise logistic regression analysis with post-operative recurrence was applied in patients with myasthenia gravis as the dependent variable. It was observed from the results that the over-age and multi-modal intervention pathway might be the risk factors affecting the prognosis of patients (P<0.05, Table 8).

# Discussion

Sarcopenia is a disorder characterized by low strength and deprived mass of the muscle. This musculoskeletal disorder is primarily considered an aging-related condition with a high prevalence in the elderly population. Previous studies indicated[15,16] that sarcopenia could increase the risk of falls and fractures in older adults. In addition, decreased muscle function could affect the swallowing and respiration functionalities, thereby increasing the risk of dysphagia and post-operative pneumonia. Moreover, it acted as a risk factor for a wide range of age-related outcomes, such as all-cause mortality, risk of hospitalization, risk of readmission, and cognitive impairment. Skeletal muscle is an important organ for insulin-mediated glucose uptake, in which the loss of skeletal muscle mass may lead to various metabolic changes, including decreased insulin sensitivity, upregulation of gluconeogenesis, enhanced lipolysis, and production of free fatty acids. Further, the resultant free fatty acids may be absorbed by the liver in the form of elevated fatty liver acids and excess glucose, thereby increasing the risk of metabolic diseases such as diabetes and osteoporosis. Notably, the prevalence of sarcopenia is similarly high in patients with malignant tumors. In recent times, it has become a common parameter for many cancers among body composition characteristics.[17] Xia and colleagues[18] review of 54 outcomes extracted from 30 meta-analyses showed that 20 out of 21 prognostic outcomes indicated that sarcopenia could be associated with gastric, hepatocellular, uroepithelial, head and neck cancers, hematologic system malignancies, pancreatic, breast, colorectal, lung, esophageal, and ovarian cancers. Interestingly, 10 of 16 post-operative outcome indicators suggested that sarcopenia significantly increased the risk of multiple post-operative complications and prolonged

hospitalization in patients with digestive tract cancers. Among age-related outcomes, sarcopenia significantly increased the risk of dysphagia, cognitive impairment, fractures, falls, hospitalization, and all-cause mortality in older adults. In addition, sarcopenia could be associated with high levels of albuminuria, depression, and risk of several metabolic disorders. The correlation between sarcopenia and prognosis of each tumor type accounted for the largest proportion of the 54 outcomes at 39%, suggesting a strong correlation between sarcopenia and different prognostic outcomes of malignant tumors.

Breast cancer has emerged as one of the most common malignant tumors with high prevalence and mortality rates in women. In addition, the sarcopenia condition is highly prevalent in breast cancer patients. Villaseñor and colleagues[19] demonstrated that 15.9% of patients with sarcopenia were diagnosed with stage I–IIIA breast cancer. In addition, several current literature reports indicated that the proportion of breast cancer patients with combined sarcopenia was more than 40%. In an instance, Prado and colleagues[7] reported that, in patients with metastatic breast cancer, sarcopenia was independently associated with a high incidence rate of treatment-induced toxicity and short time to tumor progression, independent of obesity, showing a similar effect with other types of malignancies. In another instance, Shachar and workers[20] similarly showed that sarcopenia was strongly associated with a low OS rate in neoadjuvant therapy for breast cancer. Accordingly, it has been increasingly recognized that sarcopenia could be an independent predictor of poor breast cancer survival. Along this line, sarcopenic women are almost three times more likely to be prone to death from any cause and almost twice as likely to be prone to death from breast cancer-specific causes, irrespective of obesity, compared to women without sarcopenia.

Nonetheless, several reports presented the contrary findings.[21] The main challenge of the study based on sarcopenia was the variety of definitions with various thresholds. The European sarcopenia working group has recommended the inclusion of muscle mass and muscle function in the definition of sarcopenia. As the present study was conducted as a retrospective study, it was therefore not possible to assess the muscle function (strength or performance) to define sarcopenia, which could be generally accepted only by CT scanning. In our current study, the diagnostic threshold for sarcopenia was 34.9 $cm^2/m^2$, which was close to the threshold reported by Fabbro and colleagues[22] (38.5 $cm^2/m^2$). However, there was no gold standard for defining the optimal threshold for sarcopenia in breast cancer. Thus, we relied on prospective data and meta-analysis of different cancers. It was observed that age, sarcopenia, and BMI were confirmed as independent risk factors for post-operative complications by multifactorial logistic regression analysis. In addition, sarcopenia was found to independently affect OS and PFS rates in patients with early-stage breast cancer by univariate Cox proportional risk regression analysis. The present study suggested that sarcopenia was an independent risk factor for post-operative complications and long-term prognosis of breast cancer patients, which was basically in agreement with the mainstream view in the literature.

Further, we explored the potential plausible mechanisms by which sarcopenia affects the prognosis of malignant tumors. Combined with the current literature and clinical experience, the authors believed that it might be related to the following reasons.[23,24] Among various reasons, the use of body surface area by the chemotherapy administration regimen to estimate the amount of metabolic target tissues could indicate that lean soft tissues and adipose tissues could show a greater influence on the BMI score than other tissues. The main preventive and therapeutic measures for sarcopenia currently include nutritional support and physical activity. In a healthy elderly population, the results of a systematic evaluation by Beaudart and colleagues[25] showed that the majority of exercise trials were predominantly resistance-training interventions. Moreover, improvements in muscular strength and physical function could be achieved through physical activity. Regarding the effect of dietary supplements on muscle mass, the results were consistent, with oil-derived omega-3 polyunsaturated fatty acid intake, high protein intake, and vitamin D3 supplementation contributing to the improvement and prevention of sarcopenia occurrence. Recently, a randomized controlled study reported that treatment with Bimagrumab over a 16-week period significantly increased muscle mass and strength in older adults with sarcopenia. The pharmacological treatments, such as testosterone, antibodies for muscle growth inhibitors, and activin receptors, might have a potential impact on sarcopenia treatment. In addition, The mechanisms linking sarcopenia to adverse outcomes in cancer patients are multifaceted. Tumor-induced systemic inflammation plays a central role, as elevated pro-inflammatory cytokines (eg, IL-6, TNF-α) promote muscle protein catabolism and impair muscle regeneration.[26,27] Concurrently, cancer-associated anorexia and metabolic dysregulation exacerbate nutritional

deficiencies, leading to further muscle depletion.[28] These processes not only reduce treatment tolerance by impairing physical resilience but also compromise immune surveillance, thereby increasing susceptibility to complications and disease progression.

Nevertheless, the substantial evidence demonstrating the pharmacological efficacy of treating sarcopenia remains limited.[29] In addition, β-hydroxy-β-methylbutyrate, high-intensity resistance training, and milk protein intake might be effective therapies to improve sarcopenia. In this context, fat and fish dietary patterns might be associated with a reduced risk of sarcopenia in patients with gastrointestinal cancer. Together, there is still a lack of studies to evaluate the impact of combined exercise and dietary-related interventions in patients with combined sarcopenia and malignant tumors, especially breast cancer.[30] Nevertheless, one study has indicated that exercise training, such as progressive resistance training and muscle relaxation, could help to improve the prognostic quality of breast cancer undergoing adjuvant radiotherapy. However, the dietary patterns and consumption of specific food/food nutrients could be strongly associated with breast cancer incidence, recurrence, and survival. Thus, these studies indicated that well-designed and implemented studies should be conducted in the population with combined sarcopenia of malignant tumors. Considering these attributes, in this study, the authors compared nutritional intervention, exercise intervention, and multi-modal intervention of nutrition combined with exercise. The results indicated that multi-modal intervention in patients with breast cancer patients combined with sarcopenia after surgery could improve the ALB level, complication rate, post-operative recurrence rate, and chemotherapeutic side effects, among others. Although these four groups showed no statistical differences in OS and PFS rates, the multifactorial stepwise logistic regression analysis showed that over-age and multimodal intervention pathways might be independent factors affecting patients' recurrence. Therefore, the clinical multimodal interventions combining nutrition and exercise for patients with breast cancer combined with sarcopenia could help to improve the quality of this type of patient's prognosis. Conclusively, it was also expected to guide the treatment of patients combined with sarcopenia in other types of malignant tumors.

Controlled chronic diseases such as hypertension and diabetes contribute to sarcopenia through mechanisms like chronic inflammation and metabolic dysregulation, which accelerate muscle protein degradation and impair synthesis.[31] However, due to the lack of detailed data on disease duration and management in our cohort, these variables were not included in the analysis.

Recent studies have highlighted the potential benefits of prolonged overnight fasting in improving outcomes for breast cancer patients.[32] While this finding contrasts with our results, it underscores the complex interactions between nutrition, sarcopenia, and cancer prognosis. Future studies should explore the role of dietary interventions tailored to the metabolic and physical status of patients.

This study has several limitations that should be acknowledged. First, the retrospective design limits the ability to establish causal relationships between sarcopenia, multimodal interventions, and patient outcomes. The reliance on pre-existing medical records may also introduce selection bias and inaccuracies in data collection. Second, the sample size of the sarcopenia group (n=85) was smaller than required for optimal statistical power to detect subtle differences in survival outcomes, particularly in subgroup analyses. Third, while the diagnostic criteria for sarcopenia were based on established guidelines and CT imaging, the lack of functional assessments (eg, grip strength or physical performance) limits the comprehensiveness of sarcopenia evaluation. Fourth, postoperative complications may also be related to tumor histological types and immunohistochemistry, which were not included in our dataset. This omission limits the study's ability to fully explore other prognostic factors, and we recommend this as an area for future research. Finally, adherence to multimodal interventions was self-reported and monitored bi-weekly, which may not fully capture variability in patient compliance. Future prospective studies with larger sample sizes, functional assessments, and more comprehensive datasets are needed to validate these findings and refine intervention strategies.

## Conclusion

This study demonstrates that sarcopenia is an independent prognostic factor in breast cancer patients, significantly affecting survival outcomes. Early identification and management of sarcopenia, through routine screening and comprehensive assessments, are essential to improving clinical outcomes. Multimodal interventions, combining tailored nutritional support and supervised exercise programs, have shown promise in reversing sarcopenia and enhancing treatment

tolerance. Clinicians are encouraged to integrate sarcopenia screening and intervention protocols into standard breast cancer care pathways.

## Data Sharing Statement

The data that support the findings of this study are available from Quzhou People's Hospital but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the corresponding author upon reasonable request and with permission of Quzhou People's Hospital.

## Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Quzhou People's Hospital. All methods were performed in accordance with the Declarations of Helsinki, and Signed informed consent was provided by all patients.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declared that there was no conflict of interest associated with the manuscript.

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