REVIEW

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CLINICAL ENDOSCOPY

Clinical meaning of sarcopenia in patients undergoing endoscopic treatment

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With increasing global life expectancy, the significance of geriatric assessment parameters has increased. Sarcopenia is a crucial assessment parameter and is defined as the age-related loss of muscle mass and strength. Sarcopenia is widely acknowledged as a risk factor for postoperative complications in diverse advanced malignancies and has a detrimental effect on the long-term prognosis. While most studies have primarily concentrated on the correlation between sarcopenia and advanced cancer, more recent investigations have focused on the relationship between sarcopenia and early-stage cancer. Endoscopic submucosal dissection (ESD), which is less invasive than surgical intervention, is extensively employed in the management of early-stage cancer, although it is associated with complications such as bleeding and perforation. In recent years, several reports have revealed the adverse consequences of sarcopenia in patients with early-stage cancer undergoing ESD. This literature review briefly summarizes the recent studies on the association between sarcopenia and ESD.

Keywords: Aged; Endoscopic submucosal dissection; Neoplasms; Prognosis; Sarcopenia

INTRODUCTION

The mean life expectancy worldwide will be 77.2 years by 2050, and the proportion of individuals aged 65 years and above will increase from 10% in 2022 to 16% in 2050.[1] Consequently, endoscopic treatment of older patients is no longer a minority practice but a majority practice. The risks associated with these procedures in elderly populations have become a growing concern. Sarcopenia has recently garnered considerable attention as a geriatric assessment parameter. Sarcopenia is the age-related loss of muscle mass and strength.[2,3]

Sarcopenia is often associated with poor long-term prognosis in various carcinomas, including advanced gastric, esophageal, and colorectal cancer.[4-6] Furthermore, patients with sarcopenia have been reported to have a higher risk of complications related to radical surgery or chemotherapy.[7,8] In addition, sarcopenia has also been reported to be associated with insulin resistance since skeletal muscle is the primary tissue responsible for insulin-dependent glucose uptake.[9] Sarcopenia may pose a cancer risk due to insulin resistance, and a correlation between sarcopenia and impaired immune function has been documented.[10,11] The standard treatment for sarcopenia is a combination of resistance exercises and nutritional therapy.[3] In elderly patients diagnosed with sarcopenia before gastric cancer

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surgery, combined preoperative nutritional therapy and exercise therapy significantly improved grip strength, and patients improved to non-sarcopenia.[12] Therefore, the importance of improving the nutritional status before surgery is beginning to be recognized.

Endoscopic treatment is widely performed for early-stage cancers, such as esophageal, gastric, and colorectal cancer.[13-15] Endoscopic treatment of early-stage cancer mainly includes endoscopic mucosal resection and endoscopic submucosal dissection (ESD), and ESD is among the recommended treatments according to the existing guidelines for early-stage cancer.[14-16] Generally, ESD is less invasive than surgical procedures, resulting in reduced hospitalization duration, decreased likelihood of complications, and preservation of the postoperative quality of life.[17,18] However, ESD is associated with a risk of complications, including bleeding, perforation, and pneumonia.[19,20] Considering that the ESD risk for elderly patients has been increasing, there is concern regarding whether ESD can be safely performed on the elderly. Consequently, numerous studies have been conducted on ESD protective and risk factors in aged patients.[21-23] Several recent studies have examined the correlation between the safety of ESD and sarcopenia. Thus, the primary objective of this review was to furnish a comprehensive synopsis of the hazards associated with endoscopic interventions, particularly ESD, for sarcopenic individuals in an elderly cohort.

CURRENT STATUS

Definition of sarcopenia

Sarcopenia was defined by Rosenberg in 1989 as age-related loss of skeletal muscle mass and muscle strength, derived from the Greek words "sarx", meaning flesh, and "penia", meaning loss.[24] The European Working Group on Sarcopenia in Older People published a consensus paper on sarcopenia in Europe in 2010.[25] In that article, sarcopenia was defined as a progressive loss of skeletal muscle mass and strength with a risk of adverse outcomes, such as disability, decreased quality of life, and death. Furthermore, this manuscript proposes a classification system that encompasses presarcopenia, sarcopenia, and severe sarcopenia, along with a straightforward algorithm for sarcopenia diagnosis. Owing to the divergent physiological characteristics and lifestyles observed in Asian populations compared to their Western counterparts, the Asian Working Group for Sarcopenia (AWGS) was established, and diagnostic criteria tailored specifically for Asians were released in 2014.[26] In October 2016, sarcopenia was internationally recognized as an independent disease with code M62.84, according to the International Classification of Diseases, ICD-10.[27] The latest evidence has been reviewed and revised into European Working Group on Sarcopenia in Older People (EWGSOP) 2 and AWGS 2019, respectively.[2,3]

Sarcopenia is considered a muscle disease (muscle failure). As the role of muscle weakness as a significant determinant outweighs that of muscle mass loss, EWGSOP2 indicates that muscle weakness is the primary parameter for sarcopenia.[2] The potential for sarcopenia is indicated by the loss of muscle strength. Moreover, sarcopenia is diagnosed by either loss of muscle mass or loss of muscle quality, in addition to the loss of muscle strength in EWGSOP2.[2]

The AWGS2019 guidelines also encompass the definition of reduced muscle strength and/or compromised physical capacity, in addition to age-related skeletal muscle mass decline. The age of the elderly was also set at either 60 or 65 years, depending on the situation in each country.[3] The AWGS 2019 recommends that muscle strength be assessed by grip strength; physical performance be assessed by the 6-meter walk, 5-time chair stand test, or Short Physical Performance Battery; and skeletal muscle mass be assessed using either dual-energy X-ray absorptiometry (DXA) or multifrequency bioelectrical impedance analysis (BIA).[3]

However, due to the infrequent use of BIA and DXA in routine clinical practice, alternative measurements utilizing computed tomography (CT) are often employed to assess skeletal muscle mass. This is based on the fact that skeletal muscle mass at the L3 level of the lumbar spine (SMI) or psoas muscle mass at the L3 level of the lumbar spine (PMI) has been shown to exhibit a correlation with total body skeletal muscle mass.[2] Notably, both the EWGSOP2 and AWGS2019 guidelines prioritize the assessment of muscle strength over muscle mass when screening for sarcopenia. Hence, caution must be exercised when diagnosing sarcopenia based solely on skeletal muscle mass, as there may not always be a direct correlation between muscle mass and muscle strength.[2,3,28] Notably, a novel parameter known as muscle quality has recently emerged as an additional indicator of sarcopenia, utilizing techniques such as CT and magnetic resonance imaging to evaluate the extent of fat infiltration within the muscle and explicitly measure the intramuscular adipose tissue content (IMAC).[2,29]

Table 1. Prevalence of sarcopenia in patients with early gastric cancer undergoing ESD

Study	Country	No. of patients	Definition of sarcopenia	Prevalence of sarcopenia (%)
Kim et al. (2021)[31]	Korea	280 Patients with early gastric cancer over 80 years of age	SMI of 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women	61.8
Arao et al. (2021)[30]	Japan	157 Patients with early gastric cancer over 80 years of age	SMI of 42.0 cm^2/m^2 for men and 38.0 cm^2/m^2 for women	42.0
Hisada et al. (2022)[35]	Japan	700 Patients with early gastric cancer	SMI of 40.8 cm^2/m^2 for men and 34.9 cm^2/m^2 for women	34.1
Ito et al. (2022)[33]	Japan	88 Patients with early gastric cancer over 80 years of age	PMI of 6.36 cm^2/m^2 for men and 3.92 cm^2/m^2 for women	72.7
Hisada et al. (2022)[32]	Japan	767 Patients with early gastric cancer over 65 years of age	Both low muscle quantity and low quality (low SMI of 42.0 cm^2/m^2 for men and 38.0 cm^2/m^2 for women and high IMAC of −0.31 and −0.19 for men and women, respectively)	14.2

ESD, endoscopic submucosal dissection; SMI, skeletal muscle mass index; PMI, psoas muscle mass index; IMAC, intramuscular adipose tissue content.

METHOD AND FREQUENCY OF SARCOPENIA ASSESSMENT IN ESD PATIENTS

Table 1 shows the methods and prevalence of sarcopenia in patients undergoing ESD. Gastric ESD was most frequently reported in patients with gastric cancer, and all patients were evaluated for sarcopenia using CT.[30-35] Most studies have focused solely on assessing sarcopenia using skeletal muscle mass measurements, whereas a limited number of studies have incorporated an evaluation of muscle quality.[32] All eligible patients were Asian and were considered to be 80 years of age or older,[30,31,33] 75 years of age or older,[34] 65 years of age or older,[32] or all ages.[35] Table 1 shows the prevalence of sarcopenia among individuals who underwent ESD for early gastric cancer, ranging from 14.2% to 72.7%. Conversely, a prospective study conducted in China revealed a sarcopenia prevalence of 14.4% among patients undergoing radical resection for early-stage gastric cancer.[36] Additionally, in Asian populations, the prevalence of sarcopenia among individuals over 65 and 80 years is documented as 19.6% and 41.8%, respectively.[37] As most studies have evaluated sarcopenia only in terms of muscle mass, the number of sarcopenia cases may be overestimated.

IMPACT OF SARCOPENIA ON ESD IN PATIENTS WITH EARLY GASTRIC CANCER

Short-term prognostic impact of ESD in patients with early-stage gastric cancer

Table 2 shows the correlation between the short-term prognosis of gastric ESD and the presence of sarcopenia. The Japanese guidelines for gastric cancer recommend endoscopic treatment for elderly patients, while highlighting the importance of monitoring treatment-related complications, notably pneumonia.[30,32,35,38] A retrospective study by Arao et al.[30] that included 157 patients with sarcopenia and non-sarcopenia defined as SMI ≤38.0 cm^2/m^2 for women and ≤42.0 cm^2/m^2 for men showed that pneumonia and sarcopenia were significantly correlated (21.2% vs. 7.7%, p=0.018). Conversely, no statistically significant differences were observed between the sarcopenia and non-sarcopenia groups in delayed bleeding (6.1% vs. 2.2%, p=0.24) and perforation (1.5% vs. 0%, p=0.42).

Our previous retrospective study that included 700 patients with sarcopenia and non-sarcopenia defined as SMI ≤34.9 cm^2/m^2 for women and ≤40.8 cm^2/m^2 for men, showed that ESD-related complications, as defined by Common Terminology Criteria for Adverse Events (CTCAE) ≥2 were significantly increased in the sarcopenia group (17% vs. 10%, p=0.005).[35] The short-term prognosis (e.g., delayed bleeding, perforation, pneumonia, urinary tract infection, and nausea) was evaluated using the CTCAE. Furthermore, multivariate analysis demonstrated a significant correlation between sarcopenia and CTCAE ≥2 events (odds ratio [OR],1.79; 95% confidence interval [CI],1.11–2.89; p=0.016), with pneumonia solely occurring in patients with sarcopenia (3 [1.3%] vs. 0 [0%]). There were no significant differences in the rates of *en bloc* resection (100% vs. 100%, p=1.000), R0 resection (92% vs. 93%, p=0.566), or curative resection (92% vs. 92%, p=0.718) between patients with and without sarcopenia, nor were there differences in delayed bleeding (8% vs. 5%, p=0.078) or perforation (4% vs. 2%, p=0.151) rates.

Table 2. Association between sarcopenia and short-term prognosis in patients with early gastric cancer undergoing ESD

Study	Country	No. of patients	Definition of sarcopenia	Results
Arao et al. (2021)[30]	Japan	157 Patients with early gastric cancer over 80 years of age	SMI of 42.0 cm^2/m^2 for men and 38.0 cm^2/m^2 for women	Delayed bleeding rate (6.1% vs. 2.2%, p=0.24) and perforation rate (1.5% vs. 0%, p=0.42) did not differ between the sarcopenia and non-sarcopenia groups. However, pneumonia was significantly increased in the sarcopenia group (21.2% vs. 7.7%, p=0.018).
Hisada et al. (2022)[35]	Japan	700 Patients with early gastric cancer	SMI of 40.8 cm^2/m^2 for men and 34.9 cm^2/m^2 for women	There was no difference in *en bloc* resection rate (100% vs. 100%, p=1.000), R0 resection rate (92% vs. 93%, p=0.566), or curative resection rate (92% vs. 92%, p=0.718) between the sarcopenia and non-sarcopenia groups. Similarly, the rates of delayed bleeding (8% vs. 5%, p=0.078) and perforation (4% vs. 2%, p=0.151) showed no significant discrepancies between the two groups. However, the incidence of CTCAE ≥2 was significantly higher in the sarcopenia group (17% vs. 10%, p=0.005).
Hisada et al. (2022)[32]	Japan	767 Patients with early gastric cancer over 65 years of age	Both low muscle quantity and low quality (low SMI of 42.0 cm^2/m^2 for men and 38.0 cm^2/m^2 for women and high IMAC of −0.31 and −0.19 for men and women, respectively)	There was no significant difference in *en bloc* resection (99.1% vs. 99.4%, p=0.54), R0 resection (93.6% vs. 94.5%, p=0.69), or eCura A/B rates (83.5% vs. 81.5%, p=0.48) between the two groups. However, CTCAE ≥2 was significantly increased in the sarcopenia group (22.0% vs. 12.5%, p=0.01). Sarcopenia (OR, 1.90; 95% CI, 1.05–3.45; p=0.03) was significantly correlated with CTCAE in the multivariate analysis.

ESD, endoscopic submucosal dissection; SMI, skeletal muscle mass index; CTCAE, Common Terminology Criteria for Adverse Events; IMAC, intramuscular adipose tissue content; OR, odds ratio; CI, confidence interval.

Our other previous retrospective study, encompassing a cohort of 767 patients classified as either sarcopenic or non-sarcopenic based on both SMI and IMAC, revealed that ESD-related complications, defined as CTCAE ≥2, similarly significantly increased in the sarcopenia group (22.0% vs. 12.5%, p=0.01). Furthermore, sarcopenia was associated with CTCAE ≥2 in a multivariate analysis (OR, 1.90; 95% CI, 1.05–3.45; p=0.03).[32] Additionally, patients with sarcopenia were more likely to develop pneumonia (2 [1.8%] vs. 5 [0.8%]). In contrast, there were no differences in *en bloc* resection, R0 resection, eCuraA, delayed bleeding, or perforation rates between patients with and without sarcopenia.

Our previous studies showed that CTCAE ≥2 events were significantly correlated with sarcopenia. The most common complication was delayed bleeding followed by perforation. However, there were no significant differences in delayed bleeding and perforation between patients with and without sarcopenia. Conversely, patients with sarcopenia were more likely to develop pneumonia after endoscopic treatment.

To summarize the studies so far, treatment outcomes such as *en bloc* resection rate, R0 resection rate, and curative resection rate have remained the same in patients with sarcopenia, such as delayed bleeding and perforation rates. In contrast, patients with sarcopenia may experience elevated ESD-related complications, notably pneumonia.

The lack of prospective studies examining sarcopenia requires immediate attention and should be addressed in the future. Furthermore, investigations have been conducted to explore the impact of sarcopenia on the overall survival (OS) of individuals with early gastric cancer. These findings are discussed in detail in the next section.

LONG-TERM PROGNOSTIC IMPACT OF SARCOPENIA ON ESD IN PATIENTS WITH EARLY-STAGE GASTRIC CANCER

The association between OS after gastric ESD and various nutritional indices, such as the prognostic nutritional index (PNI),

Table 3. Association between sarcopenia and long-term prognosis in patients with early gastric cancer undergoing ESD

Study	Country	No. of patients	Definition of sarcopenia	Results
Kim et al. (2021)[31]	Korea	280 Patients with early gastric cancer over 80 years of age	SMI of 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women	The 5-year OS rate was significantly lower in patients with sarcopenia than in patients without sarcopenia (68.5% vs. 84.1%, p=0.046). Sarcopenia was significantly correlated with OS in univariate analysis (HR, 1.51; 95% CI, 1.01–2.27; p=0.048) but not in multivariate analysis (HR, 1.27; 95% CI 0.84–1.92; p=0.266).
Ito et al. (2022)[33]	Japan	88 Patients with early gastric cancer over 80 years of age	PMI of 6.36 cm^2/m^2 for men and 3.92 cm^2/m^2 for women	The 3- and 5-year OS rates were 96.4% and 82.8% for the high PMI group, and 84.7% and 68.9% for the low PMI group, respectively; PMI was significantly correlated with mortality after gastric ESD on multivariate analysis (HR, 2.89; 95% CI, 1.11–7.54; p=0.030).
Hisada et al. (2022)[32]	Japan	767 Patients with early gastric cancer over 65 years of age	Both low muscle quantity and low quality (low SMI of 42.0 cm^2/m^2 for men and 38.0 cm^2/m^2 for women and high IMAC of −0.31 and −0.19 for men and women, respectively)	The 5-year OS rate was significantly lower in patients with sarcopenia than in normal patients (98.8% vs. 76.1%). Sarcopenia was significantly correlated with OS in the multivariate analysis (HR, 15.0; 95% CI, 5.82–38.5; p<0.001).
Ito et al. (2023)[34]	Japan	103 Patients in the development cohort and 295 patients in the validation cohort with early gastric cancer over 75 years of age	PMI of 6.36 cm^2/m^2 for men and 3.92 cm^2/m^2 for women	Multivariate analysis revealed that higher CCI (HR, 3.017; 95% CI, 1.377–6.609; p=0.006), lower PMI (HR, 2.206; 95% CI, 1.048–4.643; p=0.037), and age ≥80 years (HR, 1.978; 95% CI, 1.087–3.601; p=0.026) significantly correlated with OS in the development cohort. Each point was assigned to three variables. A scoring system was devised, wherein a cumulative score of two or higher points was designated as the high-risk group. The 3-year survival rates were 92.8% and 72.0% for the low and high-score groups, respectively; the 5-year survival rates for these groups were 91.5% and 57.8%, as observed in the validation cohort.

ESD, endoscopic submucosal dissection; SMI, skeletal muscle mass index; OS, overall survival; HR, hazard ratio; CI, confidence interval; PMI, psoas muscle mass index; IMAC, intramuscular adipose tissue content; CCI, Charlson comorbidity index.

neutrophil-to-lymphocyte ratio, geriatric nutritional risk index (GNRI), Eastern Cooperative Oncology Group-performance status, and Charlson comorbidity index (CCI), has been elucidated in various studies involving elderly patients.[21,39,40] Furthermore, investigations have been conducted on OS following gastric ESD in patients with sarcopenia (Table 3).[31-34] A retrospective study conducted by Kim et al.,[31] which included 280 patients with early gastric cancer aged over 80 years, showed that the 5-year OS rates were significantly lower in patients with sarcopenia (diagnosed based on SMI alone) than in those without sarcopenia (84.1% vs. 68.5%, p=0.046) in univariate analysis. However, OS was not associated with sarcopenia after multivariate analysis (hazard ratio [HR], 1.27; 95% CI, 0.84–1.92; p=0.266). Ito et al.[33] demonstrated that the 3-year and 5-year OS rates were lower in the low PMI group than in the high PMI group (84.7% vs. 96.4%, and 68.9% vs. 82.8%, respectively). Similarly, low PMI was significantly associated with poor OS in multivariate analyses (HR, 2.89; 95% CI, 1.11–7.54; p=0.030). Moreover, a multicenter retrospective study reported a scoring system with CCI ≥3, low PMI, and age ≥80 years, each with one point, defining a high-risk group with two or more points. The 5-year survival rate was significantly lower in the high-risk

group than in the low-risk group (91.5% vs. 57.8%, $p<0.001$).[34]

Our study, in which sarcopenia was diagnosed based on both SMI and IMAC, showed a significant correlation between sarcopenia and OS in the multivariate analysis (HR, 15.0; 95% CI, 5.82–38.5; $p<0.001$).[32] Similarly, GNRI, PNI, and CCI were significantly correlated with OS in the multivariate analysis (HR, 3.08; 95% CI, 1.40–6.76; $p=0.005$; HR, 2.68; 95% CI, 1.43–5.03; $p=0.002$; and HR, 1.84; 95% CI, 1.03–3.29; $p=0.04$, respectively).[32] This shows the importance of assessing sarcopenia, as well as PNI, GNRI, and CCI, before ESD.

Similar to the association between the short-term prognosis of gastric ESD and sarcopenia, numerous studies have reported that sarcopenia has a negative impact on OS after gastric ESD; however, prospective studies are lacking. Skeletal muscle mass (PMI, SMI) and quality (IMAC) have been reported as prognostic factors after pancreatic and esophageal cancer resection and liver transplantation.[29,41,42] Although comorbid stroke and other factors that could cause sarcopenia may have reduced survival after gastric ESD, sarcopenia was an independent poor prognostic factor in multivariate analysis, including CCI.[32,33] Therefore, sarcopenia is likely to be a risk factor for OS after gastric ESD. In studies on the association between sarcopenia and gastric ESD, most deaths after gastric ESD were due to cancers of other organs, and gastric cancer deaths were rarely observed.[31-33] The 5-year OS rate after gastric ESD in patients with sarcopenia has been reported to range from 68.5% to 76.1%.[31-33] A previous study reported that the 5-year survival rate of patients with untreated early gastric cancer was 64.5%.[43] Therefore, gastric ESD and additional surgical resection after noncurative resection may not have contributed to the prolonged prognosis of some patients with sarcopenia. Consequently, when considering ESD and additional surgery for noncurative resection in patients with sarcopenia, the prognosis of comorbidities, especially cancers of other organs, should also be considered.

Further studies are needed to determine whether improvement in sarcopenia is effective in prolonging OS.

IMPACT OF SARCOPENIA ON ESD FOR CARCINOMAS OTHER THAN GASTRIC CANCERS

As mentioned previously, the association between sarcopenia and ESD predominantly involves gastric ESD. However, there are some studies on the effect of sarcopenia on ESD of carcinomas other than gastric cancer. A retrospective study conducted by Goto et al.,[44] comprising 334 patients with early colorectal neoplasms, demonstrated that colorectal ESD could be safely performed regardless of sarcopenia, defined as SMI ≤39.0 cm^2/m^2 for women and ≤50.0 cm^2/m^2 for men. No significant intergroup differences were observed in the rates of *en bloc* resection, curative resection, delayed bleeding, perforation, or post-endoscopic coagulation syndrome. Additionally, a study focusing on the correlation between sarcopenia, defined by the PMI, and esophageal ESD explored whether the procedure led to increased perioperative energy expenditure using an indirect calorimeter, depending on the presence of sarcopenia.[45] Energy expenditure was measured after fasting for at least 12 hours and resting in bed for at least 30 minutes on the day of ESD and the next day. The findings of this study indicated that energy expenditure was not significantly increased in patients with sarcopenia, thereby supporting the feasibility of performing esophageal ESD in individuals with sarcopenia. To date, only a few retrospective studies have investigated the association between sarcopenia and esophageal/colorectal ESD. Therefore, further studies are needed to determine whether sarcopenia affects the short- and long-term prognoses of esophageal and colorectal ESD.

CONCLUSIONS

There is limited evidence on whether sarcopenia should be evaluated in routine practice. However, several studies have indicated that sarcopenia is linked to risk factors for gastric ESD-related complications, particularly pneumonia, and long-term post-ESD survival. All studies on the relationship between sarcopenia and ESD have been retrospective, and no prospective studies have evaluated sarcopenia. Furthermore, there are few studies on whether sarcopenia affects colorectal and esophageal ESD or whether improvement in sarcopenia affects ESD. Consequently, there is an urgent need for comprehensive large-scale studies to corroborate the impact of sarcopenia on ESD.

Conflicts of Interest

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Author Contributions

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