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THE IMPACT OF SARCOPENIA ON POSTOPERATIVE OUTCOMES IN ESOPHAGEAL CANCER PATIENTS UNDERGOING ESOPHAGECTOMY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Introduction. Esophageal cancer remains a major global health challenge, ranking among the leading causes of cancer-related mortality. Esophagectomy, a standard treatment for resectable cases, is associated with high rates of postoperative complications, significantly impacting patient outcomes. Among various risk factors, sarcopenia – a condition characterized by decreased skeletal muscle mass and strength – has emerged as a potential predictor of adverse postoperative outcomes. However, its precise influence on esophagectomy-related morbidity and mortality remains unclear, warranting further investigation.
Aim. This systematic review and meta-analysis aimed to evaluate the impact of sarcopenia on early postoperative outcomes in patients undergoing esophagectomy for esophageal cancer. Specifically, we assessed the association between sarcopenia and postoperative complications, anastomotic leakage, and mortality.
Materials and methods. A systematic literature search was conducted in MedLine and Cochrane Library Central for studies published between January 2020 and September 2024, adhering to PRISMA guidelines. Eligible studies included cohort studies and clinical trials comparing sarcopenic and non-sarcopenic patients undergoing esophagectomy. Data extraction focused on patient demographics, sarcopenia assessment methods, and postoperative outcomes. A meta-analysis was performed using a random-effects model, with results expressed as log odds ratios and 95% confidence intervals (CIs). Heterogeneity was assessed using the I^2 statistic, and publication bias was evaluated through funnel plot asymmetry tests.
Results. A total of 10 studies, encompassing 1,382 patients, met the inclusion criteria. The pooled analysis revealed that sarcopenia was significantly associated with an increased risk of postoperative complications (log odds ratio: 0.725, 95% CI: 0.221 to 1.229; p = 0.005), with moderate heterogeneity (I^2 = 49.3%). However, no significant association was found between sarcopenia and anastomotic leakage (log odds ratio: -0.376, 95% CI: -1.537 to 0.785; p = 0.525), despite high heterogeneity (I^2 = 74.1%). Similarly, no significant relationship was observed between sarcopenia and postoperative mortality (log odds ratio: 0.803, 95% CI: -2.200 to 3.806; p = 0.600), with moderate heterogeneity (I^2 = 63.1%).
Conclusions. Sarcopenia significantly increases the risk of postoperative complications in esophageal cancer patients undergoing esophagectomy, underscoring the need for preoperative muscle mass assessment and targeted nutritional or rehabilitation interventions. However, its association with anastomotic leakage and mortality remains inconclusive. Further research with standardized sarcopenia definitions and larger patient cohorts is necessary to refine clinical risk stratification and optimize perioperative care strategies.

Keywords: **Sarcopenia, Esophageal Cancer, Esophagectomy, Postoperative Complications, Anastomotic Leak, Mortality**

INTRODUCTION

Esophageal cancer is the eighth most prevalent malignancy globally and ranks sixth in cancer-related mortality [1]. For patients with resectable disease, esophagectomy remains the cornerstone of curative treatment, frequently performed alongside neoadjuvant chemoradiotherapy. Despite its therapeutic intent,

esophagectomy is associated with high morbidity and mortality rates, with anastomotic leakage recognized as one of the most critical postoperative complications.

Reported complication rates for esophagectomy range widely, from 45% to 66%, with major complications (Clavien-Dindo grade ≥ 3) occurring in approximately 30-35% of cases. Among these, anastomotic leakage represents a severe complication, affecting 20-30% of patients postoperatively [2, 3]. Assessment of surgical candidacy necessitates a comprehensive evaluation of the patient's general health, with particular emphasis on nutritional status, including both caloric and protein intake.

Malnutrition is frequently observed in individuals with esophageal cancer, largely due to the disease's obstructive symptoms that hinder sufficient food intake, leading to inadequate energy and nutrient levels. Additionally, esophageal cancer can provoke a prolonged inflammatory state and heightened metabolic activity, which worsens cachexia and contributes to ongoing weight loss. Treatment side effects often add to these nutritional challenges, complicating efforts to maintain adequate nourishment [4].

Sarcopenia, characterized by diminished muscle strength and skeletal muscle mass, is a condition prevalent in patients with esophageal cancer, with rates ranging widely from 14.4% to 81% [5] The gold standard for sarcopenia assessment is skeletal muscle mass (SMM) measurement via the skeletal muscle index (SMI), calculated from computed tomography (CT) imaging of the lumbar vertebrae. Since CT imaging is routinely conducted as part of the preoperative assessment for esophageal cancer, SMM evaluation is both feasible and cost-effective [6].

AIM

This systematic review and meta-analysis aim to elucidate the impact of sarcopenia on postoperative outcomes in patients undergoing curative esophagectomy for esophageal cancer. Through a synthesis of current evidence, this study seeks to determine the extent to which sarcopenia influences recovery, complication rates, and overall prognosis in this high-risk patient population.

MATERIALS AND METHODS

The systematic review and meta-analysis were conducted in alignment with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [7].

Eligibility Criteria

Inclusion criteria consisted of cohort studies and clinical trials involving adults (≥18 years) with sarcopenia undergoing esophagectomy for esophageal cancer. Exclusion criteria ruled out studies that did not fit the inclusion criteria, cases where surgery was performed for non-cancerous conditions, and animal studies.

Search strategy

An online search was conducted in parallel and independently by two reviewers through MedLine and Cochrane Library Central alongside a manual search of references from all included studies, previous systematic reviews and meta-analyses. The search strategy was developed from the January 2020 to September 2024 based on a combination of MeSH terms and keywords ((«sarcopenia» AND «esophagectomy» AND «esophageal cancer» AND («retrospective» OR «prospective» OR «randomized controlled trial» OR «meta-analysis» OR «systematic review»; (TITLE-ABS-KEY (sarcopenia) AND TITLE-ABS-KEY (esophagectomy) AND TITLE-ABS-KEY («esophageal cancer» AND (TITLE-ABS-KEY («postoperative outcomes») OR TITLE-ABS-KEY («postoperative complications») OR TITLE-ABS-KEY («perioperative outcomes»)).

Study selection

Study selection was performed independently by two reviewers and, in cases of disagreement, a third senior reviewer resolved conflicts after a discussion with the initial reviewers. The selection process involved screening titles and abstracts, followed by a full-text review based on the eligibility criteria. There were no restrictions on publication language or period, and no filters were applied during the selection.

Data extraction

Baseline characteristics were extracted for each study, including variables such as mean patient age, type of esophageal cancer, clinical staging, use of neoadjuvant therapy, type of esophagectomy performed, and key outcomes such as postoperative mortality, complication rates, and incidence of anastomotic leak.

Statistical analysis and data synthesis

Data were manually extracted independently by two reviewers and then meta-analyzed using the The jamovi project (2024). jamovi (Version 2.5) [Computer Software]. The summary results were expressed as risk difference (RD) for categorical variables and mean differences (MD) for continuous variables. A 95% confidence interval was applied. Statistical heterogeneity was evaluated using the I^2 test. A random effect model was applied to weigh the statistical and clinical heterogeneity. The meta-analysis was synthesized with forest plots.

Outcomes

The following outcomes were analyzed: postoperative mortality, postoperative complications, anastomotic leak.

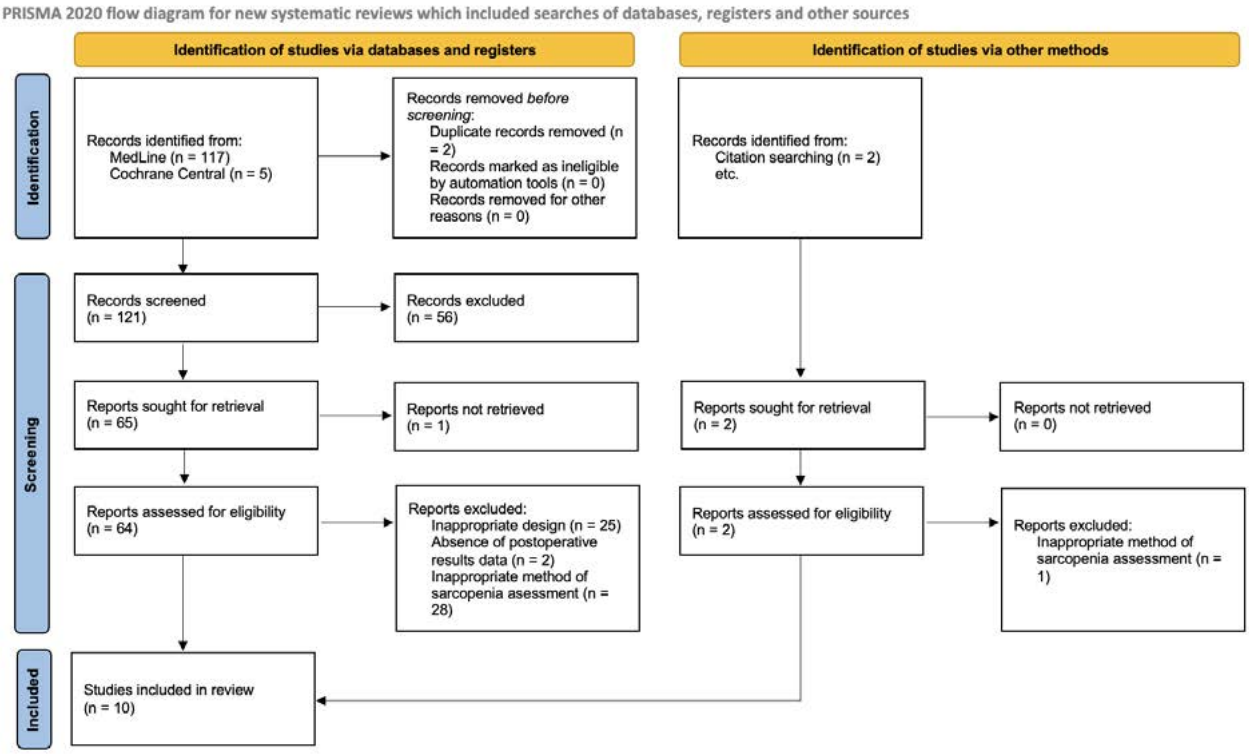

Figure 1. PRISMA flow diagram for search strategy and study selection.

RESULTS

Study characteristics

As shown in the study selection flow diagram, the initial search identified 122 records. After eliminating duplicates and excluding studies that did not meet eligibility criteria, 64 studies remained for full-text review. From these, 10 studies, including data from 1,382 patients across retrospective and prospective observational cohorts, met the final inclusion criteria (Table 1) [8-18].

Table 1

Characteristics of included studies

Study	Year	Design	Sample Size	Mean Age	Sarcopenia Assessment	Sarcopenia Definition
Fehrenbach U et al.	2021	Retrospective	85	64.3	Computed tomography	SMI ≤ 52.4 cm^2/m^2 for men; SMI ≤ 38.5 cm^2/m^2 for women;
Kawakita Y et al.	2020	Retrospective	113	64.2	Computed tomography	PMI < 3.85 cm^2/m^2 for men; PMI < 2.42 cm^2/m^2 for women;
Mayanagi S et al.	2021	Retrospective	187	62.8	Computed tomography	PMI < 6.36 cm^2/m^2 for men; PMI < 3.92 cm^2/m^2 for women;
Menezes TM et al.	2020	Retrospective	26	58	Computed tomography	MMI 43 cm^2/m^2 if BMI < 25, 53 cm^2/m^2 if BMI ≥ 25 for men; MMI 41 cm^2/m^2 for women
Murnane LC et al.	2021	Retrospective	108	66	Computed tomography	SMI < 52.4 cm^2/m^2 for men; SMI < 38.5 cm^2/m^2 for women;
Sakai M et al.	2021	Retrospective	89	64.1	Computed tomography	PMI < 3.85 cm^2/m^2 for men; PMI < 2.42 cm^2/m^2 for women;
Srpcic M et al.	2020	Retrospective	139	63.9	Computed tomography	SMI < 43.1 cm^2/m^2 for men; SMI < 32.7 cm^2/m^2 for women;
Uemura S et al.	2021	Retrospective	121	65	Computed tomography	PMI < 6 cm^2/m^2, BMI < 18.5 kg/m^2
Wakefield CJ et al.	2021	Retrospective	52	65	Computed tomography	SMI: < 43 cm^2/m^2 if BMI < 25, 53 cm^2/m^2 if BMI ≥ 25 for men; SMI < 41 cm^2/m^2 for women;
Park JS et al.	2024	Retrospective	462	67	Computed tomography	SMI < 43.1 cm^2/m^2 for men; SMI < 32.7 cm^2/m^2 for women;

SMI – Skeletal muscle mass index; BMI – Body mass index; PMI – psoas mass index; Masseter mass index;

Anastomotic leak

Anastomotic leak, one of the most severe complications after esophagectomy, was analyzed in eight studies (k = 8) included in this meta-analysis. The random-effects model yielded an estimated log odds ratio of -0.376 (95% CI: -1.537 to 0.785; p = 0.525), indicating that the risk of anastomotic leak did not differ significantly between sarcopenic and non-sarcopenic patients. Despite this, the high level of heterogeneity (I^2 = 74.1%; Q(7) = 29.57, p < 0.001) suggests substantial variability in outcomes, likely reflecting differences in surgical techniques, perioperative care, and patient characteristics. Notably, one study (Mayanagi et al., 2021) was identified as an outlier, which could have contributed to this variability (Fig. 2).

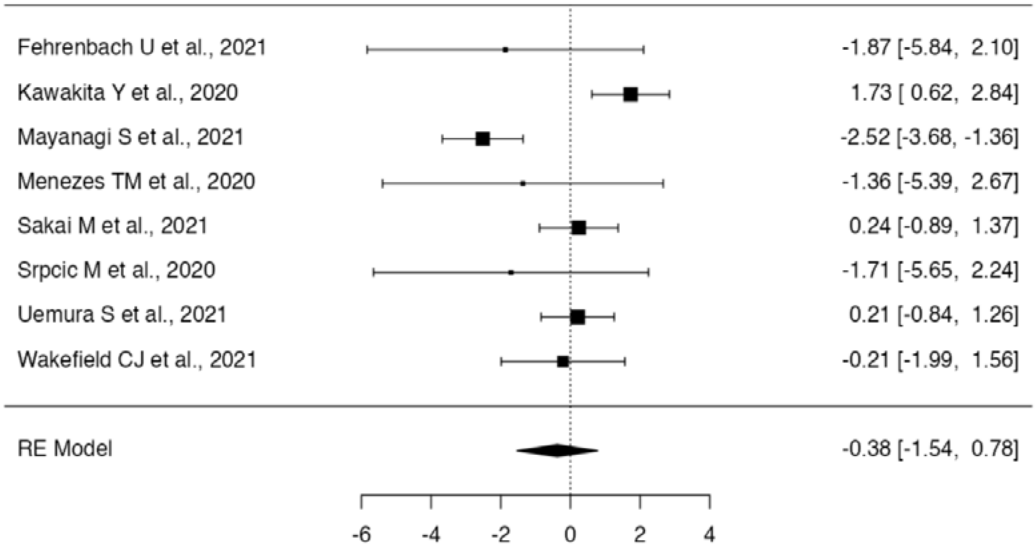

Figure 2. Anastomotic leak results with potential outlier included.

To address potential bias introduced by the outlier (Mayanagi et al., 2021), a sensitivity analysis was conducted by re-running the meta-analysis for anastomotic leak after excluding this study. In this adjusted model with seven studies (k = 7), the random-effects model yielded an estimated average log odds ratio of 0.302 (95% CI: -0.534 to 1.137; p = 0.479), indicating no statistically significant difference in the risk of anastomotic leak between sarcopenic and non-sarcopenic patients. (Fig. 3)

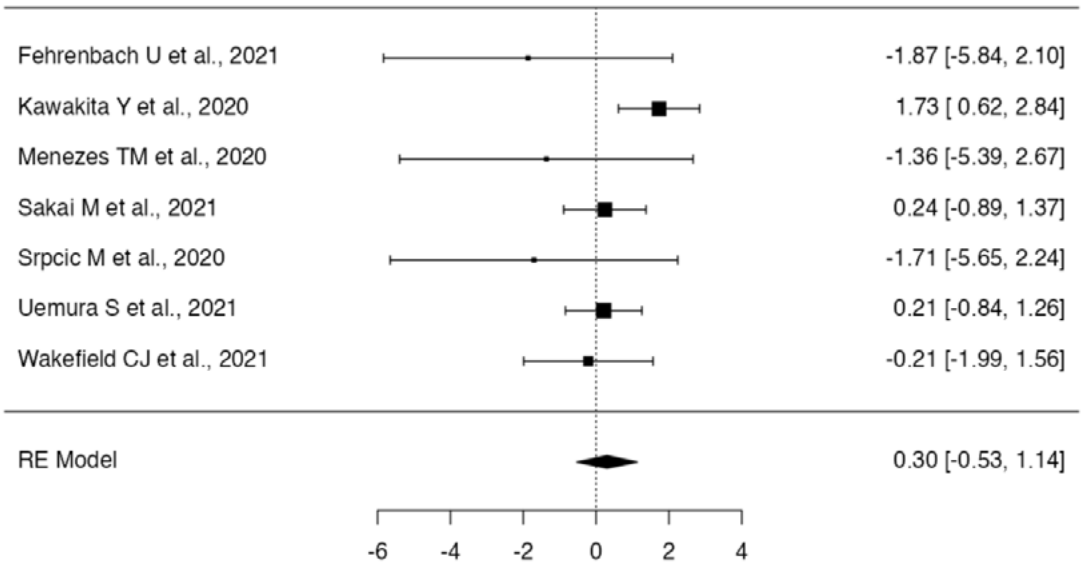

Figure 3. Anastomotic leak results after removing the outlier.

After removing the outlier, heterogeneity among studies decreased markedly, with an I^2 of 38.4% (Q(6) = 9.187, p = 0.163), suggesting moderate heterogeneity without reaching statistical significance. This reduction in heterogeneity implies that the previously observed variability may have been largely attributable to the outlier study's influence.

The 95% prediction interval ranged from -1.229 to 1.833, indicating that while the overall effect remains nonsignificant, the true effect may vary slightly across individual studies.

Complications

A meta-analysis of nine studies (k = 9) was conducted to evaluate the association between sarcopenia and overall postoperative complications in patients undergoing esophagectomy for esophageal cancer. The pooled log odds ratio for complications in sarcopenic versus non-sarcopenic patients was 0.725 (95% CI: 0.221 to 1.229; p = 0.005), indicating a statistically significant increase in complication risk for sarcopenic patients. This result suggests that sarcopenic patients are more than twice as likely to experience postoperative complications compared to their non-sarcopenic counterparts. The moderate heterogeneity (I^2 = 49.3%, Q(8) = 12.75, p = 0.121) suggests variability across studies, likely due to differences in patient characteristics, sarcopenia definitions, and complication types, but this heterogeneity did not reach statistical significance (Fig. 4).

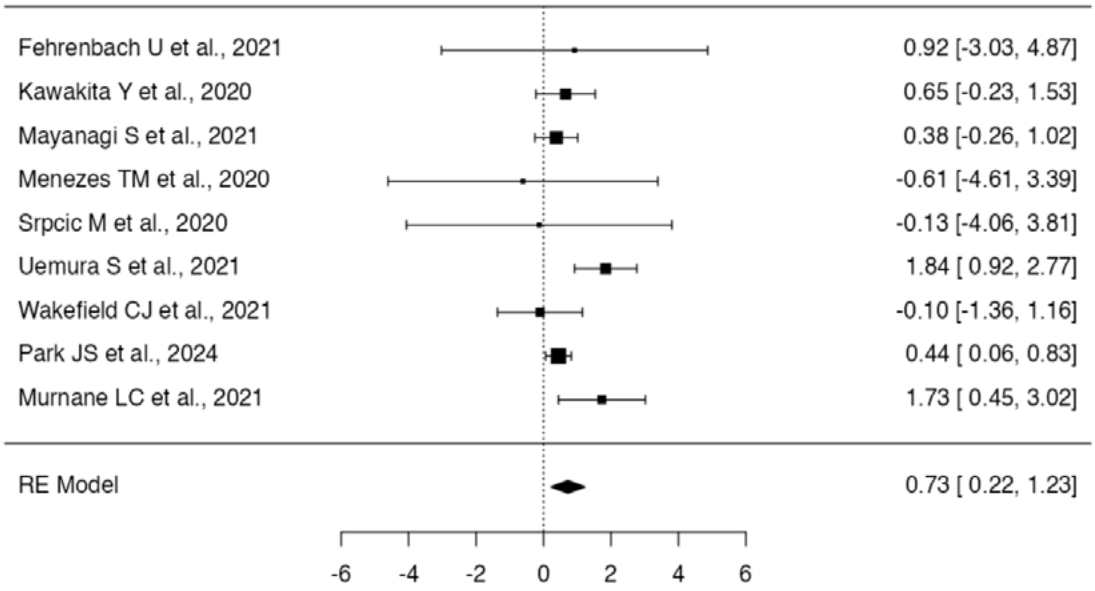

Figure 4. Overall complications rate.

Postoperative mortality

Postoperative mortality was analyzed in three studies (k = 3), comparing outcomes between sarcopenic and non-sarcopenic patients. The random-effects model showed a log odds ratio of 0.803 (95% CI: -2.200 to 3.806; p = 0.600), indicating no statistically significant association between sarcopenia and mortality risk following esophagectomy. Although the Q-test for heterogeneity was not significant (p = 0.076), a moderate level of heterogeneity was observed (I^2 = 63.1%, Q(2) = 5.15) (Fig. 5).

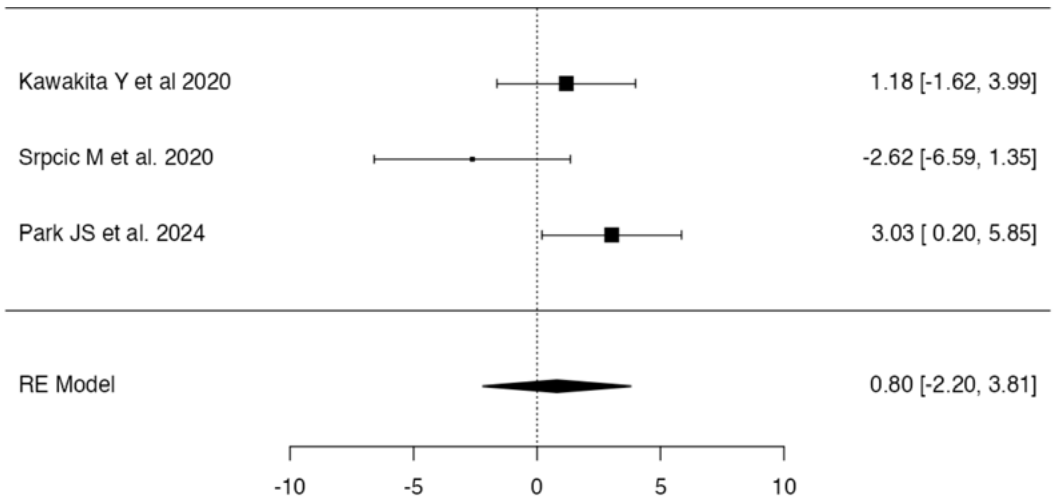

Figure 5. Postoperative mortality.

Publication bias

To evaluate publication bias across the meta-analyses, several assessments were conducted, including the fail-safe N calculation and tests for funnel plot asymmetry.

Overall Complications

For the overall complications analysis (k = 9 studies), the fail-safe N was 39 ($p < 0.001$), indicating that it would require 39 null-effect studies to render the findings non-significant at the $p = 0.05$ level. This high fail-safe N suggests robustness of the observed association between sarcopenia and increased complications. Additionally, the rank correlation test (Kendall's tau = 0.222, $p = 0.477$) and regression test for funnel plot asymmetry ($Z = -0.192$, $p = 0.848$) found no significant asymmetry, suggesting a low risk of publication bias affecting these results.

Mortality

In the mortality analysis (k = 3 studies), the fail-safe N was calculated as 0 ($p = 0.173$), indicating that the result is less robust and may be more influenced by potential unpublished studies. The regression test for funnel plot asymmetry indicated possible asymmetry ($p = 0.039$), suggesting that smaller studies with non-significant outcomes may be underrepresented. However, the rank correlation test (Kendall's tau = -0.333, $p = 1.000$) did not find asymmetry, indicating mixed evidence for potential publication bias in the mortality analysis.

Anastomotic Leak

For anastomotic leak (k = 8 studies), the fail-safe N was 0 ($p = 0.140$), implying moderate sensitivity to additional studies. The rank correlation test (Kendall's tau = -0.500, $p = 0.109$) and regression test ($Z = -1.034$, $p = 0.301$) both indicated no significant asymmetry, suggesting a low risk of publication bias for this outcome.

DISCUSSION

This systematic review and meta-analysis evaluated the impact of sarcopenia on early postoperative outcomes in esophageal cancer patients undergoing esophagectomy. Key outcomes analyzed were overall complications, anastomotic leak, and postoperative mortality. Our findings suggest that sarcopenia is significantly associated with increased postoperative complications, but not with anastomotic leak or mortality.

The significant association between sarcopenia and postoperative complications aligns with existing literature, which identifies sarcopenia as a risk factor for adverse surgical outcomes across various cancer types. Sarcopenic patients are at a disadvantage due to reduced muscle mass and strength, which may impair recovery from surgical stress and predispose to infections, wound healing issues, and respiratory complications [19]. This increased risk emphasizes the clinical relevance of preoperative sarcopenia screening and management through nutritional support or prehabilitation interventions.

The lack of association between sarcopenia and anastomotic leak in our analysis may reflect the complexity of this complication, which can result from multiple factors, including surgical technique, patient comorbidities, and perioperative care [20, 21]. Additionally, the heterogeneity observed in anastomotic leak outcomes indicates variability in study populations and sarcopenia definitions, suggesting that further research is needed to clarify under what conditions sarcopenia may impact leak rates. After excluding an identified outlier study, heterogeneity decreased, strengthening the finding of no association; however, a potential effect in certain subgroups cannot be completely ruled out.

The absence of a significant association between sarcopenia and postoperative mortality in this analysis is noteworthy, as previous studies have shown mixed results. While sarcopenia has been correlated with mortality in some cancers, this relationship may be influenced by differences in patient management, the extent of sarcopenia, and individual patient resilience. The moderate heterogeneity in mortality outcomes highlights the need for additional studies with larger sample sizes and consistent definitions of sarcopenia to determine its role in esophagectomy-related mortality.

Our findings underscore the importance of sarcopenia assessment in esophageal cancer patients. Identifying sarcopenic patients preoperatively allows clinicians to implement targeted interventions to reduce postoperative complications. Given the strong association between sarcopenia and complications, strategies such as nutritional supplementation, physical therapy, and prehabilitation programs should be considered to optimize surgical outcomes.

This meta-analysis has several limitations. First, the heterogeneity across studies, particularly in anastomotic leak and mortality outcomes, suggests variability in patient populations, definitions of sarcopenia, and perioperative practices. Furthermore, most studies included were retrospective, which may introduce bias and affect the reliability of findings. Publication bias was also a concern, particularly for the mortality outcome, as indicated by asymmetry in funnel plot analysis.

CONCLUSIONS

This systematic review and meta-analysis demonstrate that sarcopenia is a significant predictor of increased postoperative complications in esophageal cancer patients undergoing esophagectomy. Despite this association, no significant impact of sarcopenia on anastomotic leakage or postoperative mortality was observed. The findings highlight the importance of preoperative sarcopenia assessment and

targeted interventions, such as nutritional optimization and prehabilitation, to improve surgical outcomes. Future research should focus on standardizing sarcopenia definitions and investigating the efficacy of preoperative interventions in reducing surgical risk in this high-risk patient population.

Perspectives for further research should aim to standardize sarcopenia definitions and assessment methods to enable more consistent comparisons across studies. Randomized controlled trials investigating the impact of preoperative interventions to reduce sarcopenia in esophageal cancer patients would also be valuable. Additionally, larger multi-center studies could improve the generalizability of findings and clarify the potential impact of sarcopenia on anastomotic leak and mortality outcomes.

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This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

The authors declare that they have no conflicts of interest related to this study.

COMPLIANCE WITH ETHICAL REQUIREMENTS

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

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Резюме

ВПЛИВ САРКОПЕНІЇ НА ПІСЛЯОПЕРАЦІЙНІ РЕЗУЛЬТАТИ ВИКОНАННЯ ЕЗОФАГЕКТОМІЇ У ХВОРИХ НА РАК СТРАВОХОДУ: СИСТЕМАТИЧНИЙ ОГЛЯД ТА МЕТААНАЛІЗ

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Вступ. Рак стравоходу залишається серйозною проблемою світової охорони здоров'я, посідаючи одне з перших місць серед причин смертності від раку. Езофагектомія, стандартний метод лікування резектабельних випадків, асоціюється з високим рівнем післяопераційних ускладнень, що суттєво впливає на результати лікування пацієнтів. Серед різних факторів ризику саркопенія – стан, що характеризується зменшенням маси та сили скелетних м'язів – є потенційним предиктором несприятливих післяопераційних результатів. Однак її точний вплив на захворюваність і смертність після езофагектомії залишається нез'ясованим, що вимагає подальших досліджень.

Мета. Цей систематичний огляд та мета-аналіз мали на меті оцінити вплив саркопенії на ранні післяопераційні результати, зокрема загальну частоту ускладнень, частоту неспроможностей анастомозу та післяопераційну летальність у пацієнтів з раком стравоходу, які перенесли езофагектомію. Саркопенія, що характеризується зниженням м'язової маси та сили, асоціюється з поганими хірургічними результатами при різних видах раку, однак її роль в езофагектомії для лікування раку стравоходу залишається нез'ясованою.

Матеріали та методи. Згідно з керівництвом PRISMA, ми провели комплексний пошук досліджень, опублікованих у період з січня 2020 року по вересень 2024 року в MedLine та Cochrane Library Central. Були включені когортні дослідження та клінічні дослідження, які оцінювали результати у пацієнтів з саркопенією та без неї, які перенесли езофагектомію з приводу раку стравоходу. Були отримані та проаналізовані демографічні дані пацієнтів, визначення саркопенії та післяопераційні результати. Мета-аналіз проводився з використанням моделі випадкових ефектів для врахування гетерогенності, а результати виражалися у вигляді логарифмічного відношення шансів і 95% довірчих інтервалів (ДІ). Упередженість публікацій оцінювали за допомогою тестів на асиметрію funnel plot та розрахунків fail-safe N.

Результати. Критеріям включення відповідали 10 досліджень із загальною кількістю 1 382 пацієнтів. Пацієнти з саркопенією мали значно вищий ризик післяопераційних ускладнень із загальним логарифмічним відношенням шансів 0,725 (95% ДІ: 0,221 до 1,229; p = 0,005). Аналіз чутливості виявив помірну гетерогенність (I^2 = 49,3%). Натомість між саркопенією та неспроможністю анастомозу не виявлено значущої асоціації (логарифмічне відношення шансів = -0,376, 95% CI: -1,537 до 0,785; p = 0,525), хоча спостерігалася висока гетерогенність (I^2 = 74,1%), яка зменшилася після видалення одного аномального дослідження. Результати щодо післяопераційної летальності не виявили значущого зв'язку із саркопенією (логарифмічне відношення шансів = 0,803, 95% CI: -2,200 до 3,806; p = 0,600) та показали помірну гетерогенність (I^2 = 63,1%).

Висновки. Саркопенія є значущим предиктором підвищеного ризику післяопераційних ускладнень у пацієнтів з раком стравоходу, які перенесли езофагектомію, що підкреслює необхідність попередньої оцінки саркопенії та цільових інтервенцій. Хоча асоціацій із неспроможністю анастомозу або післяопераційною летальністю не виявлено, подальші дослідження зі стандартизованими визначеннями саркопенії та більшими вибірками необхідні для уточнення цих результатів.

Ключові слова: **саркопенія, рак стравоходу, езофагектомія, післяопераційні ускладнення, неспроможність анастомозу, летальність**

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