Asia-Pacific Journal of Oncology Nursing 11 (2024) 100436

Contents lists available at ScienceDirect

Asia-Pacific Journal of Oncology Nursing

journal homepage: www.apjon.org

Review

Prevalence and clinical outcomes of sarcopenia in patients with esophageal, gastric or colorectal cancers receiving preoperative neoadjuvant therapy: A meta-analysis

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ARTICLE INFO

Keywords:
Esophageal cancer
Gastric cancer
Colorectal cancer
Sarcopenia
Neoadjuvant therapy
Clinical outcomes

ABSTRACT

Objective: To investigate the prevalence of sarcopenia and its impact on clinical outcomes in patients with esophageal, gastric, or colorectal cancer (EC, GC, and CRC) receiving neoadjuvant therapy through Meta-analysis.
Methods: We searched the PubMed, Embase databases, and Cochrane Library for the prevalence of sarcopenia and its impact on clinical outcomes in EC, GC, or CRC patients treated with neoadjuvant therapy (NAT) from inception to November 2022. The primary endpoints were the prevalence of sarcopenia and overall survival in patients with EC, GC, or CRC treated with NAT. Secondary outcomes included recurrence-free survival, total postoperative complications, grade 3–4 chemotherapy toxicity, and 30-day mortality after surgery.
Results: Thirty-one retrospective studies with 3651 subjects were included. In a fixed-effects model, the prevalence of muscle loss was higher in patients with EC, GC, or CRC at 50% (95% CI = 42% to 58%). The results of the multivariate analysis showed that preoperative patients with sarcopenia had a 1.91 times shorter overall survival (95% CI = 1.61–2.27) and a 1.77 times shorter recurrence-free survival time (95% CI = 1.33–2.35) than patients without sarcopenia, and that patients with sarcopenia had a higher risk of total postoperative complications than patients without sarcopenia OR = 1.27 (95% CI = 1.03–1.57). However, the two groups had no statistical difference in grade 3–4 chemotherapy toxicity ($P = 0.84$) or 30-d postoperative mortality ($P = 0.88$).
Conclusions: The prevalence of sarcopenia in patients with EC, GC, or CRC during NAT is high, and it is associated with poorer clinical outcomes. Clinicians should closely monitor the changes in patients' body composition and guide patients to carry out a reasonable diet and appropriate exercise to improve their poor prognosis and quality of life.
Systematic review registration: CRD42023387817.

Introduction

Gastrointestinal cancer is one of the most essential malignant diseases threatening people's health. According to related reports, the global incidence of esophageal, gastric, and colorectal cancer (EC, GC, and CRC) ranks seventh, third, and fifth, respectively.[1] The case fatality rate ranked sixth, second, and fourth, respectively. Neoadjuvant therapy (NAT) is an essential part of the comprehensive treatment of gastrointestinal cancer. It has many advantages, such as reducing tumor size, improving tumor staging, improving the success rate of surgical resection, improving the overall survival rate, and so on. In the course of NAT for patients with EC, GC, and CRC, a series of related adverse reactions such as nausea, vomiting, and loss of appetite can lead to reduced food intake, weight loss, and even cancer cachexia, resulting in muscle being unable to absorb enough energy, resulting in sarcopenia.[2] The prevalence rate of sarcopenia in patients with gastrointestinal cancer is 12%–78%.[3] The European Working Group on Sarcopenia 2019 updated the definition of sarcopenia, which is a syndrome characterized by low muscle strength, decreased skeletal muscle mass and quantity, and decreased physical mobility, leading to adverse outcomes such as disability, poor quality of life, and death.[4] Sarcopenia hurts the quality of life, reduces the tolerance to anticancer therapy, and increases the risk of chemotherapy toxicity.[5,6] Pedrosa et al.[7] found that chemotherapy affects the regulation of multiple molecular pathways in skeletal muscle. Muscle atrophy and growth result

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https://doi.org/10.1016/j.apjon.2024.100436
Received 18 November 2023; Accepted 1 March 2024

from the balance of these pathways during and after chemotherapy. The catabolic pathway overcomes the anabolic pathway, aggravating the muscular dystrophy that often occurs in cancer patients. Studies by Tantai et al.[8] have shown that the severity and duration of muscular dystrophy in patients with liver cirrhosis are significantly correlated with increased mortality, seriously affecting the cumulative survival time of patients.

The diagnosis and intervention of sarcopenia are often carried out after surgery.[9–11] However, some studies have shown that the effect of diet and exercise interventions on sarcopenia diagnosed before the surgery is better than that diagnosed after the surgery.[12,13] Most studies explore the effect of postoperative diagnosis of sarcopenia on the prognosis of patients with gastrointestinal cancer.[14–16] There are few studies on the prognosis of gastrointestinal cancer patients with NAT who were diagnosed with sarcopenia before the surgery. Some studies have shown that improving the patient's ability to cope with stress, such as with chemotherapy and surgery with pre-rehabilitation, can reduce chemotherapy and postoperative complications.[17] Given the limitations of the above study, the purpose of this study is to conduct a meta-analysis. To investigate the prevalence of sarcopenia and its effect on clinical outcomes in patients with EC, GC, and CRC, who received NAT before surgery.

Methods

The protocol for this meta-analysis is registered on PROSPERO (submitted for registration) with ID number CRD42023387817 and adheres to the latest Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (checklists can be found in Supplementary file 1).

Inclusion criteria

(1) A Cohort study or a retrospective study; (2) patients aged 18 years or older with EC, GC, or CRC receiving NAT (neoadjuvant chemotherapy or radiotherapy); (3) skeletal muscle assessment before and after NAT, and a second assessment must be completed before additional treatment such as surgery or postoperative chemotherapy; (4) appropriate changes in skeletal muscle data were reported (specific values or rates of change before and after NAT were provided), as well as clinical outcomes (e.g., survival, postoperative complications, adverse effects of chemotherapy, mortality); (5) published in English only.

Exclusion criteria

(1) The study design was an animal study; (2) reviews, case reports, conference abstracts, unpublished data, and duplicate publications.

Literature search

The search strategies were based on keywords and the medical subject headings (Mesh) according to the PICO framework. The keywords for the literature search were as follows: P: “colorectal neoplasms” [Mesh] OR “esophageal neoplasms” [Mesh] OR “stomach neoplasms” [Mesh]; I: “drug therapy” [Mesh Terms] OR “therapy drug” [Title/Abstract] OR “drug therapies” [Title/Abstract] OR “therapies drug” [Title/Abstract] OR “chemotherapy” [Title/Abstract] OR “chemotherapies” [Title/Abstract] OR “pharmacotherapy” [Title/Abstract] OR “pharmacotherapies” [Title/Abstract] OR “radiotherapy” [Title/Abstract]; O: “sarcopenia” [MeSH Terms] OR “sarcopenias” [Title/Abstract] OR “muscle mass” [Title/Abstract] OR “muscle loss” [Title/Abstract] OR “muscle strength” [Title/Abstract] OR “muscle wasting” [Title/Abstract] OR “muscular atrophy” [Mesh Terms]. Details are provided in Supplementary file 2.

Study selection and data extraction

Literature screening and data extraction were performed independently by two researchers who had received systematic evidence-based training, and a third researcher judged whether there was disagreement. EndNote X9 was used to deduplicate and preliminary screen the acquired literature. The full text of the literature that met the inclusion criteria was carefully read to determine the included literature. A unified table was used to extract data, including the name of the first author, publication year, country, tumor type, clinical stage, neoadjuvant chemotherapy regimen, mean age, treatment method, measurement tool, cutoff value for diagnosis of sarcopenia, prevalence of sarcopenia during NAT, and clinical outcomes (over survival, postoperative total complications, grade 3 to 4 chemotherapy toxicity, 30-day mortality).

Quality assessment

The quality evaluation was conducted by two researchers independently, and the evaluation results were checked. If there were different opinions, the third researcher was involved. The cohort study was scored according to the Newcastle Ottawa Scale (NOS), and the evaluation content included the selection of the study population (4 items in total, with a full score of 4 points); inter-group comparability (1 item, full score of 2 points); results/measurement of exposure factors (3 items in total, full score of 3 points). The total score is 9 points; a score of 5 or less is considered low quality; a score of 6 or 7 is considered medium quality; and a score of 8 or 9 is considered high quality.

Statistical analysis

Continuous data were expressed as mean ± standard deviation, and the mean prevalence of sarcopenia, which refers to the proportion of people diagnosed with sarcopenia during NAT in the total sample, was analyzed using a random effects model. Multivariate Cox proportional hazards regression analysis was used to study the effect of sarcopenia on overall survival in the original literature. The hazard ratio (HR) and 95% confidence interval (95% Cl) of OS and recurrence-free survival (RFS) were extracted from the literature to pool effect sizes. Odds ratio (OR) and 95% confidence intervals for total postoperative complications, grade 3–4 chemotherapy toxicity, and 30-day mortality were extracted for effect size pooling. Heterogeneity was assessed using I^2, such as $I^2 < 50\%$ and $P > 0.1$ using the fixed effects model, and vice versa using the random effects model.[18] After confirming the correctness of the extracted data, subgroup analysis was performed according to the characteristics of the included studies to reduce heterogeneity, and sensitivity analysis was performed to test the stability of the results. Egger's test was used to detect publication bias; if Egger's test $P < 0.05$, further clipping and fill analysis were performed. STATA 17 and RevMan 5.4 software were used for analysis.

Results

Search results

The initial search yielded 1248 articles, and after removing duplicates, reading titles and abstracts, and the unavailability of the full text, 137 articles remained, excluding nine articles that were not measured before neoadjuvant therapy, 14 articles that were not grouped for sarcopenia versus non-sarcopenia, 47 articles that reported insufficient data, 12 case–control, 11 studies that included patients with other types of cancer, 6 articles that were not published in English, 28 articles that remained, and three articles that were manually searched, resulting in a total of 31 articles[19–49] included (Fig. 1).

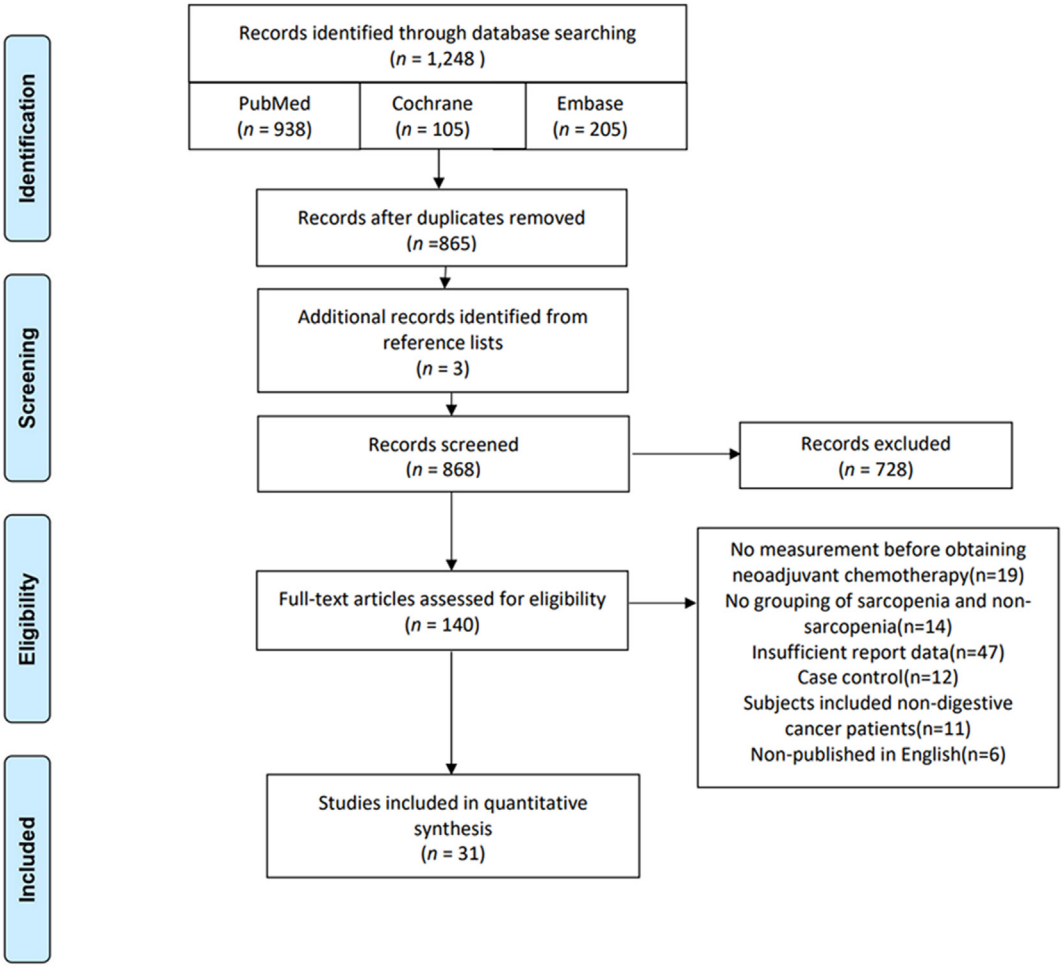

Fig. 1. PRISMA search flow diagram. PRISMA, Reporting Items for Systematic reviews and Meta-Analyses.

Study characteristic and quality assessment

A total of 31 studies involving 3651 subjects were included. All of them were retrospective studies, and 15 studies[19,20,23,24,29–31,33–36,39,40,42,48] were from the Asian population. Thirteen articles were from the European population,[21,22,25,27,28,37,38,41,43–46,49] two articles[26,32] were from South America, and one[47] was from Oceania. The average age of the included population in 30 articles[19–25,27–49] was more than 60 years old, and the average age of only one article[26] was 56.2 years old. Among them, 24 articles were on esophageal cancer,[19–21,23–25,29–31,33–36,38–47,49] two articles.[27,37] were gastroesophageal junction cancer, two articles[22,32] were gastric cancer, three articles were colorectal cancer,[26,28,48] and one[48] was rectal cancer. Neoadjuvant chemotherapy was used in 20 articles,[19–33,35,37,43,44,47] neoadjuvant radiotherapy in three articles,[38-40] neoadjuvant chemotherapy combined with radiotherapy in one article[45] and neoadjuvant chemotherapy or radiotherapy in seven articles.[34,36,41,42,46,48,49] In addition, computed tomography (CT) was the most commonly used tool to measure muscle mass, and only one study[35] used bioelectrical impedance analysis (BIA), 11 studies[19–22,24,29,33,34,36,39,42] used psoas muscle index as the diagnostic criterion, 19 studies[25–28,30–32,35,37,38,40,41,43–49] used skeletal muscle index as the diagnostic criterion, and only one study[23] used skeletal muscle mass, the characteristics of the included studies are detailed in Tables 1 and 2.

The Newcastle–Ottawa Scale demonstrated high quality for seven studies,[19,20,32,35,45,47,48] and moderate quality for 23 studies[21–31,33,34,36–44,46] (Table 3).

The prevalence of sarcopenia during neoadjuvant therapy in patients with esophageal, gastric, or colorectal cancer

Meta-analysis of the prevalence data of sarcopenia in 3651 participants from 28 studies showed that the average prevalence of sarcopenia during NAT in patients with EC, GC, or CRC was 50% (95% CI = 42% to 58%), and there was significant heterogeneity among the studies (I^2 = 94.38%; $P < 0.001$) (Fig. 2). The results showed that the prevalence of sarcopenia was 49.7% (95% CI = 41.5% to 68.2%) in patients with EC, GC, or CRC who were older than 65 years of age. It was higher than the average prevalence of patients under 65 years old, 46.7% (95% CI = 37.1% to 56.3%), but there was no statistical significance ($P > 0.05$). The results of subgroup analysis by region showed that the average prevalence of people from Asia 47% (95% CI = 34.3% to 59.8%) was slightly lower than that of people from other regions 51% (95% CI = 42.1% to 59.9%). However, the difference was not statistically significant ($P > 0.05$). The prevalence of sarcopenia in male patients with EC, GC, or CRC was 39.3% (95% CI = 30.0% to 48.5%) and 35.3% (95% CI = 22.4% to 48.2%) in female patients, and the difference was not statistically significant ($P > 0.05$). The average prevalence estimated by the method of measuring the skeletal muscle index (SMI) at the L3 level and the psoas major muscle index (PMI) at the L3 level was 50.7% (95% CI = 41.2% to 60.1%) and 47.4% (95% CI = 27.6% to 67.2%), respectively, with no significant difference (Table 4).

Table 1
Characteristics of included studies.

Author, year, country	Cancer type, stage	Neoadjuvant chemotherapy	Age (year)	Therapy method	Muscle assessment	Cut offs for sarcopenia (cm^2/m^2)
Ishida, 2021, Japan	EC I-IV	DCF or ACF	71	NAC: 100%	CT L3 PMI	M < 6.36 F < 3.92
Kamitani, 2019, Japan	EC IB-III	DCF or FP	68	NAC: 100%	CT L3 PMI	M < 52.4 F < 38.5
Tan, 2014, England	EC I-III	FP or ECX	68.6	NAC: 100%	CT L3 PMI	M < 52.4 F < 38.5
Palmela, 2017, Portugal	GC II-III	NR	69.3	NAC: 100%	CT L3 PMI	M < 43 (BMI < 25 kg/m^2); 53 (BMI ≥ 25 kg/m^2) F < 41
Miyata, 2017, Japan	EC I-IV	ACF or DCF	64.2	NAC: 100%	BIA skeletal muscle mas	< 90% of standard
Onishi, 2022, Japan	EC II-III	FP/DCF	66.2	NAC: 100%	CT L3 PMI	M < 6.36 F < 3.92
Yip, 2014, England	EC I-IV	5-FU or platinum or EXC	63	NAC: 100%	CT L3 SMI	M < 52.4 F < 38.5
Okuno, 2018, America	CRC NR	NR	56.2	NAC: 100%	CT L3 SMI	M < 43 (BMI < 25 kg/m^2); 53 (BMI ≥ 25 kg/m^2) F < 41
Boer, 2020, England	EC I-III	NR	66.1	NAC: 100%	CT L3 SMI	M < 52.4 F < 38.5
Eriksson, 2016, Sweden	CRC NR	NR	67.3	NAC: 100%	CT L3 SMI	M < 52.4 F < 38.5
Ishida, 2019, Japan	EC I-IV	DCF or ACF	66.7	NAC: 100%	CT L3 PMI	M < 6.36 F < 3.92
Mayanagi, 2017, Japan	EC II-III	Platinum + fluorouracil	63.3	NAC: 100%	CT L3 SMI	M < 52.4 F < 38.5
Harada, 2022, Japan	EC III-VI	FP or DCF	71.1	NAC: 100%	CT L3 SMI	M < 52.4 F < 38.5
Mirkin, 2017, America	GC NR	DCF or ECX or ECF or other	64.5	NAC: 100%	CT L3 SMI	M < 52.4 F < 38.5
Ishibashi, 2019, Japan	EC II-III	FP	68.3	NAC: 100%	CT L3 PMI	M < 6.36 F < 3.92
Ozawa, 2019, Japan	EC T1-3N0-3	Cisplatinum + 5-FU	63.5	NAC: 46% NCRT: 54%	CT L3 PMI	M < 6.36 F < 3.92
Kita, 2021, Japan	EC T1-4N0-3	PAF	62.8	NAC: 100%	CT L3 SMI	25th cut off
Nakayama, 2021, Japan	EC II-III	FP or DCF	66.3	NAC: 84% NCRT: 16%	CT L3 PMI	M < 6.36 F < 3.92
Awad, 2011, England	EC T1-4N0-3	ECF or capecitabine/cisplatin or epirubicin/oxaliplatin	63	NAC: 100%	CT L3 SMI	M < 52.4 F < 38.5
Hagens, 2019, Netherlands	EC T1-4N0-3	Carboplatin + paclitaxel	63.7	NCRT: 100%	CT L3 SMI	M < 43 (BMI < 25 kg/m^2); 53 (BMI ≥ 25 kg/m^2) F < 41
Kawakita, 2019, Japan	EC T1-4N0-3	Cisplatin/nedaplatin + 5-FU	64	NCRT: 100%	CT L3 PMI	M < 3.85 F < 2.42
Yoon, 2020, Korea	EC T1-4N0-3	Cisplatin + 5-FU	63.5	NCRT: 100%	CT L3SMI	M < 52.4 F < 38.5
Järvinen, 2018, Finland	EC I-III	EOX	63	NAC: 76% NCRT: 24%	CT L3SMI	M < 52.4 F < 38.5
Liu, 2016, Japan	EC T1-4N0-3	5-FU + cisplatin/nedaplatin	62.2	NAC: 76% NCRT: 24%	CT L3 PMI	NR
Reisinger, 2015, Netherlands	EC I-IV	CF or ECC or PC	63	NAC: 100%	CT L3 SMI	M < 52.4 F < 38.5
Grün, 2020, Germany	EC T1-4N0-3	NR	67.4	NAC: 100%	CT L3 SMI	M < 52.4 F < 38.5
Panje, 2019, Netherlands	EC II-IV	Docetaxe + cisplatin	61	NAC + NCRT	CT L3 SMI	M < 43 (BMI < 25 kg/m^2); 53 (BMI ≥ 25 kg/m^2) F < 41
Elliot, 2017, Ireland	EC I-III	Cisplatin + 5-FU or carboplatin + paclitaxel	61.6	NAC: 32% NCRT: 68%	CT L3 SMI	M < 52.4 F < 38.5
Paireder, 2016, Australia	EC I-III	NR	61.4	NAC: 100%	CT L3 SMI	M < 55.0 F < 39.0
Fukuoka, 2019, Japan	RC I-III	mFOLFOX6 or XELOX or XELOX + Cetuximab	66	NAC: 43% NCRT: 57%	CT L3 SMI	M < 6.36 F < 3.92
Yassaie, 2019, Netherlands	EC NR	MAGIC or carboplatin/paclitaxel	65.8	NAC: 89% NCRT: 11%	CT L3 SMI	M < 6.36 F < 3.92

5-FU, 5-fluorouracil; ACF, adriamycin + cisplatin + 5-FU; CF, cisplatin + 5-FU; CRC, colorectal cancer; DCF, docetaxel + cisplatin + 5-FU; EC, esophagus cancer; ECC, epirubicin + cisplatin + capecitabine; ECF, epirubicin + cyclophosphamide + 5-FU; ECX, cisplatin + 5-FU + capecitabine; EOX, epirubicin + oxaliplatin + capecitabine; FP, cisplatin + 5-FU; GC, gastric carcinoma; MAGIC, epirubicin + cisplatin + capecitabine; PAF, cisplatin + adriamycin + 5-FU; PC, paclitaxel + carboplatin; PMI, psoas major muscle index; RC, rectal cancer; SMI, skeletal muscle index.

Table 2
Main clinical outcomes included in meta-analysis.

Author, year	Prevalence		Clinical outcome				
	Sample (*n*)	Sarcopenia (*n*)	OS	RFS	Postoperative total complications	Grade 3 to 4 chemotherapy toxicity	30-day mortality
					(Sarcopenia/Non-Sarcopenia)		
Ishida, 2021	333	37	1.68 (1.07–2.66)		25/114		
Kamitani, 2019	90	72	2.49 (1.12–5.53)		48/6	29/3	
Tan, 2014	89	44				24/13	
Palmela, 2017	47	11					
Miyata, 2017	94	44				6/5	
Onishi, 2022	175	139	2.92 (0.86–9.96)		44/13		
Yip, 2014	35	9					
Okuno, 2018	169	22	1.82 (1.07–3.10)	1.82 (1.07–3.10)	17/94		
Boer, 2020	199	91					1/1
Eriksson, 2016	97	50	5.99 (2.43–14.79)		18/8		
Ishida, 2019	165	43			29/38		
Mayanagi, 2017	66	55					
Harada, 2022	150	23	2.49 (1.12–5.53)		13/55		
Mirkin, 2017	36	12			6/6		
Ishibashi, 2019	85	54					
Ozawa, 2019	82	21					
Kita, 2021	87	65			10/10		
Nakayama, 2021	93	47			10/4		
Awad, 2011	47	27					
Hagens, 2019	322	125	1.81 (1.30–2.52)		103/63		
Kawakita, 2019	113	27	5.45 (2.48–11.99)	2.36 (1.23–4.53)	13/28	13/43	
Yoon, 2020	248	156	2.30 (1.42–3.73)	1.57 (1.07–2.32)			
Järvinen, 2018	115	92			62/17		3/0
Liu, 2016	84	42	2.44 (0.93–6.36)		20/15		1/1
Reisinger, 2015	123	16					6/5
Grün, 2020	52	31					
Panje, 2019	61	31				15/22	
Elliot, 2017	207	49			39/98		
Paireder, 2016	130	80	1.72 (1.05–2.83)				
Fukuoka, 2019	47	15			15/32		
Yassaie, 2019	53	33					8/0

OS, overall survival; RFS, recurrence-free survival.

Table 3
Quality assessment for included studies based on the Newcastle–Ottawa Scale.

Author, year	Select	Comparability	Result	Total
Ishida, 2021	★★★★	★★	★★	8
Kamitani, 2019	★★★★	★★	★★	8
Tan, 2014	★★★★	★	★★	7
Palmela, 2017	★★★★	★	★★	7
Miyata, 2017	★★★★	☆	★★	6
Onishi, 2022	★★★★	★	★★	7
Yip, 2014	★★★	★	★★	6
Okuno, 2018	★★★★	★	★★	7
Boer, 2020	★★★★	★	★	6
Eriksson, 2016	★★★★	★	★	6
Ishida, 2019	★★★★	★	★★	7
Mayanagi, 2014	★★★★	★	★	6
Harada, 2022	★★★★	★	★★	7
Mirkin, 2017	★★★★	★	★★★	8
Ishibashi, 2019	★★★★	★	★	6
Ozawa, 2019	★★★★	☆	★★	6
Kita, 2021	★★★★	★	★★★	8
Nakayama, 2021	★★★★	★	★★	7
Awad, 2011	★★★★	★	★★	7
Hagens, 2019	★★★★	★	★	6
Kawakita, 2019	★★★★	★	★★★	8
Yoon, 2020	★★★★	★	★★	7
Järvinen, 2018	★★★★	★	★	6
Liu, 2016	★★★★	★	★	6
Reisinger, 2015	★★★★	★	★	6
Grün, 2020	★★★★	★	★	6
Panje, 2019	★★★★	★	★★★	8
Elliot, 2017	★★★★	★	★★	7
Paireder, 2016	★★★★	★★	★★★	9
Fukuoka, 2019	★★★★	★★	★★★	9
Yassaie, 2019	★★★★	★	★★	7

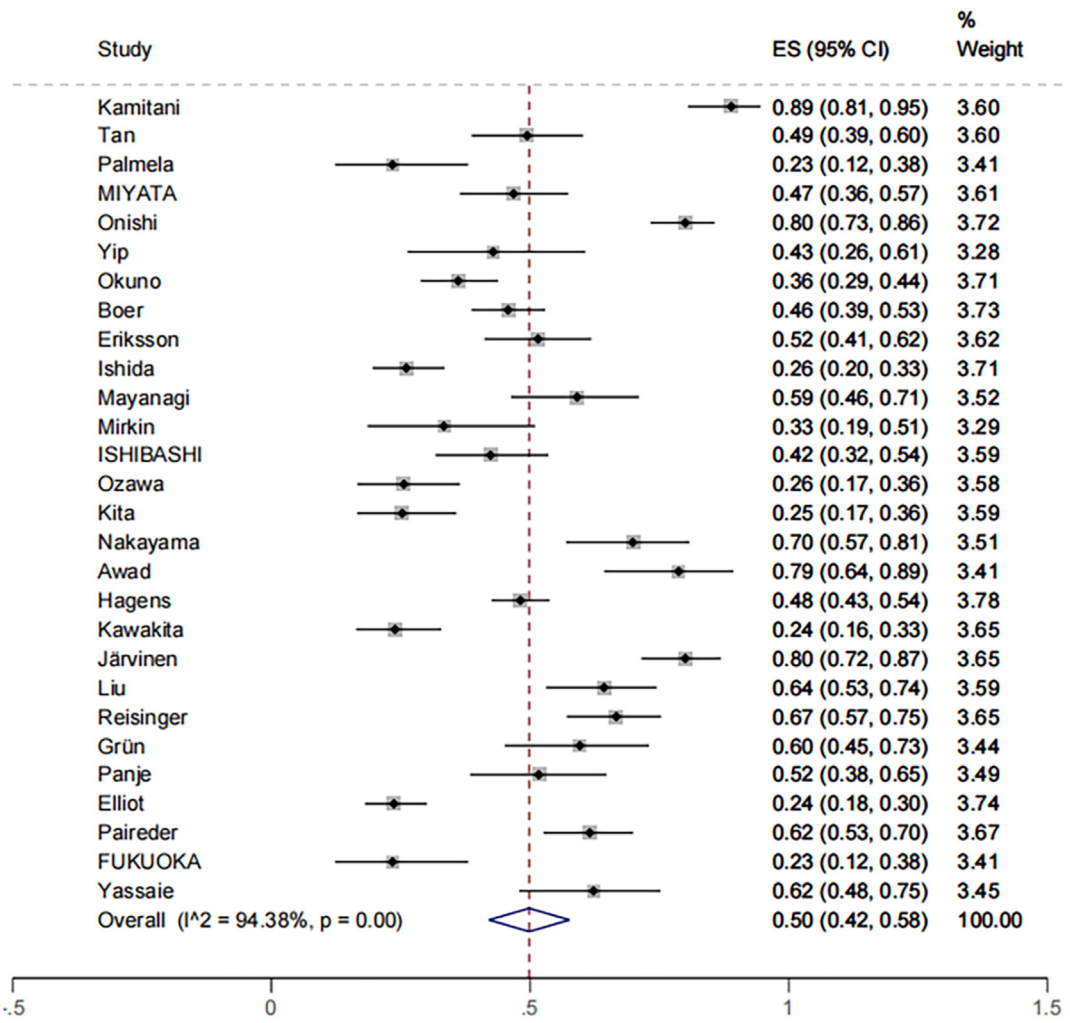

Fig. 2. The prevalence of sarcopenia preoperatively during NAT in patients with EC, GC, or CRC. CRC, colorectal cancer; EC, esophageal; GC, gastric; NAT, neoadjuvant therapy.

Relationship between sarcopenia during neoadjuvant therapy and clinical outcomes

The relationship between sarcopenia during neoadjuvant therapy and overall survival

Twelve studies[19,20,24,26,28,31,38–42,47] showed the relationship between preoperative NAT and OS in patients with EC, GC, or CRC. Multivariate Cox proportional regression survival analyses of the association between sarcopenia and OS in these studies were pooled. The results showed that the risk of shortened overall survival in patients with sarcopenia was 1.91 times that in patients without sarcopenia (HR = 1.91, 95% CI = 1.61–2.27, $Z = 7.42$, $P < 0.001$; heterogeneity test $I^2 = 65\%$, $P = 0.002$; Fig. 3). Further sensitivity analysis found that the heterogeneity of Jarvinen[41] was high, and the deletion of this article had no effect on the results of the study (HR = 2.11, 95% CI = 1.77–2.52, $Z = 8.21$, $P < 0.001$; heterogeneity test $I^2 = 30\%$, $P = 0.16$). The metaninf command was used to conduct sensitivity analysis to explore the robustness of the meta-analysis results. The results showed that no study

Table 4
Subgroup analysis of the mean prevalence of sarcopenia in patients with gastrointestinal cancer.

Subgroup	Study (*n*)	Prevalence rate (%)	95% CI	Heterogeneity across the studies		Heterogeneity between groups (*P*-value)
				I^2	*P*	
Age (year)						
< 65	17	46.7	37.1–56.3	94.68%	< 0.001	0.376
> 65	11	49.7	41.5–68.2	95.89%	< 0.001	
Studying regional						
Asia	15	47.0	34.3–59.8	97.50%	< 0.001	0.619
Other	16	51.0	42.1–59.9	96.23%	< 0.001	
Gender						
Male	23	39.3	30.0–48.5	96.68%	< 0.001	0.628
Female	23	35.3	22.4–48.2	95.64%	< 0.001	
Skeletal muscle index						
SMI	20	50.7	41.2–60.1	96.05%	< 0.001	0.769
PMI	7	47.4	27.6–67.2	96.04%	< 0.001	

PMI, psoas major muscle index; SMI, skeletal muscle index.

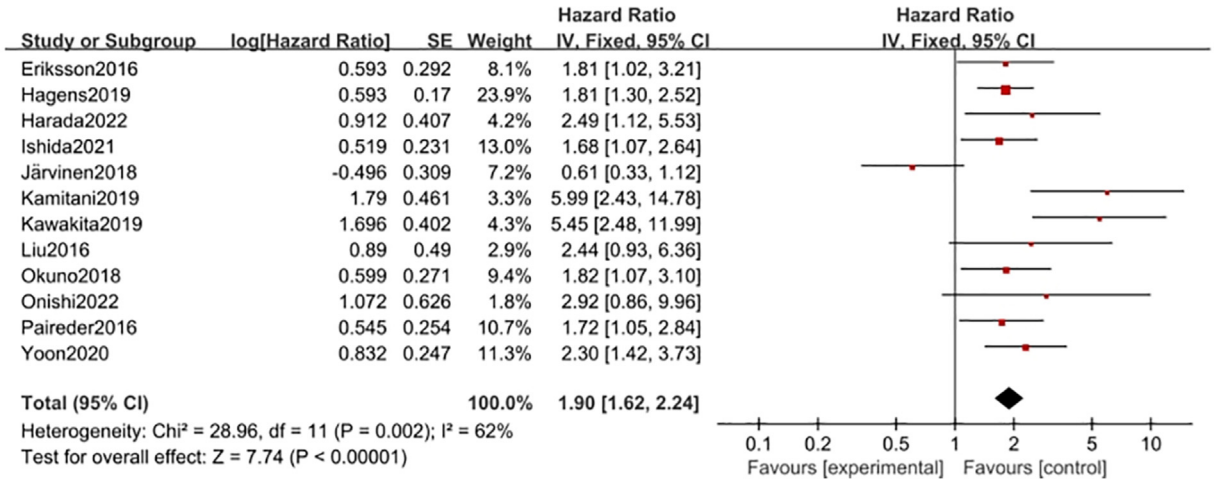

Fig. 3. Forest plots of the relationship between sarcopenia preoperative during NAT and overall survival (multivariate analysis). NAT, neoadjuvant therapy.

significantly affected the stability of the combined effect size (Fig. S1), and the funnel plot showed no high publication bias in each study (Egger's test, $P = 0.200 > 0.05$, Fig. S2).

The relationship between sarcopenia during neoadjuvant therapy and recurrence-free survival

The effect of sarcopenia on RFS was reported in three studies[26,39,40] included in this meta-analysis. In patients with EC, GC, or CRC, the meta-analysis revealed a significant reduction in RFS among patients with sarcopenia compared with those without sarcopenia (HR = 1.77; 95% CI = 1.33–2.35, $P < 0.001$; heterogeneity test $I^2 = 0\%$, $P = 0.57$; Fig. 4).

Relationship between sarcopenia during neoadjuvant therapy and postoperative outcomes

The relationship between sarcopenia during neoadjuvant therapy and postoperative total complications

There were 17 studies on the effect of intraoperative muscle loss on total postoperative complications of NAT.[20,24,26–28,31,32,34–36,38,39,41,42,46–48] The pooled results of the fixed effect model showed that sarcopenia was significantly associated with total postoperative complications (OR = 1.27; 95% CI = 1.03–1.57, $Z = 2.27$, $P = 0.02$; heterogeneity test $I^2 = 21\%$, $P = 0.21 > 0.1$; Fig. 5). No studies that significantly affected the stability of the combined effect size were found (Fig. S3). The funnel plot showed no high publication bias in each study (Egger's test, $P = 0.710 > 0.05$, Fig. S4).

The relationship between sarcopenia during neoadjuvant therapy and grade three to four chemotherapy toxicity

A total of six studies[20–23,39,45] elucidated the relationship between sarcopenia and grade 3–4 chemotherapy toxicity. One[21] study supported that sarcopenia during neoadjuvant therapy may be a predictor of increased incidence of grade 3–4 chemotherapy toxicity in patients with EC, GC, or CRC. In contrast, the remaining five studies[20,22,23,39,45] did not support this finding. However, the results of the meta-analysis showed that the effect of sarcopenia on grade 3–4 chemotherapy toxicity was not statistically significant (OR = 1.05, 95% CI = 0.68–1.60, $Z = 0.20$, $P = 0.84$; heterogeneity test $I^2 = 65\%$, $P = 0.01$; Fig. 6).

The relationship between sarcopenia during neoadjuvant therapy and postoperative 30-day mortality

Five studies[27,41–43,49] mentioned postoperative 30-day mortality, and these results all demonstrated that there were no significant differences between the sarcopenia and non-sarcopenia groups (OR = 1.09, 95% CI = 0.36–3.32, $Z = 0.63$, $P = 0.88 > 0.05$, heterogeneity test $I^2 = 16\%$, $P = 0.31$; Fig. 7).

Discussion

Clinicians increasingly consider skeletal muscle loss a new imaging biomarker, especially in diseases characterized by systemic depletion, such as cancer. Skeletal muscle loss can cause systemic metabolic damage, manifested as weakened antioxidant capacity of the body, inhibition of anabolic metabolism, insulin resistance, etc. It can ultimately lead to metabolic syndrome, malaise, dyslipidemia, etc. and poor patient prognoses.[50]

According to previous reports, the European Working Group on Sarcopenia (EWGSOP)[51] in 2010 counted the prevalence of sarcopenia as 6%–12% globally, and the Asian Working Group on Sarcopenia (AWGS) 2019 reported that the prevalence of sarcopenia in the elderly Asian population was 5.5%–25.7%.[52] Among solid tumors, the prevalence of sarcopenia was 42% in head and neck tumors,[53] 43% in nonsmall cell lung cancer, and about 25% in breast cancer.[54,55] The results of this study show that the prevalence of sarcopenia in patients with EC, GC, or CRC is 50% (95% CI = 42% to 58%), which shows that the prevalence of sarcopenia is already high in patients with EC, GC, or CRC who received NAT before surgery. This high probability may be because EC, GC, or

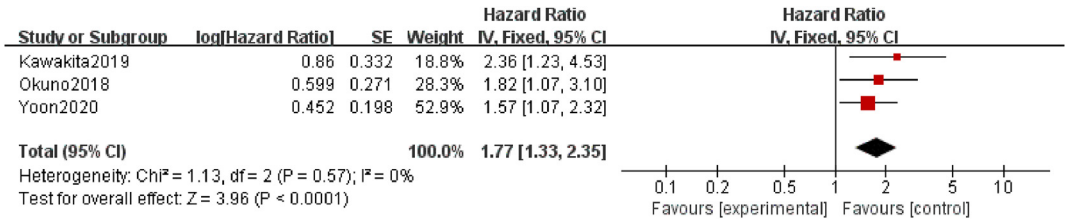

Fig. 4. Forest plots of the relationship between sarcopenia preoperative during NAT and recurrence-free survival (multivariate analysis). NAT, neoadjuvant therapy.

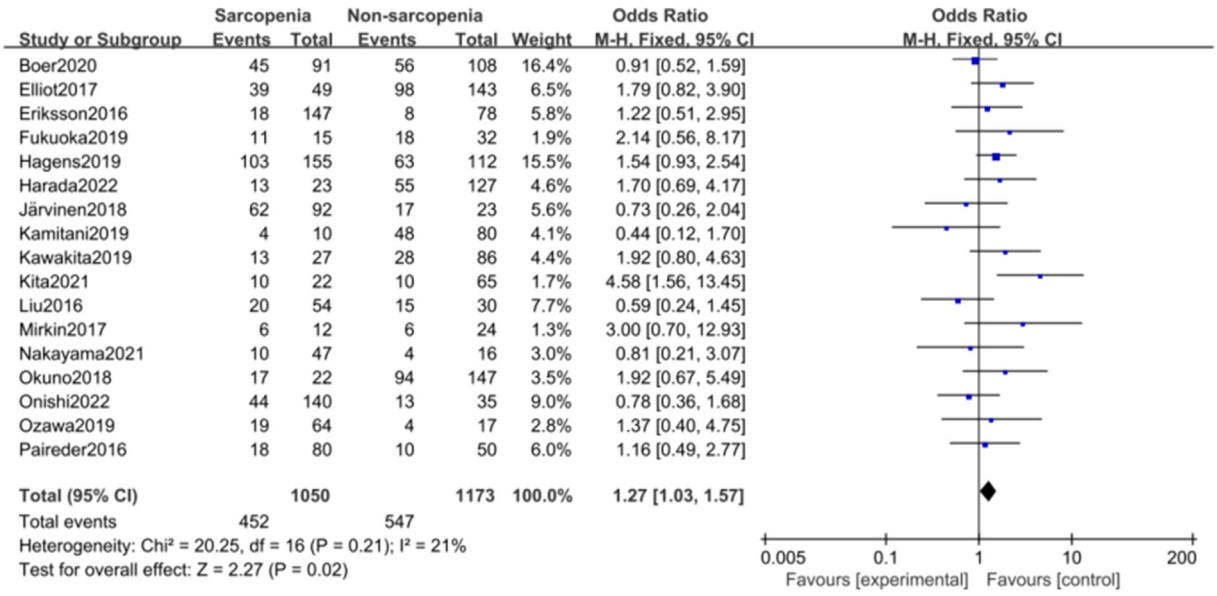

Fig. 5. Forest plots of the relationship between sarcopenia preoperative during NAT and postoperative total complications. NAT, neoadjuvant therapy.

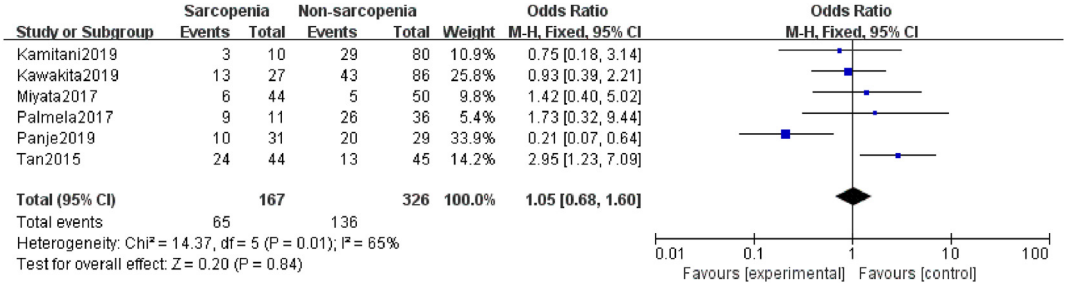

Fig. 6. Forest plots of the relationship between sarcopenia preoperative during NAT and grade 3/4 chemotherapy toxicity. NAT, neoadjuvant therapy.

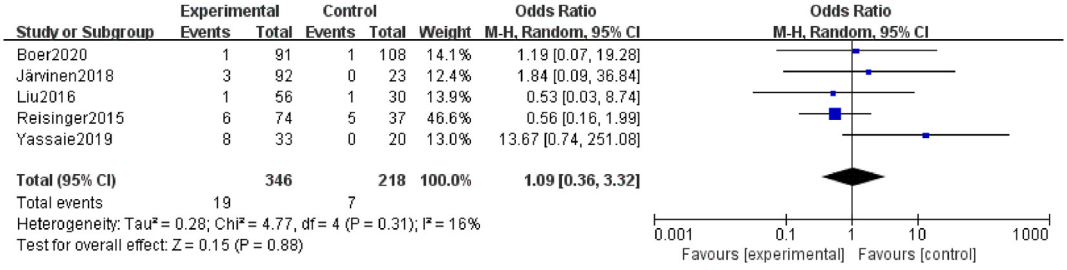

Fig. 7. Forest plots of the relationship between sarcopenia preoperative during NAT and 30-day mortality. NAT, neoadjuvant therapy.

CRC are malignant, wasting diseases with a high prevalence incidence of obstruction or hemorrhage and that tumor progression is often associated with increased levels of systemic inflammation, decreased diet, appetite, anorexia, pain, and an increased incidence of malnutrition, all of which are associated with sarcopenia prevalence.

Research has demonstrated that changes in skeletal muscle from pretreatment to posttreatment may be a more significant prognostic factor than the pretreatment status of skeletal sarcopenia.[30] Additionally, the American College of Surgeons' guidelines emphasize the importance of preoperative assessment of sarcopenia in elderly patients with gastric cancer who are undergoing surgical intervention.[56] However, most studies explore the effect of postoperative diagnosis of sarcopenia on the prognosis of patients with gastrointestinal cancer. The study found a significant association between sarcopenia and impaired overall survival, shorter recurrence-free survival, and a high incidence of postoperative complications. The combined multifactorial analyses revealed that patients with preoperative combined sarcopenia had a 1.91 times shorter overall survival, a 1.77 times shorter recurrence-free survival, and a 1.27 times higher risk of postoperative total complications compared to those who were not sarcopenic. Many of the included studies reported increased muscle loss during NAT, and a significant number of patients developed sarcopenia, indicating a continuous state of change in body composition and nutritional status. During neoadjuvant therapy, tumor patients may be susceptible to complications of sarcopenia due to various reasons, such as inflammatory response, mitochondrial dysfunction, nutritional metabolism disorders, chemotherapeutic response, and

changes in hormone levels.[57–59] It is important to note that these reasons are objective and supported by evidence. The simultaneous presence of sarcopenia may result in delayed healing of surgical incisions, an increased risk of surgical complications, shortened overall and recurrence-free survival of patients, and an increased risk of mortality.

Moreover, sarcopenia is associated with an increased risk of falls, osteoporosis, and fractures. A cross-sectional study investigating the relationship between sarcopenia and osteoporotic vertebral compression fractures (OVCF)[60] discovered that the prevalence of sarcopenia was 12.0%. Furthermore, 66.7% of patients with sarcopenia developed OVCF, indicating that individuals with sarcopenia are more vulnerable to OVCF than the general population. Sarcopenia affects not only the physical health of patients but also their self-care abilities and quality of life. Furthermore, it may be linked to an increased risk of cognitive impairment. According to a study,[61] the risk of mild cognitive impairment in the sarcopenia population with a normal body mass index (BMI) was 1.84 times higher than that in the sarcopenia population with a normal BMI. It is important to note that there is a longitudinal association between sarcopenia and mental health problems. According to a cross-sectional analysis, individuals with sarcopenia were more likely to experience depressive symptoms than those without sarcopenia.[62]

The results of this study indicate that patients with a preoperative diagnosis of sarcopenia have a poor prognosis after undergoing neoadjuvant therapy. Therefore, we speculate that early sarcopenia prevention or treatment may improve patients' prognosis and quality of life. Currently, sarcopenia interventions mainly include nutritional management, exercise guidance, etc. Early implementation of an exercise intervention or an intervention combining exercise and nutrition is an effective strategy to avoid muscle mass loss during treatment and support cancer care. The Clinical Oncology Society of Australia (COSA)[63] also proposed that exercise can help alleviate the adverse effects of cancer and its treatment; it should be part of standard practice in cancer care. Some studies[64,65] have shown that exercise increases nerve conduction velocity and reduces loss of muscle strength and volume. Among them, resistance exercise, as recommended by the American College of Sports Medicine (ACSM) exercise guidelines for cancer survivors[66] and the Chinese Expert consensus on Nutrition and Exercise Intervention for Sarcopenia,[67] can effectively enhance muscle strength and improve physical function by increasing muscle protein synthesis, reducing inflammation, and reducing oxidative stress.[68] In the nutritional management of sarcopenia, in recent years, the intake of some substances has also been emphasized, such as whey protein, branched-chain amino acids, glutathione, L-carnitine, vitamin D, etc.[69] Many studies have shown that nutritional management combined with exercise can more effectively improve the limb function, activities of daily living, and nutritional status of sarcopenia patients.[70–72] We believe that future research on whether early prevention or treatment of sarcopenia will improve the prognosis of patients is significant and promising. At the same time, the population receiving neoadjuvant chemotherapy is far beyond these three types of cancer patients, such as breast cancer, liver cancer, etc. and whether the occurrence of sarcopenia will also affect the prognosis of these patients remains to be confirmed.

There are some limitations in this study. First, all the documents included in this study are published in English, and most of the studies are of medium quality, which may increase the risk of bias. Secondly, there is some heterogeneity in this research literature, which may affect the results of this study. In addition, this study discussed the prevalence of sarcopenia in patients with EC, GC, or CRC who received NAT before surgery and its influence on the clinical outcome of patients. It did not analyze other influencing factors, such as the neoadjuvant chemotherapy scheme and pathological reactions.

Conclusions

This meta-analysis showed a higher prevalence of sarcopenia in EC, GC, or CRC patients during NAT and was associated with worse clinical outcomes. Monitoring changes in body composition, reasonable diet structure, and appropriate exercise are beneficial to reduce the occurrence of sarcopenia. Furthermore, for patients with sarcopenia, these measures may improve their prognosis. Therefore, the results of this study also call for clinicians to pay more attention to the possibility of sarcopenia and effective nursing measures in patients with EC, GC, or CRC during NAT.

Ethics statement

Not required.

Funding

This study received no external funding.

CRediT Authorship Contribution Statement

Lin Luo: Methodology, Writing – original draft preparation. **Yidan Fan**: Methodology, Formal analysis, Data curation. **Yanan Wang**: Formal analysis, Data curation. **Zhen Wang**: Visualization. **Jian Zhou**: Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

Declaration of Generative AI and AI-assisted technologies in the writing process

No AI tools/services were used during the preparation of this work.

Appendix A. Supplementary data

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.apjon.2024.100436.

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