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Original Article

Predictive value of morphological, functional, and nutritional markers in elderly patients with advanced squamous cell lung cancer receiving gemcitabine plus carboplatin: A multidimensional "triple-risk" approach

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Abstract

Aim: The management of elderly patients with advanced squamous cell lung cancer (SqCLC) necessitates a nuanced understanding of biological rather than chronological age. While platinum-based doublets remain a therapeutic component, the primary clinical challenge is maintaining treatment continuity. This study investigates the impact of a multidimensional "Triple-Risk Score"—incorporating Psoas Muscle Index (PMI), Clinical Frailty Scale (CFS), and Prognostic Nutritional Index (PNI)—on chemotherapy tolerability and treatment adherence.
Materials and Methods: Data from 43 male patients (≥ 65 years) with stage IIIB-IV SqCLC treated with first-line gemcitabine plus carboplatin were analyzed. A "Triple-Risk Score" (0–3) was derived from morphological (low PMI), functional (high CFS), and nutritional (low PNI) vulnerabilities. The primary endpoint was treatment continuity, defined by the number of completed chemotherapy cycles.
Results: Median overall survival was 16.6 months. A total of 164 cycles were administered (mean 3.8 ± 1.2 per patient). Dose modifications were required in 32.6% of cases. Multivariate analysis confirmed frailty (HR: 4.94, 95% CI: 1.72–14.15, p=0.003) and sarcopenia (HR: 3.61, 95% CI: 1.01–12.88, p=0.048) as independent predictors of mortality. While individual markers and the Triple-Risk Score did not significantly correlate with acute Grade 3–4 toxicities (p > 0.05), the score was a potent predictor of treatment attrition. Patients with a score of 3 completed significantly fewer cycles (mean 2.20 ± 0.8) compared to those with a score of 0 (mean 4.06 ± 1.1, p=0.038).
Conclusion: In elderly SqCLC, treatment failure is driven more by cumulative physiological exhaustion than isolated acute toxicity. Integrating PNI with morphological and functional assessments provides superior granularity in identifying patients at risk for premature treatment discontinuation. These findings advocate for a paradigm shift toward pre-therapeutic multidimensional optimization and proactive dose modification to safeguard treatment continuity.

Keywords: Squamous cell lung cancer, sarcopenia, gemcitabin, carboplatin, tolerability

INTRODUCTION

The therapeutic landscape for elderly patients with advanced squamous cell lung cancer (SqCLC) is characterized by physiological heterogeneity, where traditional performance scales like Eastern Cooperative Oncology Group (ECOG) often fail to predict chemotherapy tolerance (1). While the current standard of care for advanced SqCLC typically involves immunotherapy (e.g., pembrolizumab) combined with platinum-doublet chemotherapy, or immunotherapy monotherapy for patients with high PD-L1 expression (≥50%), many elderly

patients continue to receive chemotherapy-only regimens due to comorbidities, specific contraindications, or resource constraints (2). Current guidelines, including those from American Society of Clinical Oncology (ASCO), emphasize the importance of geriatric assessment in predicting chemotherapy toxicity and identifying vulnerabilities (3,4).

In this demographic, the primary clinical challenge is maintaining dose intensity and treatment continuity. Emerging evidence suggests that the synergy between sarcopenia, frailty, and malnutrition creates a "vulnerability triad (5,6)". While the prognostic value of the psoas muscle index (PMI) was established in a previous analysis of this cohort (1), the current study uniquely validates a "Triple-Risk" model as a decision-making tool. By integrating the Prognostic Nutritional Index (PNI), we aim to provide a higher level of predictive granularity for treatment attrition than previously achieved, identifying candidates for pre-treatment optimization or proactive dose modification.

MATERIALS AND METHODS

Study Setting and Population: This retrospective cohort study analyzed 43 elderly male patients (age ≥ 65) with stage IIIB-IV SqCLC treated at the oncology clinics of Bursa City Hospital and Ali Osman Sönmez Oncology Hospital. The study protocol was approved by the Clinical Research Ethics Committee of Bursa City Hospital Ref. No: 2022-18/4, Date: 21.12.2022) and conducted in accordance with the Declaration of Helsinki. Due to the retrospective nature of the research, the requirement for informed consent was waived by the ethics committee.

Patients were excluded if they had incomplete radiological data at baseline or received non-platinum-based first-line therapy.

Treatment Protocol: All patients received gemcitabine (1000 mg/m² on days 1 and 8) plus carboplatin (AUC 4-5) every 21 days. The target was the completion of at least 4 to 6 cycles, depending on clinical response and tolerability. Stage III patients were evaluated in terms of radiotherapy suitability after 3 cycles, and if appropriate, chemotherapy treatment was changed and radiotherapy was started. Antiemetic treatment was given with moderate doses of corticosteroids and 5-HT antagonists in each cycle.

Primary Outcome: The primary endpoint was treatment continuity, defined as the total number of chemotherapy cycles successfully administered before permanent discontinuation due to any cause other than disease progression. All patients receiving at least one dose of study drug were added in the toxicity analysis, which was graded according to the National Cancer Institute Common Toxicity Criteria version 6. Blood counts was assessed on days 1 and 8 of each cycle. Whether the patients used gcsf, their hospitalization, and the reasons for hospitalization were also recorded.

Statistical Analysis: Statistical analyses were performed using IBM SPSS Statistics (v26.0). Continuous variables are reported as mean ± standard deviation. Group comparisons for chemotherapy cycles across Triple-Risk categories were conducted using the Kruskal-Wallis test, followed by post-hoc Mann-Whitney U tests with Bonferroni correction for multiple comparisons. Survival associations (associations, not causality) were analyzed using Cox proportional hazards models, reporting Hazard Ratios (HR) with 95% Confidence Intervals (CI). A p-value < 0.05 was considered statistically significant.

Methodological Integrity and Self-Reference: Skeletal muscle mass assessment was performed via Computed Tomography at the L3 level to calculate the PMI (7,8). The morphological and survival characteristics of this specific patient cohort were previously described in an independent analysis focusing on sarcopenia-related mortality. The current study extends this work by uniquely integrating these parameters with the PNI to evaluate treatment tolerability.

The Triple-Risk Framework:

1. **Morphological (PMI):** Sarcopenia was defined using psoas muscle area (< 540 mm^2/m^2 for males) (7,8).
2. **Functional (CFS):** Frailty was assessed via the Clinical Frailty Scale; scores ≥5 were categorized as fragile (9).
3. **Nutritional (PNI):** Calculated as 10 * albumin (g/dL) + 0.005 * lymphocyte count (mm^3). A threshold of < 45 indicated nutritional risk (10,11).

RESULTS

Cohort Characteristics and Geriatric Profile

The study included 43 elderly male patients with a median age of 72 years (range, 65–79). At the time of diagnosis, 60.5% (n=26) presented with Stage IV disease, while 39.5% (n=17) had Stage IIIB SqCLC. Baseline comorbidities were prevalent; hypertension (51.2%) and COPD (30.2%) were the most frequent conditions, and polypharmacy (≥5 medications) was observed in 27.9% of the cohort. The detailed demographic and geriatric characteristics are summarized in Table 1.

Efficacy and Survival Outcomes

The median overall survival (OS) for the entire cohort was 16.6 months (95% CI: 8.8–24.4). The objective response rate was 55.8%, consisting of complete responses in 9.3% and partial responses in 46.5%. Multivariate Cox regression analysis identified advanced stage (HR: 5.80, p=0.005), frailty (HR: 4.94, p=0.003), and sarcopenia (HR: 3.61, p=0.048) as independent predictors of mortality.

Treatment Exposure and Continuity

A total of 164 treatment cycles were administered, with a median of 3 cycles per patient (range, 1–9). Eleven patients (25.6%) successfully completed six cycles of therapy. Among patients with stage IIIB disease, 9 transitioned to concurrent chemoradiotherapy regimens following initial chemotherapy cycles. Dose modifications were required for 14 patients (32.6%). While primary prophylaxis with G-CSF was not utilized, 14 patients (32.6%) required secondary G-CSF support at least once due to neutropenia.

Toxicity Profile and Predictive Analysis

Hematologic toxicity occurred in 37 patients (86%), though only 8 (18.6%) experienced Grade 3 or higher toxicity (Table 2). Of these high-grade cases, 5 were chemotherapy-related and 3 were associated with a history of radiotherapy. These toxicities did not lead to increased rates of febrile neutropenia, infection, or bleeding. Non-hematologic complications included two hospitalizations for pneumonia/neutropenia and one COVID-19-related death.

Treatment discontinuation due to adverse events occurred in 5 patients (11.6%), primarily driven by non-hematologic toxicities. Logistic regression analysis revealed no significant association between individual markers (PMI, CFS, PNI) and the occurrence of Grade 3-4 acute toxicities ($p > 0.05$), suggesting that these parameters influence outcomes through cumulative physiological attrition rather than acute events.

Impact of the Triple-Risk Score on Treatment Continuity

The primary finding was the significant correlation between the Triple-Risk Score and chemotherapy cycle completion. The mean number of completed cycles for the cohort was 3.8 ± 1.2. As shown in Figure 1, an increase in the Triple-Risk Score was associated with a significant decline in treatment continuity. "Low Risk" patients (Score 0) completed a mean of 4.06 cycles. In contrast, "Very High Risk" patients (Score 3)—with concurrent sarcopenia, frailty, and nutritional deficiency—tolerated a mean of only 2.20 cycles (p=0.038). This relationship between multidimensional risk and cycle completion is further detailed in Table 3, emphasizing that the convergence of these vulnerabilities is the primary driver of premature treatment attrition.

Table 1. Baseline clinical and geriatric characteristics of the study population (n=43)

Characteristic	Value
Age, median (range)	72.0 (65−79)
Gender, Male, n (%)	43 (100%)
Stage, n (%)	
Stage IIIB	17 (39.5%)
Stage IV	26 (60.5%)
Comorbidities, n (%)	
Hypertension	22 (51.2%)
COPD	13 (30.2%)
Coronary artery disease	5 (11.6%)
Polypharmacy (≥5 drugs)	12 (27.9%)
Geriatric parameters , n (%)	
Sarcopenia (Low PMI)	19 (44.2%)
Frailty (CFS ≥5)	21 (48.8%)
Low nutritional status (PNI <45)	7 (16.3%)

PMI: psoas muscle index, CFS: clinical frailty scale, PNI: prognostic nutritional ındex

Table 2. Treatment outcomes and hematologic toxicities

Outcome/toxicity	Total population (n=43)
Treatment response, n (%)	
Complete response (CR)	4 (9.3%)
Partial response (PR)	20 (46.5%)
Stable/progressive disease	19 (44.2%)
Toxicity (grade 3-4), n (%)	
Overall grade 3-4 hematologic	8 (18.6%)
Grade 3-4 neutropenia	6 (14.0%)
Grade 3-4 anemia/thrombocytopenia	2 (4.6%)
Dose modification required	14 (32.6%)
Mean chemotherapy cycles	3.8 (SD ± 1.2)

Table 3. Analysis of the "triple-risk" score on treatment continuity

Triple-risk score*	Patients (n)	Mean cycles completed	p-value
0 (Low risk)	17	4.06	
1 (Moderate risk)	10	4.50	
2 (High risk)	11	3.55	
3 (Very high risk)	5	2.20	0.038

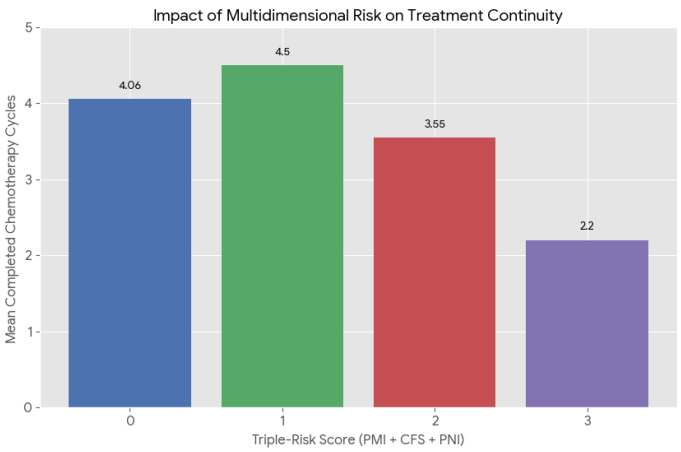

Figure 1. Impact of multidimensional risk on treatment continuity

DISCUSSION

The optimal therapeutic strategy for elderly patients with advanced SqCLC remains a subject of ongoing debate, primarily due to the delicate equilibrium between treatment efficacy and cumulative physiological cost. Our study demonstrates that the gemcitabine plus carboplatin (GC) combination is a viable first-line regimen for a selected elderly population, yielding a median overall survival (OS) of 16.6 months (1). However, the cardinal finding of this research is that chronological age and traditional performance scales are poor predictors of treatment adherence (12,13). Instead, the synergy between morphological

(sarcopenia), functional (frailty), and nutritional (PNI) status—summarized in our "Triple-Risk" model—serves as the primary determinant of chemotherapy cycle completion (12-14).

Our survival outcomes surpass those reported in landmark geriatric oncology trials such as ELVIS and MILES, which reported median OS rates of approximately 7 to 8 months (15,16). This discrepancy can be attributed to several factors, including the restriction to SqCLC histology and advancements in supportive care. Most importantly, while our preliminary analysis of this cohort established the prognostic significance of sarcopenia on mortality (1), the current multidimensional analysis reveals that even among patients with favorable ECOG scores, subclinical vulnerabilities like low PNI are associated with premature treatment attrition (17,18).

A unique contribution of this study is the integration of the PNI (10,11). While sarcopenia represents morphological decay (18), PNI reflects the immune-nutritional axis. In our cohort, patients with a PNI < 45 were significantly more likely to belong to the "Very High Risk" category, where the Triple-Risk score predicted a mean completion of only 2.2 cycles. This suggests that nutritional exhaustion acts as a catalyst, exacerbating the negative effects of sarcopenia and frailty (6,14).

Crucially, our regression analysis revealed no significant association between individual geriatric markers and the occurrence of Grade 3-4 acute toxicities. This indicates that treatment failure in the elderly is driven more by physiological attrition than by isolated acute adverse events (3,4). While hematologic toxicities were prevalent (86%), they were generally manageable and did not lead to increased febrile neutropenia or infection. The premature cessation of therapy in 11.6% of patients was primarily driven by non-hematologic adverse events and a global decline in resilience.

Regarding the observed non-linear distribution in treatment continuity, patients in the moderate-risk group (Score 1-2) showed similar adherence to those in the low-risk group. This observation suggests that moderate vulnerabilities may have been mitigated by proactive supportive care, such as the secondary G-CSF support utilized in 32.6% of our patients, or that a physiological threshold must be crossed before significant attrition occurs.

Limitations: This study is limited by its retrospective design, which allows for the identification of clinical associations rather than definitive causality. The small sample size and the exclusive inclusion of male patients limit the generalizability of the findings. Additionally, the absence of patients treated with immunotherapy is a notable limitation, as chemo-immunotherapy is the current global standard for advanced SqCLC (3,18,19). However, immunotherapy monotherapy also remains a viable and often preferred option for geriatric patients with high PD-L1 expression (2). Despite these limitations, our findings remain highly relevant for clinical settings where platinum-based doublets continue to be a necessary therapeutic component.

CONCLUSION

In conclusion, our study demonstrates that chronological age and traditional ECOG performance scales are insufficient for predicting chemotherapy tolerance in elderly patients with advanced SqCLC. Treatment attrition in this population is primarily driven by a "vulnerability triad"—the synergy of morphological (sarcopenia), functional (frailty), and nutritional (low PNI) deficits.

A critical finding is the dissociation between acute toxicity and treatment continuity; while individual markers did not significantly correlate with Grade 3–4 toxicities, the Triple-Risk Score was a potent predictor of premature treatment discontinuation. This suggests that high-risk elderly patients often experience a global failure of physiological resilience and cumulative exhaustion rather than a single catastrophic adverse event.

The Triple-Risk Score provides a practical, multidimensional tool for clinical decision-making. Identifying high-risk patients (Score 3) prior to chemotherapy allows for personalized pre-therapeutic optimization, proactive dose modifications, and intensified supportive care. Integrating nutritional assessments (PNI) alongside functional and morphological markers offers the necessary granularity to safeguard treatment continuity and improve the therapeutic index in this vulnerable population.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that there is no financial support.

Ethical Approval
The study protocol was approved by the Clinical Research Ethics Committee of Bursa City Hospital (Ref. No: 2022-18/4, Date: 21.12.2022) and conducted in accordance with the Declaration of Helsinki.

Patient Consent
Due to the retrospective nature of the research, the requirement for informed consent was waived by the ethics committee.

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