Effects of sarcopenia on short- and long-term outcomes in patients with gastric neuroendocrine neoplasms after radical gastrectomy: Results from a large, two-institution series.

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Abstract

Background: The relationship between sarcopenia and the prognoses of patients with gastric neuroendocrine neoplasms (g-NENs) is unclear. This study was designed to explore the effects of sarcopenia on short-term and long-term outcomes of patients with g-NENs after radical gastrectomy.

Methods: This study retrospectively collected data from 138 patients with g-NENs after radical gastrectomy. The skeletal muscle index (SMI) diagnostic threshold for sarcopenia was determined using X-tile software. Cox regression analyses were performed to determine the independent risk factors for 3-year overall survival (OS) and 3-year recurrence-free survival (RFS).

Results: In this study, 59 patients (42.8%) were diagnosed with sarcopenia. Among patients in the sarcopenia group and nonsarcopenia group, the incidences of total postoperative complications were 33.9% and 30.4%, incidences of serious postoperative complications were 0% and 3.7%, incidences of postoperative surgical complications were 13.6% and 15.2%, and incidences of postoperative systemic complications were 20.3% and 15.2%, respectively (all p>0.05). The 3-year OS and RFS rates were significantly worse in the sarcopenia group than in the nonsarcopenia group (OS: 42.37% vs 65.82%, p=0.004; RFS: 52.54% vs 68.35%, p=0.036). The multivariate analysis revealed a relation between sarcopenia and the long-term prognoses of patients with g-NENs. A stratified analysis based on the pathological type revealed that the Kaplan-Meier curve was only significantly different in patients with gastric mixed adenoneuroendocrine carcinoma (gMANEC) (OS: 40.00% vs 71.79%, p=0.007; RFS: 51.43% vs 74.36%, p=0.026); furthermore, the multivariate analysis identified sarcopenia as an independent risk factor for patients with gMANEC (p<0.05).

Conclusions: Sarcopenia is not related to the short-term prognoses of patients with g-NENs. Sarcopenia is an independent risk factor for patients with gMANEC after radical surgery.

Background

Gastric neuroendocrine neoplasms (g-NENs) is a class of tumors with significant heterogeneity, accounting for approximately 4% of all neuroendocrine tumors[1], and its incidence is gradually increasing[2, 3]. G-NENs including three categories: gastric neuroendocrine tumor (gNET), gastric neuroendocrine carcinoma (gNEC) and gastric mixed adenoneuroendocrine carcinoma (gMANEC)[4]. Surgery is the main treatment for all types of g-NENs[5]. Because of its different clinicopathological features, the understanding and the prognostic factors of g-NENs are still rarely studied[6–9]. Therefore, to improve the prognosis of g-NENs patients, it is important to explore the factors influencing short-term and long-term outcomes of g-NENs patients after radical surgery.

In recent years, studies have shown that sarcopenia is closely related to the prognosis in cases of gastric cancer, liver cancer, colorectal cancer, and other malignant tumors[10–16]. However, no studies have reported the effect of sarcopenia on the short-term and long-term postoperative outcomes of g-NENs.

This study retrospectively analyzed the clinicopathological data of 138 patients with g-NENs in two institutions, aiming to explore the effect of sarcopenia on the short-term and long-term outcomes of g-NENs patients after radical gastrectomy.

Methods

Patient Selection
The clinicopathological data of patients diagnosed with g-NENs in the Fujian Medical University Union Hospital (FMUUH) and the First Affiliated Hospital of Fujian Medical University (FMUFAH) from December 2009 to December 2015 were retrospectively analyzed. The inclusion criteria were as follows: (1) patients diagnosed with g-NENs by pathology; (2) without distant metastasis, as assessed by preoperative examination; and (3) R0 excision was performed. The following were the exclusion criteria: (1) distant metastasis was found preoperatively and intraoperatively; (2) patients received neoadjuvant chemotherapy or radiotherapy before surgery; and (3) basic clinical data and computed Tomography (CT) images were incomplete. A total of 138 patients with g-NENs were finally included in this study (111 patients in FMUUH and 27 patients in FMUFAH, Supplementary Table 1). The tumor size, location, T stage and N stage were comprehensively determined by two attending physicians according to the findings of gastroscopy, abdominal CT and other auxiliary examinations performed preoperatively. The type of surgical resection were performed according to the location of the tumor. Lymph node dissection was performed according to the Japanese gastric cancer treatment guidelines (13th Edition)[17]. For patients at stage II or above, fluorine-based postoperative adjuvant chemotherapy was recommended[18]. The study was approved by the Ethics Committee of FMUUH and FMUFAH.

Diagnosis and Classification of g-NENs

According to the 2010 WHO classification of tumors of the digestive system, g-NENs were classified as gNET, including NET1 and NET2 grades; gNEC, including large-cell carcinomas and small-cell carcinomas; and gMANEC. Neuroendocrine cells were confirmed, diagnosed and classified by microscopic histomorphological features and immunohistochemical staining to detect neuroendocrine tumor-related biomarkers (such as CgA, CD56 and Syn). The pathological findings were confirmed by two experienced pathologists.

CT Image Analysis

A preoperative abdominal CT scan within one month was considered to accurately reflect the patient's muscle status. The researcher who was blinded to the outcome measured the skeletal muscle cross-sectional area (cm$^2$) at the level of the third lumbar vertebra (L3) by using Osirix 3.3 software (32-bit; http://www.osirix-viewer.com)[19]. The researcher was trained to accurately identify lumbar vertebrae and muscles (Supplementary Fig. 1). The average surface (cm$^2$) of two consecutive slices was used for analysis. If necessary, the area of the selected area could be manually adjusted to accurately calculate the area value. The tissue discrimination threshold of skeletal muscle is -29 to + 150 Hounsfield units (HU)[20]. Muscle area (cm$^2$) was standardized by height (m$^2$) to obtain the L3 skeletal muscle index (SMI) (cm$^2$/m$^2$)[21].

Optimal SMI Cutoff Value and Definition of Sarcopenia

Separate X-tile plots were constructed for men and women. For the men, when the SMI value was 44.3 cm$^2$/m$^2$, the maximum Chi-square log-rank value of 4.2611 was achieved, therefore a SMI ≤ 44.3 cm$^2$/m$^2$ was defined as sarcopenia, and a SMI > 44.3 cm$^2$/m$^2$ was defined as nonsarcopenia (p = 0.038) (Supplementary Fig. 2).

For the women, a SMI ≤ 32.4 cm$^2$/m$^2$ was defined as sarcopenia in the same way ($\chi^2 = 1.0039, p = 0.214$) (Supplementary Fig. 2).

Variables and Definitions

Overall survival (OS) was defined as the time from surgery to the last follow-up, death, or the deadline from the follow-up database (such as loss of follow-up or death from other diseases). Recurrence-free survival (RFS) was defined as the time from surgery to the initial recurrence. Postoperative complications were classified according to the Clavien-Dindo classification[22]. Total postoperative complications were defined as Clavien-Dindo grade 2 and above. Severe
complications were defined as Clavien-Dindo 3 and above[11]. Postoperative surgical complications were defined as complications related to the surgical procedure. Systemic complications were defined as complications not directly related to the surgical field or the incision.

**Follow-Up**

The median follow-up time was 36 months (range: 1-102 months). Physical and laboratory examinations were performed regularly after surgery, once every 3 months for 2 years, every 6 months for the next 3 years, and once a year after 5 years. In addition, imaging examinations, including chest radiographs, abdominal and pelvic CTs, and endoscopy, were performed at least once a year. If necessary, additional MRI or PET studies were obtained to determine whether there was a recurrence.

**Statistical Analysis**

All the data were statistically analyzed by SPSS 22.0 software. Continuous variables are reported as the means ± SD or median (interquartile range). X-tile plots were used as a new bioinformatics tool for biomarker assessment and outcome-based cut-point optimization[10, 23]. Categorical and continuous variables were compared using a $\chi^2$ test or Fisher's exact test and a t-test, respectively. The OS and RFS rates were calculated by the Kaplan-Meier method, and the differences were assessed with log-rank tests. The Cox proportional hazards regression model was used to analyze the independent prognostic factors of 3-year OS and RFS rates. Values of p less than 0.05 were considered statistically significant.

**Results**

**1. Clinicopathologic Characteristics**

In 138 patients, there were 59 patients (42.8%) in the sarcopenia group and 79 patients (57.2%) in the nonsarcopenia group. The comparison of clinical data between the two groups showed that the incidence of sarcopenia was higher in the subgroup of male patients, aged 65 years, with a BMI of < 25 and a tumor larger than 50 mm (all p < 0.05). However, there was no significant difference in other variables between the two groups (all p > 0.05) (Table 1).
| Variable                        | All (n = 138) | Low (n = 59) | High (n = 79) | P  |
|--------------------------------|---------------|--------------|---------------|----|
| Gender                         |               |              |               |    |
| Male                           | 105           | 51           | 54            |    |
| Female                         | 33            | 8            | 25            |    |
| Age (years)                    |               |              |               |    |
| < 65                           | 80            | 26           | 54            |    |
| ≥ 65                           | 58            | 33           | 25            |    |
| BMI (kg/m²)                    |               |              |               |    |
| < 25                           | 115           | 55           | 60            |    |
| ≥ 25                           | 23            | 4            | 19            |    |
| ASA                            |               |              |               |    |
| 1                              | 69            | 28           | 41            |    |
| 2                              | 54            | 23           | 31            |    |
| 3                              | 15            | 8            | 7             |    |
| Comorbidities                  |               |              |               |    |
| No                             | 40            | 19           | 21            |    |
| Yes                            | 98            | 40           | 58            |    |
| Tumor diameter (mm)            |               |              |               |    |
| < 50                           | 68            | 23           | 45            |    |
| ≥ 50                           | 70            | 36           | 34            |    |
| Tumor location                 |               |              |               |    |
| Upper                          | 63            | 26           | 37            |    |
| Middle                         | 27            | 12           | 15            |    |
| Lower                          | 33            | 16           | 17            |    |
| Mix                            | 15            | 5            | 10            |    |
| T stage                        |               |              |               |    |
| T1 + T2                        | 77            | 35           | 42            |    |
| T3 + T4                        | 61            | 24           | 37            |    |
| N stage                        |               |              |               |    |
| N0                             | 46            | 16           | 30            |    |

Table 1  
Clinicopathological characteristics
### Table 1

| SMI | 82  | 56  | 72  |
| --- |-----|-----|-----|
| N1  | 92  | 43  | 49  |
| Surgical method |     |     | 0.103 |
| Open | 43  | 14  | 29  |
| Laparoscopic | 95  | 45  | 50  |
| Gastrectomy extent |     |     | 0.67 |
| Total | 101 | 45  | 56  |
| Distal | 33  | 13  | 20  |
| Proximal | 4   | 1   | 3   |
| Pathological type |     |     | 0.318 |
| NET | 12  | 3   | 9   |
| NEC | 52  | 21  | 31  |
| MANEC | 74  | 35  | 39  |
| Ki-67 positive index (%) |     |     | 0.439 |
| < 60 | 59  | 23  | 36  |
| ≥ 60 | 79  | 36  | 43  |
| Complications |     |     | 0.984 |
| No | 82  | 35  | 47  |
| Yes | 56  | 24  | 32  |
| Adjuvant chemotherapy |     |     | 0.193 |
| No | 66  | 32  | 34  |
| Yes | 72  | 27  | 45  |

SMI, skeletal muscle index; BMI, body mass index; ASA, American Society of Anesthesiologists; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; MANEC, mixed adenoneuroendocrine carcinoma.

### 2. Effects of Sarcopenia on Postoperative Complications

In this study, postoperative complications occurred in 44 patients (31.9%), and serious complications occurred in 3 patients (2.2%). In the sarcopenia group and the nonsarcopenia group, the incidence of total postoperative complications was 33.9% and 30.4% respectively, and the incidence of serious complications was 0% and 3.7% (all p > 0.05). Postoperative surgical and systemic complications occurred in 20 patients (14.5%) and 24 patients (17.4%) in the whole group. In the sarcopenia group and the nonsarcopenia group, the incidence of postoperative surgical complications was 13.6% and 15.2% respectively, and the incidence of postoperative systemic complications was 20.3% and 15.2% (all p > 0.05). In addition, according to the physical location of the complication, the analysis showed that there were no significant differences in the incidence of specific types of complications between the two groups (all p > 0.05) (Table 2).
Table 2
Postoperative complications in 138 patients[Case(%)]

|                          | Sarcopenia | Nonsarcopenia | P     |
|--------------------------|------------|---------------|-------|
| Total complications      | 20 (33.9)  | 24 (30.4)     | 0.661 |
| Serious complications    | 0 (0)      | 3 (3.7)       | 0.26  |
| Surgical complications   | 8 (13.6)   | 12 (15.2)     | 0.788 |
| Systemic complications   | 12 (20.3)  | 12 (15.2)     | 0.43  |
| Physical location        |            |               |       |
| Pulmonary infection      | 12 (20.3)  | 12 (15.2)     | 0.43  |
| Abdominal infection      | 4 (6.8)    | 3 (3.8)       | 0.461 |
| Incision infection       | 1 (1.7)    | 0 (0)         | 0.428 |
| Chylous fistula          | 0 (0)      | 3 (3.8)       | 0.26  |
| Intestinal obstruction   | 0 (0)      | 2 (2.5)       | 0.507 |
| Anastomotic fistula      | 1 (1.7)    | 2 (2.5)       | 1     |
| Abdominal bleeding       | 1 (1.7)    | 2 (2.5)       | 1     |
| Anastomotic stenosis     | 1 (1.7)    | 0 (0)         | 0.428 |

3. Effects of Sarcopenia on the Prognosis of g-NENs Patients

The 3-year OS rates were 42.37% and 65.82%, and the 3-year RFS rates were 52.54% and 68.35% in the sarcopenia and nonsarcopenia groups (all p < 0.05, Fig. 1A B). Univariate analysis showed that the Anesthesiology Society of America (ASA) score, pT, pN, Ki-67-positive index and sarcopenia were related to the 3-year OS rates, whereas the ASA score, pN, Ki-67-positive index, and sarcopenia were related to the 3-year RFS rates (all p < 0.05, Table 3). Multivariate analysis showed that only the ASA score, pN, Ki-67-positive index and sarcopenia were related to the 3-year OS and RFS rates (all p < 0.05, Table 3).
Table 3
Uni- and multivariate analyses of factors associated with 3-year overall survival (OS) and recurrence-free survival (RFS) rates in g-NENs patients.

| Variable       | 3-year OS | 3-year RFS | 3-year OS | 3-year RFS |
|----------------|-----------|------------|-----------|------------|
|                | HR (95% CI) | P | HR (95% CI) | P |
| Gender         |           |   |           |   |
| Male           | 1         |   | 1         |   |
| Female         | 0.650 (0.338–1.248) | 0.195 | 0.813 (0.419–1.580) | 0.542 |
| Age (years)    |           |   |           |   |
| < 65           | 1         |   | 1         |   |
| ≥ 65           | 1.112 (0.669–1.847) | 0.683 | 0.851 (0.488–1.483) | 0.569 |
| BMI (kg/m²)    |           |   |           |   |
| < 25           | 1         |   | 1         |   |
| ≥ 25           | 0.694 (0.330–1.460) | 0.336 | 0.709 (0.320–1.570) | 0.396 |
| ASA            |           |   |           |   |
| 1              | 1         |   | 1         |   |
| 2              | 1.934 (1.118–3.347) | 0.018 | 1.869 (1.069–3.269) | 0.028 |
| 3              | 2.54 (1.172–5.504) | 0.018 | 2.029 (0.917–4.486) | 0.081 |
| Comorbidity    |           |   |           |   |
| No             | 1         |   | 1         |   |
| Yes            | 1.346 (0.751–2.411) | 0.318 | 0.993 (0.552–1.785) | 0.981 |
| Tumor (mm)     |           |   |           |   |
| < 50           | 1         |   | 1         |   |

g-NENs, gastric neuroendocrine neoplasms; HR, hazard ratio; CI, confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; MANEC, mixed adenoneuroendocrine carcinoma; SMI, skeletal muscle index.
| Variable          | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |
|-------------------|---------------------|-----------------------|---------------------|-----------------------|
|                   | 3-year OS           | 3-year OS             | 3-year RFS          | 3-year RFS            |
|                   | HR (95% CI)         | P                     | HR (95% CI)         | P                     |
| ≥ 50              | 1.596 (0.957–2.659) | 0.073                 | 1.449 (0.841–2.496) | 0.181                 |
| Tumor location    |                     |                       |                     |                       |
| Upper             | 1                   |                       | 1                   |                       |
| Middle            | 0.664 (0.314–1.403) | 0.283                 | 0.778 (0.349–1.734) | 0.540                 |
| Lower             | 0.917 (0.484–1.735) | 0.789                 | 1.104 (0.571–2.135) | 0.769                 |
| Mix               | 1.253 (0.593–2.649) | 0.555                 | 1.147 (0.494–2.664) | 0.749                 |
| T stage           |                     |                       |                     |                       |
| T1 + T2           | 1                   | 1                     | 1                   |                       |
| T3 + T4           | 1.748 (1.054–2.898) | 0.031                 | 1.445 (0.843–2.476) | 0.181                 |
| N stage           |                     |                       |                     |                       |
| N0                | 1                   | 1                     | 1                   | 1                     |
| N1                | 5.032 (2.385–10.616)| <.001                 | 3.554 (1.624–7.778) | 0.002                 |
| Surgical method   |                     |                       |                     |                       |
| Open              | 1                   |                       | 1                   |                       |
| Laparoscopic      | 0.797 (0.472–1.344) | 0.395                 | 0.875 (0.496–1.546) | 0.647                 |
| Gastrectomy extent|                     |                       |                     |                       |
| Total             | 1                   | 1                     | 1                   |                       |
| Distal            | 0.74 (0.400–1.368)  | 0.337                 | 1.080 (0.584–1.994) | 0.807                 |

g-NENs, gastric neuroendocrine neoplasms; HR, hazard ratio; CI confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; MANEC, mixed adenoneuroendocrine carcinoma; SMI, skeletal muscle index.
| Variable | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |
|----------|---------------------|----------------------|---------------------|----------------------|
|          | 3-year OS           | 3-year OS            | 3-year RFS          | 3-year RFS           |
|          | HR (95% CI)         | P                    | HR (95% CI)         | P                    |
| Proximal | 0.418 (0.058–3.029) | 0.388                | 0.528 (0.072–3.850) | 0.529                |
| Pathological type | | | | |
| NET      | 1                   |                      | 1                   |                      |
| NEC      | 2.352 (0.712–7.773) | 0.161                | 1.521 (0.524–4.414) | 0.441                |
| MANEC    | 1.839 (0.563–6.008) | 0.313                | 1.172 (0.410–3.350) | 0.767                |
| Ki-67 positive index (%) | | | | |
| < 60     | 1                   | 1                    | 1                   | 1                    |
| ≥ 60     | 4.753 (2.469–9.152) | <.001                | 3.492 (1.772–6.879) | <.001                |
|          | 5.978 (2.810–12.718)| <.001                | 4.304 (1.981–9.350) | <.001                |
| Complication | | | | |
| No       | 1                   |                      | 1                   |                      |
| Yes      | 1.645 (0.994–2.723) | 0.053                | 1.245 (0.699–2.220) | 0.457                |
| Adjuvant chemotherapy | | | | |
| No       | 1                   |                      | 1                   |                      |
| Yes      | 1.409 (0.843–2.355) | 0.191                | 1.559 (0.894–2.719) | 0.117                |
| Martin et al. [29] | | | | |
| High     | 1                   |                      | 1                   |                      |
| Low      | 1.181 (0.709–1.968) | 0.523                | 1.377 (0.790–2.400) | 0.260                |

g-NENs, gastric neuroendocrine neoplasms; HR, hazard ratio; CI, confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; MANEC, mixed adenoneuroendocrine carcinoma; SMI, skeletal muscle index.
**4. Effects of Sarcopenia on the Prognosis of Patients with Different Types of g-NENs**

According to the stratified analysis of postoperative pathological types, in gNET patients, the 3-year OS rates of the sarcopenia group and nonsarcopenia group were 66.67% and 77.78%, respectively, and the 3-year RFS rates were 66.67% and 66.67%, respectively (all p > 0.05, Fig. 1C D). In gNEC patients, the 3-year OS rates of the sarcopenia group and nonsarcopenia group were 42.86% and 54.84%, respectively, and the 3-year RFS rates were 52.38% and 61.29%, respectively (all p > 0.05, Fig. 1E F). In patients with gMANEC, the 3-year OS rates of the sarcopenia group and nonsarcopenia group were 40.00% and 71.79%, respectively, and the 3-year RFS rates were 51.43% and 74.36%, respectively (all p < 0.05, Fig. 1G H). To more accurately evaluate the impact of sarcopenia on the prognosis of different types of g-NENs patients, we further carried out a multivariate analysis for each subgroup of the population. However, because there were few patients in the gNET subgroup, and the Kaplan-Meier analysis showed that there was no significant difference between the two groups in the gNET subgroup. Therefore, the gNET subgroup was not included in further multivariate analyses. Multivariate analysis showed that the 3-year OS rates were associated with comorbidities, pN and the Ki-67-positive index (all p < 0.05), and the 3-year RFS rates were associated with pN and the Ki-67-positive index (all p < 0.05), both OS rates and RFS rates were not associated with sarcopenia, in patients with gNEC (Supplemental Table 2). However, in gMANEC patients, the pN, Ki-67-positive index and sarcopenia were related to the 3-year OS rates and the 3-year RFS rates (all p < 0.05, Table 4).
Table 4
Uni- and multivariate analyses of factors associated with 3-year overall survival (OS) and recurrence-free survival (RFS) rates in gMANEC patients.

| Variable       | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |
|---------------|---------------------|-----------------------|---------------------|-----------------------|
|               |                     |                       |                     |                       |
|               | 3-year OS           | 3-year OS             | 3-year RFS          | 3-year RFS            |
|               | HR (95% CI)         | P                     | HR (95% CI)         | P                     |
| Gender        |                     |                       |                     |                       |
| Male          | 1                   | 1                     | 1                   | 1                     |
| Female        | 0.788 (0.341–1.823) | 0.578                 | 1.020 (0.431–2.412) | 0.964                 |
| Age (years)   |                     |                       |                     |                       |
| < 65          | 1                   | 1                     | 1                   | 1                     |
| ≥ 65          | 1.234 (0.616–2.472) | 0.554                 | 0.929 (0.431–2.002) | 0.851                 |
| BMI (kg/m²)   |                     |                       |                     |                       |
| < 25          | 1                   | 1                     | 1                   | 1                     |
| ≥ 25          | 0.856 (0.300–2.442) | 0.772                 | 0.809 (0.243–2.687) | 0.729                 |
| ASA           |                     |                       |                     |                       |
| 1             | 1                   | 1                     | 1                   | 1                     |
| 2             | 2.261 (1.038–4.929) | 0.04                  | 1.548 (0.701–3.422) | 0.280                 |
| 3             | 3.732 (1.371–10.156)| 0.01                  | 1.898 (0.628–5.730) | 0.256                 |
| Comorbidity   |                     |                       |                     |                       |
| No            | 1                   | 1                     | 1                   | 1                     |
| Yes           | 0.846 (0.401–1.789) | 0.662                 | 0.528 (0.245–1.139) | 0.104                 |

gMANEC, gastric mixed adenoneuroendocrine carcinoma; HR, hazard ratio; CI, confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists; SMI, skeletal muscle index.

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| Variable          | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |
|-------------------|---------------------|-----------------------|---------------------|-----------------------|
|                   | 3-year OS           | 3-year OS             | 3-year RFS          | 3-year RFS            |
|                   | HR (95% CI)         | P                     | HR (95% CI)         | P                     |
| Tumor (mm)        |                     |                       |                     |                       |
| < 50              | 1                   |                       | 1                   |                       |
| ≥ 50              | 1.528 (0.754–3.098) | 0.239                 | 1.264 (0.591–2.701) | 0.546                 |
| Tumor location    |                     |                       |                     |                       |
| Upper             | 1                   |                       | 1                   |                       |
| Middle            | 0.573 (0.188–1.741) | 0.326                 | 0.802 (0.255–2.521) | 0.706                 |
| Lower             | 0.852 (0.369–1.970) | 0.708                 | 1.100 (0.456–2.656) | 0.832                 |
| Mix               | 1.625 (0.583–4.531) | 0.353                 | 1.140 (0.317–4.094) | 0.841                 |
| T stage           |                     |                       |                     |                       |
| T1 + T2           | 1                   |                       | 1                   |                       |
| T3 + T4           | 2.197 (1.082–4.464) | 0.029                 | 2.145 (0.985–4.668) | 0.055                 |
| N stage           |                     |                       |                     |                       |
| N0                | 1                   |                       | 1                   |                       |
| N1                | 4.586 (1.756–11.979) | 0.002                 | 3.134 (1.148–8.551) | 0.026                 |
|                   |                     |                       |                     |                       |
| Surgical method   |                     |                       |                     |                       |
| Open              | 1                   |                       | 1                   |                       |

gMANEC, gastric mixed adenoneuroendocrine carcinoma; HR, hazard ratio; CI confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists; SMI, skeletal muscle index.

29. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(12):1539-47. doi: 10.1200/jco.2012.45.2722. PubMed PMID: 23530101.
| Variable                        | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |
|--------------------------------|---------------------|-----------------------|---------------------|-----------------------|
|                                | 3-year OS           | 3-year OS             | 3-year RFS          | 3-year RFS            |
|                                | HR (95% CI)         | P                     | HR (95% CI)         | P                     |
| Laparoscopic                   | 0.698 (0.330–1.474) | 0.346                 | 0.778 (0.340–1.779) | 0.552                 |
| Gastrectomy extent             |                     |                       |                     |                       |
| Total                          | 1                   | 1                     |                     |                       |
| Distal                         | 0.691 (0.310–1.540) | 0.366                 | 1.201 (0.539–2.673) | 0.654                 |
| Proximal                       | 0 (0)               | 0.982                 | 0 (0)               | 0.984                 |
| Ki-67 positive index (%)       |                     |                       |                     |                       |
| < 60                           | 1                   | 1                     | 1                   | 1                     |
| ≥ 60                           | 4.874 (1.872–12.689)| 0.001                 | 3.710 (1.372–10.033)| 0.010                 |
| Complication                   |                     |                       |                     |                       |
| No                             | 1                   | 1                     |                     |                       |
| Yes                            | 1.645 (0.820–3.298) | 0.161                 | 1.200 (0.525–2.742) | 0.666                 |
| Adjuvant chemotherapy          |                     |                       |                     |                       |
| No                             | 1                   | 1                     |                     |                       |
| Yes                            | 1.428 (0.697–2.925) | 0.33                  | 1.248 (0.579–2.691) | 0.572                 |
| Martin et al. [29]             |                     |                       |                     |                       |
| High                           | 1                   | 1                     |                     |                       |

gMANEC, gastric mixed adenoneuroendocrine carcinoma; HR, hazard ratio; CI, confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists; SMI, skeletal muscle index.

29. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2013;31(12):1539-47. doi: 10.1200/jco.2012.45.2722. PubMed PMID: 23530101.
| Variable | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |
|----------|---------------------|-----------------------|---------------------|-----------------------|
|          | 3-year OS           | 3-year OS             | 3-year RFS          | 3-year RFS            |
|          | HR (95% CI)         | P                     | HR (95% CI)         | P                     |
| Low      | 1.667 (0.789–3.523) | 0.181                 | 1.868 (0.817–4.272) | 0.138                 |
| SMI      |                     |                       |                     |                       |
| High     | 1                   | 1                     | 1                   | 1                     |
| Low      | 2.639 (1.270–5.483) | 0.009                 | 2.735 (1.246–6.001) | 0.012                 |
|          |                     |                       | 2.356 (1.077–5.153) | 0.032                 |
|          |                     |                       | 2.825 (1.250–6.386) | 0.013                 |

gMANEC, gastric mixed adenoneuroendocrine carcinoma; HR, hazard ratio; CI, confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists; SMI, skeletal muscle index.

29. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2013;31(12):1539-47. doi: 10.1200/jco.2012.45.2722. PubMed PMID: 23530101.

**Discussion**

NENs is a type of digestive system tumor with different clinical symptoms and biological characteristics[24]. It is important to identify patients with different prognoses according to their clinical and pathological conditions to provide individualized treatment to improve the efficacy of g-NENs treatments. However, there are still few studies evaluating the prognostic factors in g-NENs patients[8, 9]. Recently, the influence of preoperative body composition parameters (such as skeletal muscle mass) on postoperative short-term and long-term outcomes has attracted the attention of scholars in the east and the west. Sarcopenia is characterized by a progressive decline in systemic muscle mass, muscle strength, or muscle physiological function associated with aging[25]. At present, several studies have shown that sarcopenia is closely related to the prognosis of various malignant tumors[10–16]. However, the effect of sarcopenia on the prognosis of g-NENs patients undergoing radical gastrectomy has not been reported. Therefore, this study combined the clinicopathological data of 138 patients from two institutions to explore the effect of sarcopenia on the short-term and long-term postoperative outcomes of g-NENs patients.

Based on the definition of sarcopenia of the European Working Group on Sarcopenia (EWGSOP)[26] and the Asian Working Group for Sarcopenia (AWGS)[27], sarcopenia is diagnosed with low skeletal muscle mass, low muscle strength and poor low physical performance. However, in the current research, low skeletal muscle mass is mostly used as the definition of sarcopenia. A meta-analysis to explore the relationship between sarcopenia and the risk of postoperative complications of gastrointestinal tumors included a total of 29 studies related to sarcopenia, of which 26 used low skeletal muscle mass as the definition of sarcopenia[28]. In both eastern[10, 11] and western[15, 21, 29] studies, researchers tend to use low skeletal muscle mass as the definition of sarcopenia. And the data of the patient's muscle mass can be obtained by analyzing the abdominal CT scan[10]. Abdominal CT scan is also a routine follow-up item for patients with g-NENs after radical gastrectomy[30]. Using low skeletal muscle mass as the definition of sarcopenia can help clinicians to make treatment decisions more conveniently and quickly.
At present, the value of the cutoff point of sarcopenia is still controversial. The most commonly used definitions were defined by Prado et al.\cite{21} and Martin et al.\cite{29}. In the past, our center used x-tile software to analyze the 3-year OS rates of 924 patients with gastric adenocarcinoma after R0 resection and defined sarcopenia as a SMI < 32.5 cm$^2$/m$^2$ for males and a SMI < 28.6 cm$^2$/m$^2$ for females\cite{10}. However, when previous definitions were applied, we found that only those of Martin et al. could obtain the prevalence of sarcopenia similar to those in the previous studies (Supplementary Table 3). Therefore, we included the cutoff point defined by Martin et al. in the analysis. The Kaplan-Meier analysis, Cox regression analysis indicated that the cutoff points defined by Martin et al. could not serve as prognostic factors for g-NENs patients in our study (Tables 3, 4, Supplemental Table 2, Supplementary Fig. 3). Therefore, this study used x-tile software to analyze the 3-year OS rates of 138 g-NENs patients from the two institutions and defined a SMI < 44.3 cm$^2$/m$^2$ for males and a SMI < 32.4 cm$^2$/m$^2$ for females as sarcopenia, and the incidence of sarcopenia in our study was 42.8% (59/138). There's no significance survival difference in female group (Supplementary Fig. 2), maybe it's because the proportion of female patients in this study is relatively small (33/138 cases, 23.9%). But in the previous studies of sarcopenia, different values of the cutoff point of sarcopenia are usually used in male and female groups\cite{14, 15, 29, 31}. This is mainly because there are great differences in the strength and quality of skeletal muscle between male and female groups. And in this study, compared the average SMI in male and female g-NENs cohort, there was a significant difference in the average value of SMI between male and female groups (45.2 cm$^2$/m$^2$ in male, 37.5 cm$^2$/m$^2$ in female, p < 0.05). Therefore, in order to better evaluate the effect of sarcopenia on the prognosis of g-NENs patients, we used different diagnostic criteria for men and women in this study.

The effect of sarcopenia on short-term postoperative outcomes in patients with malignant tumors is still controversial. Previous studies have confirmed that sarcopenia is associated postoperative short-term prognosis in patients with multiple malignant tumors\cite{11, 13, 15, 32}. In a Chinese study, analysis of 937 patients with gastric cancer after radical gastrectomy showed that sarcopenia was related to severe postoperative complications\cite{11}. An American study showed that sarcopenia was associated with the short-term outcomes in patients with pancreatic cancer after pancreatectomy\cite{32}. However, some studies have indicated opposite opinions\cite{31, 33}. Tegels’ study showed that although the incidence of sarcopenia was high in patients with gastric cancer, it was not associated with a poor postoperative prognosis\cite{31}. Ouchi’s study showed that sarcopenia did not increase the incidence of total and severe postoperative complications in patients with colorectal cancer\cite{33}. In this study, there was no significant difference in the incidence of total postoperative complications, surgical complications and systemic complications between the g-NENs patients with and without sarcopenia. According to the physical location of the complications, the results showed that there was no significant correlation between sarcopenia and specific types of complications in patients with g-NENs.

In recent years, studies have confirmed that sarcopenia is closely related to the long-term prognosis of patients with multiple malignant tumors\cite{10, 12, 14, 16}. Studies by Voron have shown that sarcopenia is an independent prognostic factor for long-term outcomes in patients with hepatocellular carcinoma after hepatectomy\cite{12}. Tan’s study suggested that sarcopenia was associated with poor prognosis of pancreatic cancer patients\cite{16}. Similar to previous studies, our study showed that preoperative sarcopenia was an independent risk factor for the long-term prognosis of g-NENs patients. For this result, we have examined the interaction between sarcopenia and the gastrectomy status and tumor aggressiveness. There was no significant difference in surgical methods, laparoscopic gastrectomy extent and pathological stage between the sarcopenia group and the nonsarcopenia group (Table 1). Multivariate analysis showed that pN stage and sarcopenia were independent prognostic factors of 3-year OS and RFS rates in g-NENs patients, while surgical methods, laparoscopic gastrectomy extent and pT stage were not (Table 3). And The HR value of sarcopenia changed little between univariate and multivariate analysis in our study (Table 3). This shows that the prognostic effect of preoperative sarcopenia is less affected by the gastrectomy status and tumor aggressiveness in
g-NENs patients. However, g-NENs can be divided into three different pathological types, namely, gNET, gNEC, and gMANEC. The degree of tumor differentiation, grade level, and cell components of three pathological types are not the same[4], and the treatment strategy and prognosis also show significant differences with different pathological types[34, 35]. In this study, a further stratified analysis showed that sarcopenia was related to the 3-year OS and RFS rates in patients with gMANEC. In view of this result, we think it may be related to the following reasons. First, for the subgroup of the gNET population, gNET is a highly differentiated neuroendocrine tumor, of mostly low or moderate malignancy, presenting as G1 and G2[3]. The lower tumor invasiveness and the lower effect on skeletal muscle mass may be the reason why sarcopenia cannot be used as a prognostic factor for gNET patients. Second, compared with gNEC and gMANEC, gNEC is a poorly differentiated neuroendocrine carcinoma, which is mostly highly malignant and manifests as G3. GMANEC is defined as a malignant tumor with morphological components of glandular epithelial cells and neuroendocrine cells, both of which account for at least more than 30%. Previous studies have shown that the clinical characteristics of gMANEC largely depend on the proportion of neuroendocrine carcinoma components[36, 37]. Fernandes et al. believe that the prognosis of gMANEC might be related to whether certain tumor components are more invasive[38]. Furthermore, previous studies have confirmed that sarcopenia is associated with the long-term prognosis of gastric adenocarcinoma patients[10, 11]. Therefore, we think that the mechanism may be influenced by the presence of more adenocarcinoma components in gMANEC, then sarcopenia is only related to the long-term prognosis of gMANEC patients and has nothing to do with the prognosis of gNET and gNEC patients in this study. The underlying molecular mechanism needs to be further elucidated.

This study had some limitations. First, because most gNET patients received endoscopic treatment, the number of gNET patients in this study was limited, which may cause bias. Second, this study is a retrospective case-control study conducted in an Asian population, the results of which need to be confirmed by prospective studies and data from western regions. Third, the proportion of female patients in this study is relatively small (33/138 cases, 23.9%), so the prognostic effect of sarcopenia on female g-NENs patients needs to be further tested by a larger population study, and we will conduct related studies in the future. Fourth, this study did not analyze the effect of postoperative adjuvant chemotherapy and the effect postoperative sarcopenia caused by the gastrectomy status and tumor aggressiveness on long-term outcome, which may also bias the results. Nevertheless, as far as we know, this study is the first to explore the effect of sarcopenia on the short-term and long-term outcomes in patients with g-NENs by using data from two independent large-volume institutions, thus providing a reference for future clinical trials.

### Conclusion

In this study, a SMI < 44.3 cm²/m² for males and a SMI < 32.4 cm²/m² for females were found to be the optimal cutoff points for sarcopenia in g-NENs. Sarcopenia was not significantly associated with postoperative complications in patients with g-NENs. Sarcopenia is an independent risk factor for the long-term prognosis of gMANEC patients undergoing radical gastrectomy. Further prospective multicenter studies are needed to confirm the prognostic value of sarcopenia in patients with g-NENs.

### Abbreviations

- g-NENs, gastric neuroendocrine neoplasms
- OS, overall survival
- RFS, recurrence-free survival
- SMI, skeletal muscle index
- BMI, body mass index
- ASA, American Society of Anesthesiologists
- gNET, gastric neuroendocrine tumor
- gNEC, gastric neuroendocrine carcinoma
- gMANEC, gastric mixed adenoneuroendocrine carcinoma

### Declarations
Ethics approval and consent to participate

The study protocol conformed to the Ethics Committee of Fujian Medical University Union Hospital. Written informed consent was obtained before resection.

Consent for Publication

Not applicable.

Availability of Data and Materials

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

Competing Interest

There are no conflicts of interest or financial ties to disclose from any of author.

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Author contributions:

JBW, ZX, JL and QLH, CMH and CHZ conceived the study, analyzed the data, and drafted the manuscript; CMH, CHZ helped critically revise the manuscript for important intellectual content; ZFZ, BBX, PL, JWX, YX, JXL, QYC, LLC, ML, RHT, ZNH and JLL helped collect data and design the study. All authors have read and approved the manuscript.

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Figures
Figure 1

Kaplan-Meier analysis for 3-year overall survival (OS) and recurrence-free survival (RFS) rates of patients with gastric neuroendocrine neoplasms (g-NENs) according to sarcopenia (A)(B); and stratification analysis based on pathological types: (C)(D) gastric neuroendocrine tumor (gNET), (E)(F) gastric neuroendocrine carcinoma (gNEC), (G)(H) gastric mixed adenoneuroendocrine carcinoma (gMANEC).

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