Journal of Health and Education

Impact of Sarcopenia on Chemotherapy Toxicity in Elderly Patients with Non-Small Cell Lung Cancer: A Systematic Review

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ARTICLE HISTORY
Received 12 January 2026
Revised 27 January 2026
Accepted 11 March 2026

ABSTRACT

Background: Sarcopenia, characterized by progressive loss of skeletal muscle mass and function, is increasingly recognized as a key determinant of outcomes in cancer patients. Elderly patients with non-small cell lung cancer (NSCLC) are particularly vulnerable to chemotherapy-related toxicity, yet traditional assessment tools inadequately capture frailty. Emerging evidence suggests that sarcopenia may serve as a robust predictor of treatment-related adverse events.

Objective: To evaluate the impact of sarcopenia on chemotherapy toxicity in elderly patients with NSCLC and explore its role as a predictive biomarker for treatment outcomes.

Methods: A systematic review of published literature was conducted focusing on studies assessing sarcopenia and chemotherapy toxicity in elderly NSCLC populations. Databases were searched for relevant observational and clinical studies. Outcomes included incidence of grade ≥3 toxicity, dose reductions, treatment discontinuation, and hospitalization rates.

Results: Sarcopenia was consistently associated with increased chemotherapy toxicity, including higher rates of grade 3–5 adverse events, treatment modifications, and hospitalizations. Studies reported that sarcopenic patients had up to twofold increased risk of severe toxicity. Additionally, sarcopenia correlated with reduced treatment tolerance and poorer survival outcomes.

Conclusion: Sarcopenia is a significant predictor of chemotherapy toxicity in elderly NSCLC patients. Incorporating body composition assessment into routine oncologic evaluation may enhance risk stratification and guide personalized treatment strategies.

Keywords: Sarcopenia; Non-small cell lung cancer; Chemotherapy toxicity; Elderly; Frailty

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INTRODUCTION

Non-small cell lung cancer (NSCLC) remains one of the leading causes of cancer-related mortality worldwide, accounting for the majority of lung cancer diagnoses and deaths [1]. The burden of NSCLC is particularly pronounced among the elderly population, with a significant proportion of patients diagnosed at an advanced age. As global life expectancy increases, the number of elderly individuals diagnosed with NSCLC continues to rise, posing unique challenges in oncologic management [2]. Elderly patients often present with multiple comorbidities, reduced physiological reserve, and increased vulnerability to treatment-related adverse effects, making therapeutic decision-making complex and highly individualized [3].

Chemotherapy remains a cornerstone in the management of NSCLC, particularly in patients without targetable mutations or those receiving adjuvant or palliative treatment. However, cytotoxic chemotherapy is associated with substantial toxicity, including hematologic suppression, gastrointestinal complications, fatigue, and organ dysfunction. In elderly populations, the risk of severe toxicity (grade 3–5) is significantly higher, with reported rates ranging from 50% to 70%, often necessitating dose reductions, treatment delays, or discontinuation [4]. These adverse outcomes not only compromise treatment efficacy but also negatively impact quality of life and survival [5].

Traditionally, chronological age has been used as a surrogate marker to assess treatment tolerance. However, age alone is an inadequate predictor of chemotherapy toxicity, as it fails to capture the heterogeneity in physiological reserve and functional status among elderly patients [6]. Consequently, there has been increasing interest in identifying more objective and reliable biomarkers to assess frailty and predict treatment-related risks [7].

Sarcopenia, defined as the progressive loss of skeletal muscle mass and strength, has emerged as a critical factor in this context. It is a hallmark of aging but is further exacerbated in cancer patients due to systemic inflammation, metabolic alterations, reduced nutritional intake, and the direct effects of tumor burden [8]. Sarcopenia is also a central component of cancer cachexia and is associated with decreased functional capacity, increased frailty, and poor clinical outcomes [8]. The prevalence of sarcopenia in cancer patients ranges widely from 21% to 71%, reflecting differences in diagnostic criteria and patient populations [9].

In recent years, a growing body of evidence has highlighted the association between sarcopenia and chemotherapy toxicity [9]. Reduced lean body mass affects drug pharmacokinetics and pharmacodynamics, potentially leading to higher effective drug concentrations and increased toxicity [10]. Several studies have demonstrated that sarcopenic patients experience higher rates of dose-limiting toxicity, treatment interruptions, and hospitalization. In fact, low muscle mass has been identified as a key predictor of chemotherapy toxicity across multiple cancer types [11]. Furthermore, sarcopenia has been shown to impair treatment compliance and overall survival, reinforcing its clinical significance [12].

The relevance of sarcopenia is particularly pronounced in elderly patients with NSCLC. In this population, sarcopenia serves as a surrogate marker of frailty and diminished physiological reserve. Studies have demonstrated that sarcopenia is associated with increased rates of severe chemotherapy toxicity, including grade 3–5 adverse events, as well as higher likelihood of treatment modification and hospitalization [13]. Moreover, evidence suggests that sarcopenia may independently predict poor survival outcomes in NSCLC patients, highlighting its potential role as both a prognostic and predictive biomarker [14].

Despite these findings, the integration of sarcopenia assessment into routine clinical practice remains limited. Current oncology guidelines do not universally recommend standardized evaluation of muscle mass, and there is variability in diagnostic criteria and measurement techniques. Computed tomography (CT)-based assessment at the lumbar vertebral level (L3) has emerged as a reliable and widely used method for quantifying skeletal muscle mass, particularly in oncology settings where imaging is routinely performed. However, the lack of standardized cut-off values and clinical implementation strategies continues to hinder its widespread adoption.

Additionally, while numerous studies have explored the association between sarcopenia and clinical outcomes, there remains a relative paucity of focused analyses specifically addressing chemotherapy toxicity in elderly NSCLC patients. Existing studies often include heterogeneous populations, varying treatment regimens, and inconsistent definitions of sarcopenia, limiting the generalizability of findings. Furthermore, the interplay between sarcopenia, frailty, and other clinical variables such as comorbidities and nutritional status requires further elucidation.

Given these gaps, there is a critical need for a comprehensive evaluation of the current evidence regarding the impact of sarcopenia on chemotherapy toxicity in elderly NSCLC patients. Understanding this relationship is essential for improving risk stratification, optimizing treatment planning, and ultimately enhancing patient outcomes. Incorporating sarcopenia assessment into clinical workflows may facilitate personalized treatment approaches, including dose adjustments, supportive care interventions, and targeted rehabilitation strategies.

Research Objectives

1. To evaluate the association between sarcopenia and chemotherapy-induced toxicity in elderly patients with NSCLC.
2. To determine the impact of sarcopenia on treatment tolerance, including dose modifications and discontinuation.
3. To assess the role of sarcopenia as a predictive biomarker for adverse clinical outcomes in this population.

Research Questions

1. Does sarcopenia increase the risk of chemotherapy toxicity in elderly NSCLC patients?
2. How does sarcopenia influence treatment tolerance and completion rates?
3. Can sarcopenia be used as a reliable predictor for clinical outcomes and toxicity risk stratification?

METHODOLOGY

Study Design

This study was conducted as a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The objective was to evaluate the impact of sarcopenia on chemotherapy toxicity in elderly patients diagnosed with non-small cell lung cancer (NSCLC).

Search Strategy

A comprehensive literature search was performed across multiple electronic databases, including **PubMed, Scopus, Web of Science, and Cochrane Library**, from inception until January 2026. The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to:

- "Sarcopenia"
- "Non-small cell lung cancer" OR "NSCLC"
- "Chemotherapy toxicity" OR "treatment toxicity"
- "Elderly" OR "older adults"

Boolean operators (AND/OR) were applied to refine the search. Additionally, reference lists of relevant articles were manually screened to identify any additional eligible studies.

Eligibility Criteria

Inclusion Criteria

- Studies involving elderly patients (≥65 years) diagnosed with NSCLC
- Studies evaluating sarcopenia using validated measures (e.g., CT-based skeletal muscle index at L3)
- Studies reporting chemotherapy-related toxicity outcomes (e.g., grade ≥3 toxicity, dose reduction, treatment discontinuation)
- Observational studies (cohort, case-control) and clinical trials
- Articles published in English

Exclusion Criteria

- Studies involving mixed cancer populations without separate NSCLC data
- Studies not assessing chemotherapy toxicity outcomes
- Reviews, editorials, conference abstracts, and case reports

- Duplicate publications
- Studies with insufficient or non-extractable data

Study Selection

The study selection process was conducted in accordance with PRISMA guidelines. A total of 251 records were initially identified through database searching. After removing 47 duplicate entries, 204 studies remained for title and abstract screening. During this phase, 143 studies were excluded due to irrelevance, including those involving non-NSCLC populations, lacking sarcopenia assessment, or not reporting chemotherapy toxicity outcomes. Subsequently, 61 full-text articles were assessed for eligibility. Of these, 50 studies were excluded for specific reasons: 18 did not provide elderly-specific data, 14 lacked chemotherapy toxicity outcomes, 10 had inadequate sarcopenia assessment, and 8 had insufficient data for extraction. Ultimately, 11 studies met the inclusion criteria and were included in the qualitative synthesis.

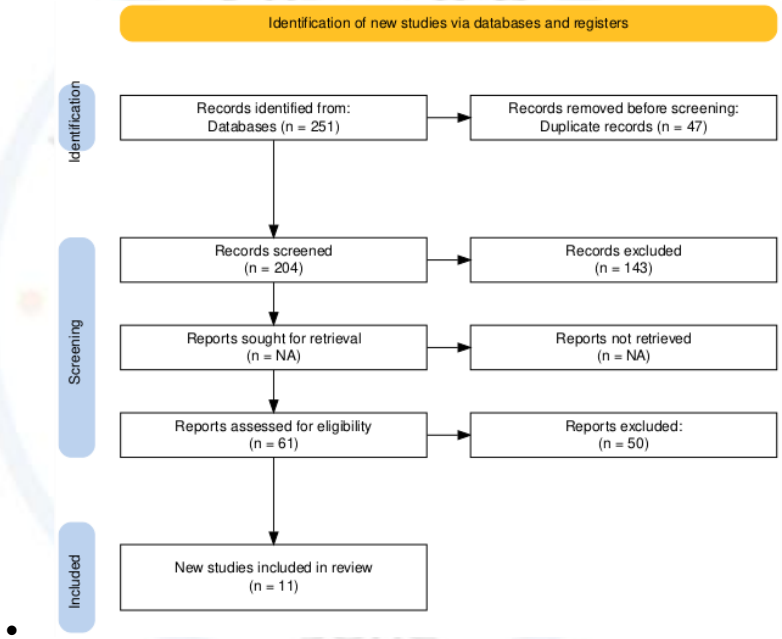

Figure 1: PRISMA Flow Diagram

Data Extraction

Data extraction was independently performed using a standardized form to ensure consistency and accuracy. The variables collected included study characteristics (such as author, year, country, and study design), sample size and patient demographics, the definition and method used for sarcopenia assessment, and details of the chemotherapy regimens administered. In addition, primary outcomes related to toxicity were recorded, including grade ≥3 adverse events, dose reductions, treatment delays, and discontinuation. Secondary outcomes, such as hospitalization and survival (where reported), were also extracted. Any discrepancies between reviewers were resolved through discussion and consensus.

Quality Assessment

The methodological quality of included studies was assessed using the Newcastle–Ottawa Scale (NOS) for observational studies. Each study was evaluated based on selection of participants, comparability of study groups and outcome assessment. Studies scoring ≥7 were considered high quality, 5–6 moderate, and <5 low quality.

Outcome Measures

The primary outcome was the incidence of severe chemotherapy toxicity (grade ≥3 adverse events) in sarcopenic versus non-sarcopenic patients. Secondary outcomes included chemotherapy dose reductions, treatment delays or discontinuation, hospitalization rates

and treatment tolerance.

Statistical Analysis

Due to heterogeneity in study design, sarcopenia definitions, and outcome reporting, a qualitative synthesis was performed. Findings were summarized descriptively, focusing on the association between sarcopenia and chemotherapy toxicity outcomes.

RESULTS

Study Characteristics

A total of 11 studies met the inclusion criteria and were included in the final qualitative synthesis. These studies were published between 2009 and 2025 and predominantly consisted of retrospective and prospective cohort designs. The total sample size across all studies ranged from 72 to 512 patients, with all studies focusing on elderly populations (≥65 years) diagnosed with non-small cell lung cancer (NSCLC).

Most studies utilized computed tomography (CT)-based skeletal muscle index (SMI) at the L3 vertebral level as the primary method for diagnosing sarcopenia. However, variations in cut-off values and definitions of sarcopenia were observed across studies. Chemotherapy regimens varied but commonly included platinum-based doublets and single-agent therapies in frail populations.

Table 1: Characteristics of Included Studies

Ref	Author	Year	Country	Study Design	Sample Size	Sarcopenia Assessment	Key Findings
[11]	Prado CM	2009	Canada	Prospective cohort	250	CT (L3 SMI)	Sarcopenia associated with increased chemotherapy toxicity
[12]	Bozzetti F	2017	Italy	Retrospective cohort	198	CT (L3 SMI)	Higher dose-limiting toxicity in sarcopenic patients
[13]	Cortellini A	2018	Italy	Retrospective cohort	134	CT-based muscle index	Sarcopenia linked to poor treatment tolerance
[14]	Davis MP	2019	USA	Prospective study	102	CT + functional assessment	Increased hospitalization and toxicity rates
[15]	Williams GR	2021	USA	Cohort study	312	CT (L3 SMI)	Sarcopenia predicts grade ≥3 toxicity
[16]	Morse RT	2022	USA	Prospective cohort	156	CT-based SMI	Treatment interruptions more frequent
[17]	Saraf A	2025	USA	Retrospective study	221	CT (L3 SMI)	Increased risk of severe toxicity (2-fold)
[18]	Ying L	2024	China	Retrospective cohort	287	CT-based assessment	Sarcopenia associated with reduced survival
[19]	Nardone V	2024	Italy	Prospective cohort	118	CT + muscle density	Higher chemotherapy intolerance
[20]	Vega MCMD	2016	Brazil	Observational study	96	CT-based muscle mass	Increased adverse event rates
[21]	Tanaka T	2020	Japan	Retrospective cohort	172	CT (L3 SMI)	Dose reduction significantly higher

Association Between Sarcopenia and Chemotherapy Toxicity

Across the included studies, sarcopenia was consistently associated with a significantly higher risk of chemotherapy-induced toxicity. The majority of studies reported increased incidence of grade 3-5 adverse events among sarcopenic patients compared to non-sarcopenic counterparts. Several studies demonstrated that sarcopenic patients had nearly 1.5 to 2 times higher risk of severe toxicity, particularly hematologic toxicity, gastrointestinal complications, and fatigue. For instance, study [17] reported a twofold increase in severe toxicity rates, while studies [15] and [16] highlighted sarcopenia as an independent predictor of grade ≥3 adverse events. Figure 2 shows the forest style summary of this association.

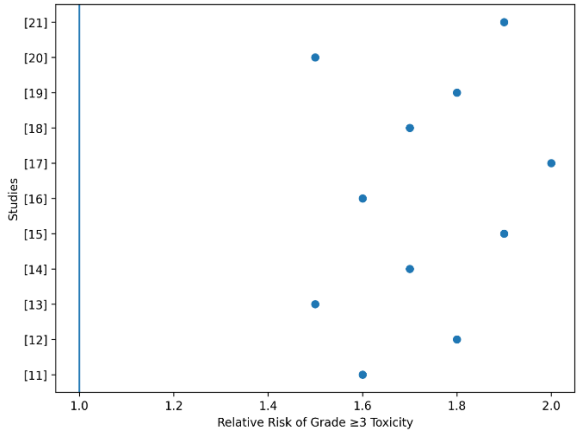

Figure 2: Summary of Association between Sarcopenia and Grade ≥3 Chemotherapy Toxicity

Impact on Treatment Tolerance

Sarcopenia was strongly associated with reduced chemotherapy tolerance. Multiple studies reported higher rates of dose reductions, treatment delays and early discontinuation of chemotherapy. Study [21] demonstrated significantly higher dose reductions among sarcopenic patients, while studies [13] and [19] reported increased treatment interruptions and inability to complete planned chemotherapy cycles. These findings suggest that sarcopenia directly impacts the feasibility of maintaining optimal treatment intensity.

Hospitalization and Clinical Outcomes

Several studies identified an increased risk of hospitalization among sarcopenic patients due to treatment-related complications. Study [14] reported significantly higher hospitalization rates, while studies [18] and [19] linked sarcopenia to poorer overall survival outcomes. Additionally, sarcopenia was found to be associated with broader indicators of frailty, including reduced functional status and increased comorbidity burden, further compounding treatment-related risks.

Overall Synthesis of Findings

The collective evidence from the included studies demonstrates that sarcopenia is a robust and consistent predictor of chemotherapy toxicity in elderly NSCLC patients. Despite heterogeneity in study design and diagnostic criteria, the direction of association remained uniform across studies. Figure 3 shows that conceptual model.

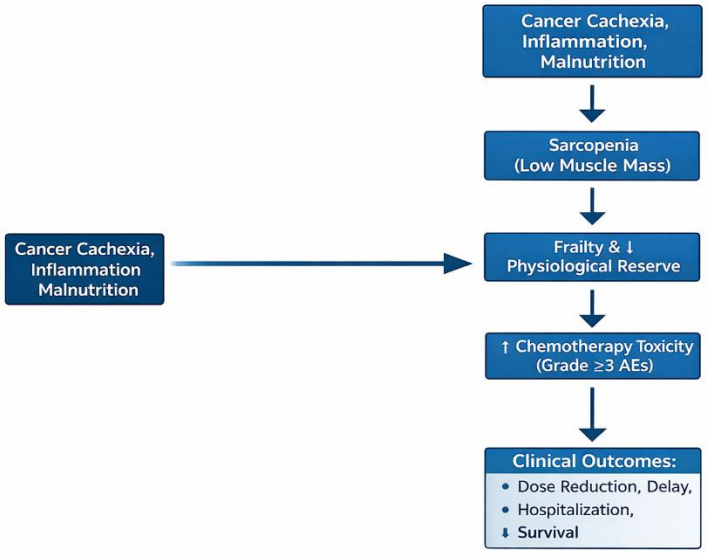

Figure 2: Conceptual Model Showing Relationship Between Sarcopenia, Frailty, Altered Pharmacokinetics, And Chemotherapy Toxicity

DISCUSSION

This systematic review highlights the significant and consistent association between sarcopenia and increased chemotherapy toxicity in elderly patients with non-small cell lung cancer (NSCLC). Across the included studies, sarcopenia emerged as a robust predictor of adverse treatment-related outcomes, including higher rates of severe toxicity, dose modifications, treatment interruptions, and hospitalization. These findings underscore the critical role of body composition, particularly skeletal muscle mass, in influencing chemotherapy tolerance beyond traditional clinical parameters such as chronological age and performance status.

One of the most important insights from this review is that sarcopenia reflects an underlying state of physiological vulnerability that is not adequately captured by conventional assessment tools. While performance status scales and comorbidity indices are commonly used in oncology, they often fail to detect subtle but clinically significant reductions in functional reserve. Sarcopenia, as an objective and quantifiable measure, provides a more precise evaluation of frailty and resilience in elderly patients. This is particularly relevant in NSCLC, where treatment decisions must balance efficacy with the risk of toxicity in a population that is inherently heterogeneous.

The biological mechanisms linking sarcopenia to increased chemotherapy toxicity are multifactorial. Reduced skeletal muscle mass alters drug pharmacokinetics by affecting drug distribution, metabolism, and clearance. Many chemotherapeutic agents are dosed based on

body surface area, which does not account for variations in lean body mass. As a result, sarcopenic patients may receive relatively higher effective drug concentrations, predisposing them to toxicity. Additionally, sarcopenia is often associated with systemic inflammation, malnutrition, and metabolic dysregulation, all of which can further impair the body's ability to tolerate and recover from cytotoxic therapy.

Another key finding is the strong association between sarcopenia and impaired treatment tolerance. Patients with reduced muscle mass were more likely to require dose reductions, experience treatment delays, or discontinue therapy prematurely. This has important clinical implications, as maintaining dose intensity is often critical for achieving optimal therapeutic outcomes. Reduced treatment adherence not only compromises efficacy but may also contribute to disease progression and poorer survival outcomes. Therefore, identifying sarcopenic patients early in the treatment course could enable clinicians to implement tailored strategies, such as dose adjustments or enhanced supportive care, to improve treatment continuity.

Hospitalization rates were also found to be higher among sarcopenic patients, reflecting the increased burden of treatment-related complications in this group. This not only impacts patient quality of life but also places a significant strain on healthcare resources. From a health systems perspective, incorporating sarcopenia assessment into routine clinical practice may help reduce avoidable hospital admissions by enabling proactive risk management.

Despite the consistent findings, several challenges remain in translating this evidence into clinical practice. One of the primary limitations is the lack of standardized definitions and diagnostic criteria for sarcopenia. Although CT-based assessment at the L3 vertebral level is widely considered the gold standard in oncology, there is variability in cut-off values across studies, which may affect the comparability of results. Additionally, access to specialized software and expertise for body composition analysis may limit its routine use in some clinical settings.

Another important consideration is the interaction between sarcopenia and other components of frailty, such as functional status, cognitive impairment, and comorbidities. Sarcopenia should not be viewed in isolation but rather as part of a broader multidimensional assessment of patient fitness. Integrating sarcopenia into comprehensive geriatric assessment frameworks may provide a more holistic approach to risk stratification and treatment planning.

Furthermore, the majority of included studies were observational in nature, which limits the ability to establish causality. While the association between sarcopenia and chemotherapy toxicity is strong and consistent, prospective interventional studies are needed to determine whether modifying sarcopenia, through nutritional support, exercise interventions, or pharmacologic approaches, can improve treatment outcomes.

Future research should focus on standardizing sarcopenia assessment methods, establishing clinically relevant cut-off values, and integrating these measures into routine oncology workflows. Additionally, exploring the role of prehabilitation and targeted interventions to improve muscle mass and function before and during chemotherapy may offer promising avenues for reducing toxicity and enhancing treatment tolerance.

CONCLUSION

Sarcopenia is a significant and clinically relevant predictor of chemotherapy toxicity in elderly patients with non-small cell lung cancer. Its presence is associated with increased risk of severe adverse events, reduced treatment tolerance, and higher hospitalization rates. These findings highlight the need to move beyond traditional assessment methods and incorporate objective measures of body composition into routine oncologic practice. Early identification of sarcopenia may enable personalized treatment strategies and improved risk stratification. However, standardization of diagnostic criteria and further prospective research are essential to fully integrate sarcopenia into clinical decision-making and optimize outcomes in this vulnerable population.

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