



Osteosarcopenia in patients with cancer A systematic review and meta-analysis

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Abstract

Background: Osteosarcopenia is frequent, and the relative risk of fracture is higher among patients with sarcopenia. It is a strong predictor of poor outcomes in older adults undergoing cancer treatment, suggesting that osteosarcopenia is important in an aging society. This study aimed to evaluate the overall survival (OS) and disease-free survival (DFS) of patients with cancer with and without osteosarcopenia.

Methods: Five electronic databases—Embase, PubMed, Web of Science, Scopus, and CINAHL—were searched for relevant articles published before February 2024. Studies that met the criteria were used to evaluate the OS and DFS of patients with cancer with and without osteosarcopenia. From the 603 initially identified articles, 8 involving 1608 participants were included in the meta-analysis.

Results: We observed that patients with cancer diagnosed with osteopenia, sarcopenia, or osteosarcopenia had worse DFS than those without these conditions. Specifically, osteopenia (pooled hazard ratio [HR] = 1.70, P = .01) and osteosarcopenia (pooled HR = 2.17, P = .0001) emerged as independent predictors of DFS. However, sarcopenia was significantly associated with DFS. The quality of the included studies was generally good, and no publication bias was detected among them for either OS or DFS.

Conclusion: These meta-analysis results suggest that osteopenia and osteosarcopenia are associated with worse DFS among patients with cancer. The use of different case definitions appeared to be a major source of heterogeneity among studies. Further studies are warranted to confirm our findings, especially those regarding OS and DFS.

Abbreviations: CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, OS = overall survival.

Keywords: cancer, meta-analysis, osteoporosis, osteosarcopenia, sarcopenia

1. Introduction

Sarcopenia is a disease characterized by progressive and generalized loss of skeletal muscle mass and strength. It is associated with the risk of adverse outcomes such as physical disability, poor quality of life, and death.^[1-3] Osteoporosis and osteopenia are characterized by different grades of low bone mass and deterioration of bone tissue and are associated with increased bone fragility.^[4] Both conditions are common among patients with cancer. Osteosarcopenia, characterized by the concurrent deterioration of bone and muscle mass, represents a critical yet

often underrecognized complication in patients with cancer. It not only poses significant challenges to patients' mobility and quality of life but also has profound implications for their treatment outcomes and survival rates.^[5–7]

Recent research has increasingly emphasized the interplay between sarcopenia and osteopenia and their combined impact on the health outcomes of patients with cancer. Studies have shown that osteosarcopenia is associated with a higher risk of fractures, physical disability, and even mortality, [8,9] particularly in oncology settings where patients already face significant morbidity from

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

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cancer and its treatments.^[10,11] However, osteosarcopenia has received insufficient attention in cancer care protocols, often leading to delayed or missed diagnoses. A comprehensive synthesis of available evidence through a systematic review and meta-analysis is crucial for understanding the broader landscape and guiding evidence-based clinical decision-making.

The impact of osteosarcopenia extends beyond individual patient outcomes, affecting the broader healthcare system with increased hospitalizations, longer stays, and higher costs.[12,13] Therefore, identifying effective strategies to prevent, diagnose, and manage osteosarcopenia could significantly improve patient outcomes and reduce the economic burden on healthcare services. Furukawa et al examined the association between osteosarcopenia and both disease-free (DFS) and OS in patients with cancer, these HRs are being estimated in very different situations, given that sometimes chemotherapy is a significant protective factor and sometimes a risk factor. [14] Many articles have reviewed the prevalence, diagnostic criteria, treatment approaches, and clinical outcomes of osteosarcopenia. [7,9,15,16] However, most focus on the older population, with relatively few discussing osteosarcopenia in oncology settings. Therefore, we sought to examine the existing literature on osteosarcopenia in patients with cancer to identify research gaps and suggest future directions.

Ultimately, the findings of this systematic review and meta-analysis will inform healthcare professionals, researchers, and policymakers about the complex relationship between cancer, sarcopenia, and osteoporosis. Moreover, they will underscore the importance of implementing multidisciplinary interventions to address these musculoskeletal complications and improve the overall well-being of patients with cancer across the care continuum. In this meta-analysis, we aimed to evaluate the OS and DFS of patients with cancer with and without osteosarcopenia.

2. Methods

2.1. Literature search

Ethical approval was not necessary since this study was a meta-analysis. A thorough search was conducted of the following biomedical databases: Embase, PubMed, Web of Science, Scopus, and CINAHL to identify relevant articles with data on the association between osteosarcopenia and survival in cancer patients. We searched all records published, from inception through February 2024, the English search terms were based on a combination of relevant MeSH terms, that is, "malignant neoplasm" and "cancer" combining with "osteopenia," "osteoporosis," "osteosarcopenia," "fractur," "sarcopenia," and "survival" as key words. We further manually searched the bibliographies of retrieved publications to identify relevant articles that did not appear in the database search (Table 1).

2.2. Study selection

The inclusion criteria for the review included: (1) Observational study designs such as case-control, cross-sectional, and longitudinal cohort studies; (2) The study population was the cancer patients with osteosarcopenia and non-osteosarcopenia; (3) Clear and valid diagnosis of osteopenia/osteoporosis and sarcopenia; (4) Relevant data on the rate of survival, as well as relevant risk factors in the form of HR (95% confidence interval, CI) were provided or could be generated from the raw data in the study.

The exclusion criteria included: (1) Reviews, article reviews, lectures, case reports, conference abstracts, and animal experiments; (2) Poor data quality, small sample data, repeated publications, or similar studies; (3) Data with obvious errors, incomplete data that cannot be utilized, poor quality literature, and inability to obtain the data needed for the study.

Two authors screened abstracts and selected appropriate studies. They were published in English. Two authors independently examined the full text of the remaining articles for eligibility. Disagreements between the 2 reviewers were resolved by discussion to achieve consensus or by consulting a third member of the review team. The study selection algorithm is reported in Figure 1.

2.3. Quality appraisal

In this meta-analysis, we applied the Newcastle-Ottawa Scale^[17] for evaluating study quality, as applying this scale

Table 1

4

Strategies used for searching electronic databases.

("osteoporosis" [MeSH Terms] OR "osteoporosis" [All Fields] OR "osteoporoses" [All Fields] OR "osteoporosis, postmenopausal" [MeSH Terms] OR ("osteoporosis" [All Fields] AND "postmenopausal" [MeSH Terms] OR ("bone" [All Fields] AND "diseases" [All Fields] AND "metabolic" [MeSH Terms] OR ("bone" [All Fields] AND "diseases" [All Fields] OR "osteopenia" [All Fields] OR "osteopenias" [All Fields] OR "osteopenias" [All Fields] OR "osteopenias" [All Fields] OR "osteopenias" [All Fields] OR "cancerated" [All Fi

Search terms

- 2 "Osteosarcopenia" [All Fields] AND ("cancer s" [All Fields] OR "cancerated" [All Fields] OR "canceration" [All Fields] OR "cancerization" [All Fields] OR "c
- 3 ("fracture" [All Fields] OR "fractures" [All Fields] OR "cancerated" [All Fields] OR
 - ("osteoporosis" [MeSH Terms] OR "osteoporosis" [All Fields] OR "osteoporoses" [All Fields] OR "osteoporosis, postmenopausal" [MeSH Terms] OR ("osteoporosis," [All Fields] AND "postmenopausal" [All Fields] OR ("bone diseases, metabolic" [MeSH Terms] OR ("bone" [All Fields] AND "diseases" [All Fields] AND "metabolic" [All Fields]) OR "metabolic" [All Fields] OR "osteopenia" [All Fields] OR "osteopenia" [All Fields]) OR "metabolic" [MeSH Terms] OR ("soteopenia" [All Fields]) OR "sarcopenia" [MeSH Terms] OR ("bone" [All Fields]) OR "sarcopenia" [MeSH Terms] OR ("bone" [All Fields]) OR "bone" [All Fields]) OR "bone" [All Fields]) OR "bone and bones" [MeSH Terms] OR ("bone" [All Fields]) OR "bone" [All Fields]) OR "cancerated" [All Fields]) OR "cancera

to evidence-based reviews and meta-analyses may produce highly objective results. The quality of the study was evaluated by 8 items under the 3 categories of participant selection, comparability of study groups, and ascertainment of outcome or exposure. A score of ≥7 is classified as high-quality literature. All studies were independently scored in each domain by the 2 coauthors. Consensus was reached after classification by the individual researchers (Table 2).

2.4. Measures

Overall mean effect sizes were estimated using either random-effects or fixed-effects models depending on the heterogeneity among the included studies, which was assessed using the I^2 statistic (random-effects models were used if $I^2 > 50\%$, otherwise, the fixed-effects model was used). To evaluate publication bias, we used funnel plots and Begg test. All statistical analyses were performed using RStudio Version 1.3.1093. The "metafor" package was applied to conduct meta-analyses. Significance was defined as a 2-tailed P < .05.

2.5. Data extraction

The data extracted included author names, participant characteristics, sample size (osteosarcopenia/non-osteosarcopenia), inclusion criteria, and outcomes. Data extraction was carried out independently by 2 authors to ensure accuracy and consistency.

3. Results

Of the 603 relevant articles retrieved, 344 remained after removing duplicate articles. Next, another 329 articles were excluded after reviewing the titles and abstracts. The remaining 15 articles underwent full-text review, of which 8 involving 1608 patients were included in the meta-analysis (Table 3).

The 8 included studies were published between 2021 and 2024 with sample sizes of 41 to 325. In total, these studies included 411 patients with cancer with osteosarcopenia and 1197 patients with cancer without osteosarcopenia. Osteopenia was assessed by pixel density in the mid-vertebral core of the 11th thoracic vertebra, and sarcopenia was assessed by the psoas muscle areas at the third lumbar vertebra. Osteosarcopenia was defined as the concomitant occurrence of osteopenia and sarcopenia.

The quality of these studies was assessed using the Newcastle–Ottawa Scale. The exposed cohort's representativeness, selection of the nonexposed cohort, clarity in descriptions of comparability, and follow-up time were all deemed clear and thorough, resulting in quality scores ≥ 7, indicating high quality.

The results showed that patients with cancer with osteopenia, sarcopenia, or osteosarcopenia had worse DFS than those without these conditions. Osteopenia (pooled HR = 1.70, 95% CI = 1.16–2.47) and osteosarcopenia (pooled HR = 2.17, 95% CI = 1.62–2.92) were identified as independent predictors of DFS. However, sarcopenia was not significantly associated with DFS (Figs. 2–4).

While osteopenia (HR = 2.00, 95% CI = 1.58–2.53, $I^2 = 0.0\%$), sarcopenia (HR = 2.58, 95% CI = 1.79–3.71,

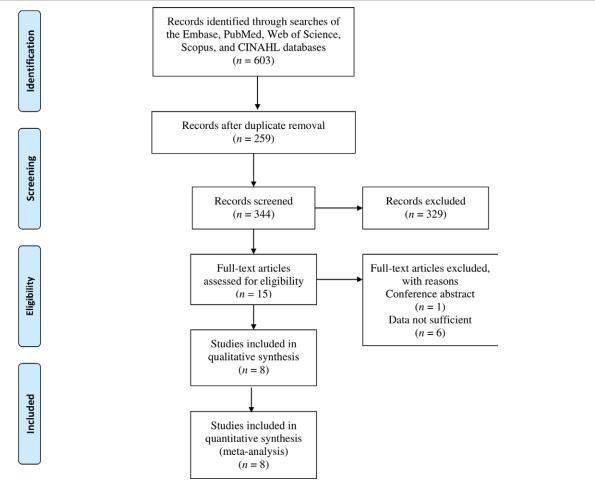


Figure 1. PRISMA flowchart of study selection.

 $I^2 = 0.0\%$), and osteosarcopenia (HR = 2.67, 95% CI = 2.11–3.37, $I^2 = 26.0\%$) were associated with OS the associations were not statistically significant (Figs. 5–8).

4. Discussion

The findings of this meta-analysis shed light on the prognostic significance of osteopenia, sarcopenia, and osteosarcopenia in patients with cancer, particularly regarding their DFS and OS. Incorporating data from 8 relevant studies, our analysis underscores the importance of considering these musculoskeletal factors when assessing and managing patients with cancer. Firstly, our results indicate that osteopenia and osteosarcopenia are

independent predictors of worse DFS in patients with cancer. Specifically, those with osteopenia have a 1.70-fold higher risk of cancer recurrence or progression than those without osteopenia. Similarly, those with osteosarcopenia have an even greater risk, with a hazard ratio of 2.17. These findings align with previous research suggesting that compromised bone and muscle health may contribute to the aggressiveness and metastatic potential of cancer, ultimately impacting disease outcomes, including quality of life and treatment adherence. [14] These findings also underscore the need for clinical protocols incorporating both nutritional and exercise interventions as standard care for patients with cancer, a recommendation supported by the guidelines of the American Society of Clinical Oncology. [24]

Table 2

Quality ratings of selected papers by study design.

	Selec	tion (0–4 stars))	Comparabilit	ty (0–2 stars)		Outcome (0-3	stars)	
Studies	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Total NOS score (0–9)
Abe et al (2024) ^[17]	*	*	*	*	*	*	*	*	8
Abe et al (2023)[18]	*	*	*	*	*	*	*	*	8
Furukawa et al (2021)[14]	*	*	*	*	*	*	*	*	8
Matsumoto et al (2023)[19]	*	*	*	*	*	*	*	*	8
Takano et al (2023)[20]	*	*	*	*	*	*	*	*	8
Takeda et al (2023)[21]	*	*	*	*	*	*	*	*	8
Takeda et al (2023)[22]	*	*	*	*	*	*	*	*	8
Taniai et al (2022) ^[23]	*	*	*	*	*	*	*	*	8

Q1: Representativeness of the exposed cohort.

[&]quot;*" represents one point.

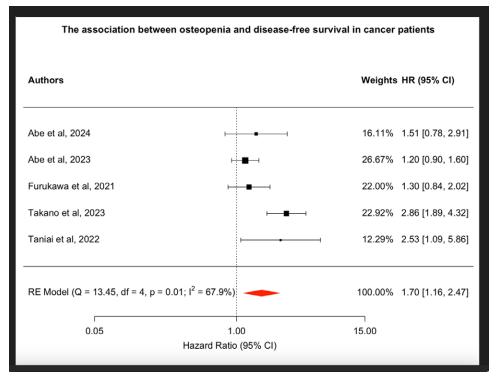


Figure 2. The association between osteopenia and disease-free survival in patients with cancer.

Q2: Selection of the nonexposed cohort.

Q3: Ascertainment of exposure.

Q4: Demonstration that outcome of interest was not present at the start of the study.

Q5: Comparability of cohorts on the basis of the design or analysis.

Q6: Assessment of outcome.

Q7: Was followed up long enough for outcomes to occur.

Q8: Adequacy of follow-up of cohorts.

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Abe et al (2024) ^{וות} ו	Hepato- cellular	102 (33/69)	Surgery	N R	R	Third lumbar vertebra (3) using transverse CT, cutoff values were 38 cm²/	BMD cutoff value: 160 HU	Concomitant occurrence of SP and OP	SP: 1.47 (20.64–1.99) 0P: 1.51 (20.78–2.90)	SP: 2.24 (20.93–4.98) OP: 1.94 (20.90–4.18)
Abe et al (2023) ^[18]	carcinoma Pancreatic cancer	75/190	75/190 Surgery	N	114/151	III- for women and 42 curyffir for fifeir Cutoff preoperative SMI value was defined as 47.1 and 36.6 for male	BMD cutoff: Men = 308.82- 2.49 × age; Wom-	Co-existence of SP and OP	USP: 2.44 (1.30-4.33) OP: 1.20 (20.90-1.60) OSP: 1.53 (1.11-2.10)	OSF: 3.23 (1.11-6.67) ADJ: 0.47 (20.31-0.71) OP: 1.98 (1.40-2.80)
Furukawa et al (2021) ^[14]	Colorectal with liver metastases	38/80	Surgery	0SP: 68 (61–75) Non-0SP:	N N	and female patients Psoas muscle areas at the third lumbar vertebra	en = 311.84–2.41 × age BMD cutoff: Men = 308.82– 2.49 × age; Wom- en = 311.84–2.41 × age	Concomitant occurrence of OP and SP	SP: 1.53 (20.98–2.39) 0P: 1.30 (20.83–2.01) 0SP: 1.42 (20.90–2.23)	OSP: 1.98 (1.40–2.80) ADJ: 1.77 (20.99–3.19) SP: 2.13 (1.14–4.00) OP: 1.81 (20.99–3.29)
Matsumoto et al	Ĭ	38/100	38/100 Surgery	(60–74) 71 (35–87)	44/94	Psoas muscle areas at the third lumbar vertebra	BMD cutoff: Men = 308.82–2.49 × age; Wom-	Coexistence of OP and SP	0SP: 3.36 (2.06-5.50)	ADJ: 0.82 (20.51–1.32) OSP: 3.82 (2.28–6.40)
(2023) ^[19] Takano et al (2023) ^[20]	cancer Cancer type	Population (OSP/non-OSP)	Treatment	Age of subjects (mean		Diagnostic criteria of sarcopenia	en = 311.84–2.41 × age Diagnostic criteria of osteopenia	Definition of osteo- sarcopenia	DFS/ HR (95% CI)	0S/ HR (95% CI)
Takeda et al Colorectal (2023) ^[21] cancer Takeda et al Biliary trac (2023) ^[22] cancer	Colorectal cancer Biliary tract cancer	84/241	Surgery + palli- ative chemo- therapy Surgery + palli- ative chemo-	age) (F/M) 76 (65–98) M:185 70 (64–76) 127/179		SMI below the cutoff value <43.75 cm²/m² for men and < 41.10 cm²/m² for women SMI < 42 cm²/m² for men and SMI < 38 11111444cm²/m²	BMD cutoff: Men = 308.82- 2.49 × age; Wom- en = 311.84-2.41 × age BMD < 135 HU	Coexistence of OP and SP, and penia-free was as neither of them Coexistence of OP and SP	SP: 2.63 (1.65–4.21) OP: 2.86 (1.90–4.33) OSP: 4.34 (2.66–7.08) OSP: 1.60 (1.18–2.17)	SP: 2.92 (1.66–5.13) OP: 2.08 (1.29–3.36) OSP: 2.79 (1.55–5.03) NR
Taniai et al (2022) ^[23]	Ĭ	59/254	S	N R	139/174	SMI $<$ 42 cm ² /m ² for men and SMI $<$ 38 cm ² /m ²	BMD < 135 HU	Coexistence of OP and SP	OSP: 1.81 (1.33–2.46)	N
Abe et al (2024)انتا	cancer Cholangiocar- cinoma/ resection	18/23	therapy Surgery	63 (55–68)	20/21	Psoas muscle areas at the third lumbar vertebra	BMD cutoff: Men = 308.82– 2.49 × age; Wom- en = 311.84–2.41 × age	Coexistence of OP and SP	SP: 2.73 (1.03–7.24) OP: 2.53 (1.09–5.84) OSP: 3.38 (1.49–7.68)	ADJ: 0.49 (20.20-1.22) SP: 4.90 (1.13-21.24) OP: 2.66 (20.96-7.41) OSP: 6.36 (1.72-23.58)

*ADJ = neoadjuvant chemotherapy, BMD = bone mass density, Cl = confidence interval, DFS = disease-free survival, HR = hazard ratio, OP = osteopenia, OS = overall survival, OSP = osteoparcopenia, SMI = skeletal mass index, SP = sarcopenia,

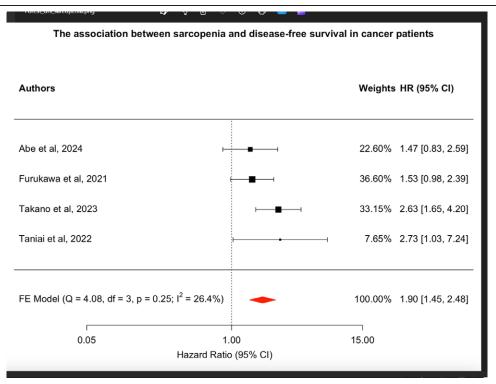


Figure 3. The association between sarcopenia and disease-free survival in patients with cancer.

The association between osteosarcopenia and disease-free survival in cancer patients

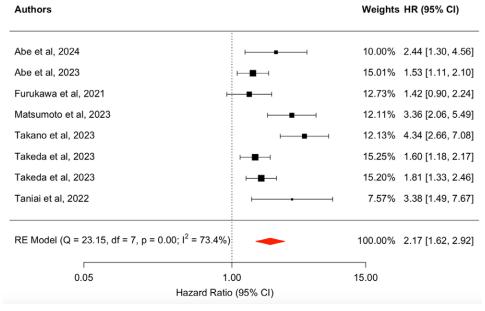
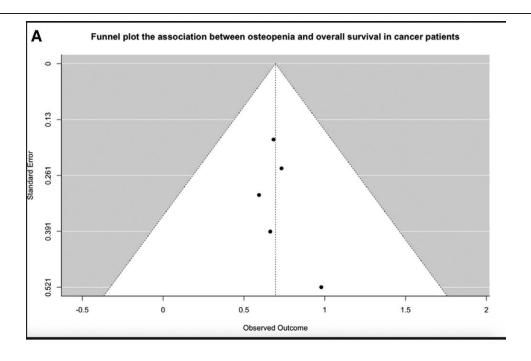


Figure 4. The association between osteosarcopenia and disease-free survival in patients with cancer.

However, our analysis did not find a significant association between sarcopenia and DFS in patients with cancer. This discrepancy may be attributed to various factors, including differences in study populations, diagnostic criteria for sarcopenia, and treatment modalities. Further research is warranted to elucidate the specific mechanisms underlying the relationship between sarcopenia and disease progression in patients with cancer. Furthermore, our analysis explored the impact of osteopenia, sarcopenia, and osteosarcopenia on OS in patients with cancer. While all 3 conditions were associated with an increased mortality risk, the associations did not reach statistical significance. These findings suggest that while musculoskeletal complications may contribute to overall mortality risk in patients with cancer, other factors such as disease stage, comorbidities, and treatment response may play a more significant role in determining their long-term survival.



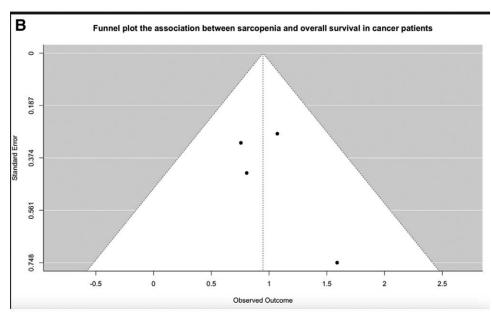


Figure 5. (A) Funnel plot of osteopenia and overall survival; (B) Funnel plot of sarcopenia and overall survival.

Advancements in diagnostic methodologies, such as biomarker profiles, can potentially enable earlier and more accurate osteosarcopenia diagnoses. Previous studies have explored insulin-like growth factor 1^[25] and parathyroid hormone^[26] as endocrine factors, as well as procollagen type 1 N-terminal propeptide^[27] and osteocalcin^[27,28] as bone metabolism markers. However, these studies primarily focused on biomarkers associated with osteoporosis. Inoue et al reported that elevated thyroid-stimulating hormone levels, bone-specific alkaline phosphatase levels, and estimated glomerular filtration rate increased the likelihood of osteosarcopenia. Conversely, elevated 25-hydroxyvitamin D, blood urea nitrogen, and potassium levels decreased the likelihood of osteosarcopenia.^[29] Implementing these advanced diagnostic tools in routine clinical practice could transform patient management by allowing for

earlier intervention and tailored treatment strategies, thus preventing osteosarcopenia progression and improving OS.

The potential for pharmacological interventions to manage osteosarcopenia is vast. The pharmacotherapy for osteoporosis is well established, with most current therapies targeting bone separately from muscle, including bisphosphonates, denosumab, and teriparatide. As osteoporosis and sarcopenia are closely associated, several new therapies are currently under development to target bone and muscle simultaneously, including selective androgen receptor modulators, such as andarine. [30] Another potential therapeutic target is irisin, [31,32] a hormone-like myokine abundantly produced by skeletal muscle cells in response to exercise. New anti-myostatin antibodies have shown promise in experimental studies, [33] although successful clinical trials are still pending. In the ROMANA studies, the novel non-peptide

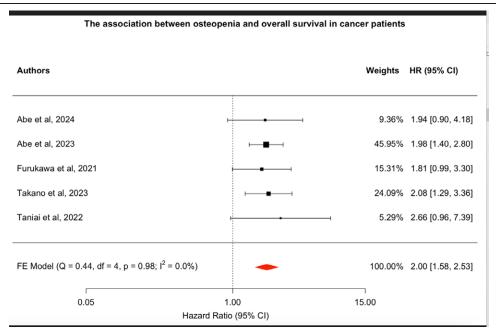


Figure 6. The association between osteopenia and overall survival in patients with cancer.

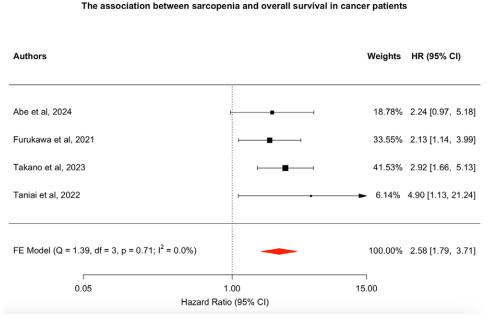


Figure 7. The association between sarcopenia and overall survival in patients with cancer.

ghrelin analog anamorelin caused a significant increase in lean body mass compared to placebo in patients with non-small-cell lung cancer. Clinical trials exploring these drugs in the oncology patient population could provide groundbreaking treatment solutions that address the multifaceted challenges of osteosarcopenia in cancer care.

The benefits of exercise in older patients are evident, including increased bone density, preservation of muscle structure and function, improved balance to prevent falls, and decreased fracture risks. [34-38] A meta-analysis of randomized controlled trials revealed that well-designed, guided, and supervised aerobic, strength, or combined training programs could positively impact patients with advanced-stage cancer. Participation in

these programs increased muscle mass and improved fatigue, dyspnea, quality of life, autonomy, and sleep quality and duration.^[39]

In cancer, loss of muscle mass most commonly occurs within the context of cancer cachexia syndrome, characterized by the involuntary loss of skeletal muscle mass, often accompanied by adipose tissue wasting.^[40] Excessive muscle loss is associated with poor prognosis. Cancer-associated sarcopenia differs from age-related wasting in that it might not be responsive to nutritional intervention and exercise. This difference is attributed to its unique pathogenesis, which involves diverse and interconnected mechanisms such as inflammation, disordered metabolism, proteolysis, and autophagy.^[41] Investigating the molecular

Authors Weights HR (95% CI) Abe et al. 2024 6.82% 3.23 [1.32, 7.92] Abe et al. 2023 45.62% 1.98 [1.40, 2.80] Furukawa et al, 2021 7.97% 3.17 [1.38, 7.27] Matsumoto et al, 2023 20.58% 3.82 [2.28, 6.40] Takano et al, 2023 15.82% 2.79 [1.55, 5.03] Taniai et al. 2022 3.20% 6.36 [1.72, 23.55] FE Model (Q = 6.76, df = 5, p = 0.24; I^2 = 26.0%) 100.00% 2.67 [2.11, 3.37] 0.05 1.00 15.00 Hazard Ratio (95% CI)

Meta-analysis of the association between osteosarcopenia and overall survival in cancer patients

Figure 8. The association between osteosarcopenia and overall survival in patients with cancer.

pathways involved in inflammation-mediated muscle and bone loss in patients with cancer could uncover new therapeutic targets.

The presence of osteosarcopenia in patients with cancer demands a multidimensional strategy that incorporates clinical, systemic, and policy-level responses. Clinically, it is imperative to implement routine screenings for osteosarcopenia in cancer care protocols to ensure its early detection and management. From a systemic viewpoint, healthcare providers must be equipped with the necessary tools and knowledge to address this complex condition effectively. On a policy level, adjustments in health insurance frameworks to cover preventive and therapeutic measures for osteosarcopenia are crucial to facilitate comprehensive care delivery. Such efforts are vital to encourage early detection and proactive management, which can significantly mitigate the impacts of this condition on cancer survival. Finally, the complexity of osteosarcopenia intertwined with cancer suggests a rich area for future research. Studies aimed at unraveling the molecular mechanisms linking muscle and bone degradation to cancer progression are particularly needed. Additionally, clinical trials investigating the efficacy of emerging drugs targeting both sarcopenia and osteopenia could offer new hope for interventions that extend the life and improve the quality of life of patients with cancer.

However, it is essential to acknowledge the limitations of this meta-analysis, including potential heterogeneity among the included studies, variations in the diagnostic criteria for osteopenia and sarcopenia, and the retrospective nature of some studies. Future research should address these limitations through prospective, well-designed studies with standardized methodologies.

5. Conclusions

In conclusion, this meta-analysis highlights the prognostic significance of osteopenia and osteosarcopenia in patients with cancer, particularly regarding DFS. While sarcopenia was in our analysis, further research is warranted to elucidate its role in cancer progression. These findings underscore the importance of comprehensive musculoskeletal assessment and management in the care of patients with cancer, aiming to optimize treatment outcomes and OS.

Author contributions

Conceptualization: Chien-Chieh Wang, Hsuan-Chih Liu.

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