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RESEARCH ARTICLE

Health-Related Quality of Life in Iraqi Patients with Advanced NSCLC and Coexisting COPD Following Systemic Therapy: A Multicenter Cross-Sectional Study

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Abstract

Introduction: Coexisting chronic obstructive pulmonary disease (COPD) may exacerbate respiratory symptoms and impair functional status in patients with advanced non–small cell lung cancer (NSCLC). However, comparative real-world data evaluating health-related quality of life (HRQOL) across systemic treatment modalities in this comorbid population remain limited. To evaluate HRQOL among patients with advanced NSCLC and COPD receiving systemic therapy in routine clinical practice and to compare outcomes across chemotherapy, pembrolizumab, and atezolizumab groups. **Materials and Methods:** This multicenter real-world cross-sectional study was conducted at two oncology centers in Iraq. Patients with stage IV NSCLC and documented COPD who completed six cycles of systemic therapy were included. HRQOL was assessed using the EORTC QLQ-LC13 questionnaire after treatment completion. Pulmonary function (FEV1%) was measured post-treatment at the same time point. Statistical analyses included ANOVA with Bonferroni correction, effect size estimation (η^2), multivariable linear regression adjusting for age, sex, FEV1%, smoking status, and PD-L1 expression. **Results:** A total of 120 patients were analyzed. Significant differences in HRQOL symptom scores were observed across treatment groups, with chemotherapy generally associated with higher symptom burden. Effect size analysis demonstrated large to very large differences across most domains. In multivariable analysis, pembrolizumab remained associated with lower symptom scores across most domains, while atezolizumab showed variable associations after adjustment. No statistically significant differences in post-treatment FEV1% were observed between groups ($p = 0.094$), despite numerically higher values in the immunotherapy groups. Hepatic parameters showed some differences between groups but without consistent clinical patterns. **Conclusions:** In this cross-sectional real-world study, treatment modality was associated with differences in HRQOL outcomes among patients with advanced NSCLC and COPD. These findings should be interpreted with caution due to the cross-sectional design, potential selection bias related to inclusion of patients completing six treatment cycles, and the absence of baseline HRQOL assessment.

Keywords: NSCLC- Quality of Life- Iraq

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Introduction

Advanced non–small cell lung cancer (NSCLC) continues to represent a major therapeutic challenge despite ongoing advances in systemic treatment strategies. [1].

Health-related quality of life (HRQOL) has become an essential endpoint in the evaluation of patients with advanced NSCLC [2]. International oncology guidelines increasingly emphasize the importance of patient-reported outcomes when assessing treatment effectiveness and tolerability [3]. Patients with advanced lung cancer frequently experience substantial symptom burden that negatively affects functional status and daily activities,

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and this burden may be further exacerbated by shared inflammatory and pathogenic pathways between lung cancer and chronic obstructive pulmonary disease (COPD) [4, 5].

The presence of COPD in patients with lung cancer has been associated with worse clinical outcomes and increased disease burden [6]. Patients with coexisting NSCLC and COPD often report greater symptom severity and reduced quality of life compared with those without respiratory comorbidity [7]. Clinical studies have demonstrated that COPD is associated with systemic inflammation, functional impairment, and measurable reductions in quality of life [8, 9].

Immune checkpoint inhibitors have substantially changed the therapeutic landscape of advanced NSCLC [10]. These agents have demonstrated improved survival outcomes and favorable toxicity profiles compared with conventional chemotherapy [11]. In addition to survival benefits, immunotherapy has been associated with improved or maintained HRQOL in patients with advanced NSCLC [12]. Real-world studies have provided important evidence regarding outcomes of immunotherapy-based regimens in routine oncology practice [13, 14].

However, despite the increasing use of immunotherapy, real-world evidence comparing HRQOL outcomes across different systemic treatment modalities in patients with advanced NSCLC and coexisting COPD remains limited. Recent literature has further highlighted the clinical overlap between NSCLC and COPD and its potential impact on treatment outcomes [15]. Nevertheless, the influence of this overlap on patient-reported outcomes in routine clinical practice has not been adequately characterized, particularly in low- and middle-income settings.

Therefore, this study aimed to evaluate and compare HRQOL outcomes among patients with advanced NSCLC and coexisting COPD receiving systemic therapy in a real-world setting. We hypothesized that immunotherapy-based treatments would be associated with more favorable HRQOL profiles compared with chemotherapy.

Materials and Methods

Study Design and Setting

This multicenter real-world cross-sectional study was conducted at two public oncology centers in Iraq: Al-Diwaniyah Oncology Center and Najaf National Cancer Center. Both institutions provide government-funded systemic anticancer therapy and serve as regional referral centers for thoracic malignancies. Data collection was performed between March 2025 and December 2025. The study aimed to evaluate health-related quality of life (HRQOL) among patients with advanced non–small cell lung cancer (NSCLC) and coexisting chronic obstructive pulmonary disease (COPD) receiving systemic therapy in routine clinical practice. Given the cross-sectional design, the study was intended to evaluate associations rather than establish causal relationships.

Participants and Eligibility Criteria

A total of 120 consecutive patients with advanced NSCLC and documented COPD who completed at least six cycles of systemic therapy were included in the final analysis. The inclusion of patients who completed ≥6 cycles reflects routine clinical practice; however, this approach may introduce survivorship (selection) bias.

Inclusion Criteria

Patients were eligible if they met all of the following criteria:

1. Age ≥18 years.
2. Histologically confirmed NSCLC (adenocarcinoma or squamous cell carcinoma).
3. Stage IV disease managed in routine clinical practice.
4. Documented physician-diagnosed COPD in the medical records.
5. Completion of at least six cycles of systemic anticancer therapy.
6. Ability to complete the quality-of-life questionnaire.
7. Provision of written informed consent.

Patients were recruited consecutively during the study period.

Exclusion Criteria

Patients were excluded if they had:

1. Participation in a clinical trial during the study period.
2. Another active malignancy requiring systemic therapy.
3. Discontinuation of treatment before completing six cycles.
4. Missing key clinical data.
5. Severe clinical or cognitive impairment preventing questionnaire completion.

Assessment of COPD

COPD status was determined based on documented physician diagnosis recorded in patients' medical records at the participating oncology centers. Respiratory history, pulmonology follow-up, and the use of COPD-related medications (e.g., inhaled bronchodilators and corticosteroids) were reviewed to support the diagnosis.

Standardized spirometric confirmation and GOLD classification were not consistently available across centers; therefore, COPD severity could not be formally stratified.

Formal GOLD staging was not applied due to the absence of baseline spirometry prior to systemic therapy initiation. Pulmonary function parameters, including forced expiratory volume in one second (FEV1%), were measured after completion of six treatment cycles and reported descriptively.

Treatment Groups

Patients were categorized according to systemic therapy received during routine clinical care into three groups:

• Chemotherapy

• Pembrolizumab
• Atezolizumab

Treatment decisions were made by treating oncologists according to institutional protocols and routine practice. As treatment allocation was not randomized, it may have been influenced by patient clinical characteristics, introducing potential treatment selection bias.

Quality-of-Life Assessment

HRQOL was assessed after completion of six treatment cycles using the validated lung cancer–specific European Organisation for Research and Treatment of Cancer questionnaire (EORTC QLQ-LC13). Scores were calculated according to the EORTC scoring manual and transformed to a 0–100 scale. Higher symptom scores indicate greater symptom burden and poorer quality of life. The questionnaire was administered through face-to-face interviews at the oncology centers.

The QLQ-LC13 was selected due to its specificity for lung cancer–related symptoms. However, the absence of the EORTC QLQ-C30 and baseline HRQOL measurements limits the assessment of global quality of life and changes over time [16].

Data Collection

Demographic and clinical data were obtained from medical records and included age, sex, treatment modality, pulmonary function parameters, and laboratory results. Information related to COPD diagnosis and respiratory treatment history was also collected.

Additional variables, including smoking status and PD-L1 expression, were recorded where available. However, other relevant clinical variables such as ECOG performance status, line of therapy, and comorbidity burden were not consistently documented and therefore were not included in the final analysis.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics software. Continuous variables were expressed as mean ± standard deviation, and categorical variables as frequencies and percentages. Between-group comparisons were conducted using one-way analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables. Post-hoc analyses were performed when appropriate.

To address potential confounding, multivariable linear regression analyses were performed to evaluate the independent association between treatment group and HRQOL outcomes, adjusting for age, sex, smoking status, PD-L1 expression, and post-treatment FEV1%. Variable selection was based on clinical relevance and data availability. Model assumptions, including normality of residuals and absence of multicollinearity, were evaluated. Missing data were handled using complete-case analysis.

The inclusion of post-treatment FEV1% as a covariate was based on its availability as an indicator of pulmonary function at the time of HRQOL assessment. However, as FEV1% was measured after treatment exposure, it may represent a post-exposure variable and could act as a mediator or collider in the relationship between treatment and HRQOL outcomes. Therefore, results from adjusted models including FEV1% should be interpreted with caution.

Effect size estimates (η^2) were calculated to quantify the magnitude of differences across groups.

Interpretation of clinical significance was guided by established EORTC recommendations, where differences of approximately 10 points or more are generally considered clinically meaningful based on previously published thresholds.

To control for multiple comparisons across the 12 QLQ-LC13 symptom domains, Bonferroni correction was applied to post-hoc pairwise comparisons, with an adjusted significance threshold of $p < 0.0042$ (0.05/12). Results from regression analyses were reported using β coefficients with corresponding 95% confidence intervals. A p-value <0.05 was considered statistically significant for primary analyses.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the institutional review boards of the participating centers. Written informed consent was obtained from all participants prior to data collection.

Results

A total of 120 patients with advanced NSCLC and coexisting COPD were included in the analysis after completing six cycles of systemic therapy. Patients were categorized into chemotherapy (n=31), pembrolizumab (n=39), and atezolizumab (n=50) groups.

Baseline demographic characteristics are summarized in Table 1. Mean age was comparable across groups ($p = 0.747$), with values of 65.03 ± 7.57 years in the chemotherapy group, 64.23 ± 8.55 years in the pembrolizumab group, and 65.74 ± 10.59 years in the atezolizumab group. Sex distribution did not differ significantly among groups ($p = 0.960$).

No statistically significant differences were observed in mean FEV1% among treatment groups ($p = 0.094$), as

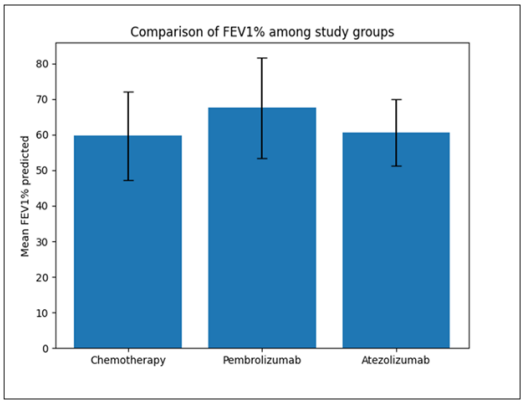

Figure 1. Mean FEV1% Predicted Across the Three Study Groups after Six Cycles of Treatment. Error bars indicate standard deviation. Differences between groups were not statistically significant ($p = 0.094$).

Table 1. Demographic Characteristics

Characteristics	Chemotherapy Group 31 cases	Pembrolizumab Group 39 cases	Atezolizumab Group 50 cases	p
Age (years)				
Mean ±SD	65.03 ±7.57	64.23 ±8.55	65.74 ±10.59	0.747 N
Range	52 -84	48 -86	45 -84	
Sex				
Male	22 (71.0 %)	27 (69.2 %)	36 (72.0 %)	0.960 N
Female	9 (29.0 %)	12 (30.8 %)	14 (28.0 %)	

N: not significant

Table 2. Pulmonary Function (FEV1%) across Study Groups

Characteristics	Chemotherapy Group	Pembro Group	Atezo Group	p
FEV1%				
Mean ±SD	59.7 ± 12.4	67.5 ± 14.2	60.6 ± 9.3	
Range	41 – 85	45.3 – 78.5	55 – 80	0.094 N

N: not significant

presented in Table 2. Although the pembrolizumab group showed numerically higher mean FEV1% values (67.5 ± 14.2) compared with the chemotherapy (59.7 ± 12.4) and atezolizumab groups (60.6 ± 9.3), these differences did not reach statistical significance.

As shown in Table 3, mean serum ALT and ALP levels did not differ significantly among groups ($p = 0.421$ and $p = 0.565$, respectively). However, significant variations were observed in AST levels ($p = 0.004$), with the highest mean value in the atezolizumab group (28.14 ± 8.75 IU/L). Total serum bilirubin levels also differed significantly ($p < 0.001$), with higher values observed in the atezolizumab group compared with the other groups.

Significant differences were observed across all EORTC QLQ-LC13 symptom domains among the three treatment groups (Table 4). Patients receiving chemotherapy reported consistently higher symptom scores for respiratory symptoms, treatment-related toxicities, and pain domains compared with both immunotherapy groups (all $p < 0.001$). Pembrolizumab-treated patients demonstrated the lowest overall symptom burden, while the atezolizumab group showed intermediate scores. Overall, immunotherapy was associated with more favorable HRQOL outcomes compared with chemotherapy.

Effect size analysis using eta-squared (η^2) demonstrated that the differences observed across QLQ-LC13 symptom domains were of moderate to very large magnitude (Table 5). The largest effect sizes were observed for hemoptysis (Q32), sore mouth (Q36), dysphagia (Q37), neuropathy (Q38), and hair loss (Q39), indicating substantial differences between treatment groups in these domains. Moderate to large effect sizes were also noted for dyspnea-related symptoms and pain domains, including chest pain (Q40) and arm/shoulder pain (Q41).

Multivariable linear regression analysis was performed to evaluate the independent association between treatment group and HRQOL outcomes after adjusting for age, sex, smoking status, PD-L1 expression, and post-treatment FEV1% (Table 6). Pembrolizumab remained significantly associated with lower symptom scores across all QLQ-LC13 domains compared with chemotherapy. In contrast, atezolizumab showed significant associations in several domains, particularly hemoptysis, sore mouth, dysphagia, neuropathy, and other pain, while no statistically significant differences were observed for dyspnea on exertion (Q34 and Q35), chest pain (Q40), and arm/shoulder pain (Q41). while pembrolizumab demonstrated consistently lower symptom scores across most domains, atezolizumab showed significant improvements in several but not all domains after adjustment.

Discussion

The present multicenter real-world cross-sectional study evaluated health-related quality of life (HRQOL) among patients with advanced NSCLC and coexisting COPD receiving systemic therapy. The coexistence of COPD in advanced lung cancer represents a clinically important challenge, as respiratory comorbidity may influence treatment tolerance, pulmonary reserve, and overall outcomes. Previous evidence has shown that COPD may affect response to immune checkpoint inhibitors and overall prognosis in advanced lung cancer populations [17]. In this context, evaluating patient-reported outcomes in real-world NSCLC populations with COPD is of substantial clinical relevance.

Given the observational cross-sectional design, the findings of this study should be interpreted as associations rather than causal relationships. Furthermore, potential confounding factors and the non-randomized nature of treatment allocation in real-world settings should be

Table 3. Liver Function Test

Characteristics	Chemotherapy Group	Pembro Group	Atezo Group	p
ALT U/L				
Mean ±SD	31.48 ±14.84	27.54 ±11.83	28.76 ±11.66	0.421 N
Range	5-67	5-56	Aug-53	
AST U/L				
Mean ±SD	24.52 ±10.28	21.33 ±9.27	28.14 ±8.75	0.004 S
Range	5-45	5-38	10-46	
ALP U/L				
Mean ±SD	113.13 ±60.38	101.72 ±43.36	105.84 ±32.34	0.565 N
Range	30 -254	30 -190	60 -189	
TSB mg/dL				
Mean ±SD	0.74 ±0.33	0.67 ±0.25	0.98 ±0.33	<0.001 S
Range	0.26 -1.54	0.2 -1.22	0.27 -1.71	

S: significant; N: not: significant

considered when interpreting these results.

Baseline demographic characteristics were comparable across treatment groups, which may reduce the likelihood that observed HRQOL differences were driven by major demographic imbalances. Older age and increased comorbidity burden have been associated with poorer functional status and diminished quality of life in advanced lung cancer [18].

The relatively balanced distribution of age and sex across groups supports comparability between treatment groups; however, residual confounding related to unmeasured clinical variables cannot be excluded. Therefore, the observed differences in HRQOL should not be attributed entirely to treatment effects.

No statistically significant differences in mean FEV1% were observed among treatment groups. Although numerically higher values were observed in the pembrolizumab group, these differences did not reach statistical significance. This study was based on the available real-world sample and was not specifically powered for all multivariable comparisons. Therefore, the possibility of type II error should be considered, particularly for outcomes such as post-treatment FEV1%, where numerical differences were observed without reaching statistical significance.

Impaired pulmonary function has consistently been associated with increased symptom burden and reduced quality of life in patients with lung cancer and COPD [19, 20].

Therefore, the observed HRQOL differences cannot be explained by differences in pulmonary function alone. Chronic airway inflammation and airflow limitation are known to exacerbate dyspnea, fatigue, and exercise intolerance, all of which negatively impact HRQOL [21].

Although formal GOLD staging was not uniformly available, the observed differences in FEV1% may reflect underlying patient characteristics rather than treatment-related effects. Similar interactions between COPD status and immunotherapy outcomes have been reported in prior studies [22] suggesting a potential link between pulmonary function and patient-reported outcomes in this population. However, as FEV1% was measured after treatment completion and baseline pulmonary function data were not available, these findings should be interpreted with caution.

The inclusion of post-treatment FEV1% in the adjusted model introduces a potential methodological limitation, as it may lie on the causal pathway between treatment and HRQOL (i.e., acting as a mediator) rather than a baseline confounder. This may influence the interpretation of adjusted associations and should be considered when interpreting the results.

Liver function parameters were largely comparable across groups, suggesting no major differences in hepatic safety profiles. Mild variations in AST and bilirubin were observed but were not clinically alarming. Immune checkpoint inhibitors are generally associated with manageable hepatic toxicity compared with cytotoxic chemotherapy [23] and real-world evidence suggests low rates of clinically significant hepatotoxicity with PD-1/PD-L1 inhibitors [24].

However, these findings should be interpreted cautiously, as laboratory parameters were assessed cross-sectionally and may not fully capture longitudinal treatment-related hepatic effects.

Patients receiving chemotherapy demonstrated higher symptom scores across most EORTC QLQ-LC13 domains compared with immunotherapy-treated patients.

Most observed differences between treatment groups exceeded the established minimal clinically important difference (MCID) threshold of approximately 10 points for EORTC QLQ-LC13 scores, indicating that the observed differences were not only statistically significant but also clinically meaningful [25].

These findings are consistent with randomized trials suggesting improved tolerability and patient-reported outcomes with immune checkpoint inhibitors compared with chemotherapy in advanced NSCLC [26].

The more favorable toxicity profile of immunotherapy, characterized by fewer systemic adverse effects such as

Table 4. Response of Patients to Individual Questions Related to Quality of Life Assessment

Characteristics	Chemotherapy Group	Pembro Group	Atezo Group	p
Q31 Coughing				
Mean ±SD	47.70 ±11.03	33.71 ±8.99	37.76 ±7.90	<0.001 S
Range	29.98 -72.65	20.6 -49.1	23.1 -52.6	
Q32 Coughing up blood				
Mean ±SD	45.64 ±11.12	34.62 ±9.51	18.20 ±5.82	<0.001 S
Range	29.64 -77.02	20.2 -49.6	7.5 -30.2	
Q33 Shortness of breath at rest				
Mean ±SD	45.74 ±13.28	34.49 ±8.49	37.32 ±12.07	<0.001 S
Range	16.52 -75	20.8 -47.9	17.6 -59.7	
Q34 Shortness of breath when walking				
Mean ±SD	48.42 ±10.97	34.08 ±9.08	47.77 ±11.53	<0.001 S
Range	28.06 -79.62	20.2 -49.6	29.3 -68.7	
Q35 Shortness of breath when climbing stairs				
Mean ±SD	47.77 ±11.86	34.78 ±8.46	52.16 ±13.65	<0.001 S
Range	33.55 -97.85	20.5 -48.1	25.3 -72.6	
Q36 Sore mouth or tongue				
Mean ±SD	50.51 ±9.85	35.44 ±8.49	25.34 ±3.85	<0.001 S
Range	35.52 -70.05	20.2 -49.2	17.3 -36.3	
Q37 Trouble swallowing				
Mean ±SD	50.80 ±11.57	37.44 ±9.26	27.71 ±5.95	<0.001 S
Range	31.4 -84.56	20.5 -49.7	16 -40	
Q38 Tingling hands or feet				
Mean ±SD	45.92 ±11.30	34.27 ±8.31	27.94 ±4.05	<0.001 S
Range	21.7 -71.12	20.9 -49.3	19.8 -37	
Q39 Hair loss				
Mean ±SD	48.37 ±11.50	33.44 ±8.23	35.35 ±4.03	<0.001 S
Range	25.61 -75.11	20.4 -48.9	28.4 -45.7	
Q40 Pain in chest				
Mean ±SD	47.46 ±12.81	34.72 ±9.61	47.14 ±15.94	<0.001 S
Range	28.94 -87.84	20.5 -48.8	15.5 -75	
Q41 Pain in arm or shoulder				
Mean ±SD	46.91 ±12.36	36.88 ±8.71	42.53 ±15.29	0.005 S
Range	16.79 -79.48	20.3 -49.7	12.7 -66.7	
Q42 Pain in 4 parts				
Mean ±SD	50.02 ±11.95	34.23 ±9.82	34.54 ±9.50	<0.001 S
Range	32.05 -80.89	20.3 -49.6	17.7 -54.1	

SD: Standard Deviation S:Significant

mucositis, neuropathy, and alopecia, may partially explain the observed differences in symptom burden and daily functioning.

Similarly, atezolizumab-treated patients showed lower symptom scores compared with chemotherapy, consistent with randomized evidence demonstrating maintenance of quality of life with PD-L1 inhibitors [27].

Overall, immunotherapy was associated with lower symptom burden, supporting findings from systematic reviews indicating HRQOL advantages of immune checkpoint blockade over conventional chemotherapy. [28].

However, these findings should be interpreted as associations rather than causal effects, given the observational cross-sectional design of the study.

In real-world clinical practice, treatment allocation is not randomized and is often influenced by patient-related factors, including functional status, comorbidity burden, and clinician judgment. This introduces the possibility of confounding by indication, whereby patients receiving immunotherapy may have had more favorable baseline characteristics. Furthermore, treatment decisions are frequently influenced by PD-L1 expression and other clinical considerations, which may contribute to differences in observed outcomes. These real-world prescribing patterns should be considered when interpreting the association between treatment modality and HRQOL [29].

Table 5. Effect Size Estimates (η^2) for QLQ-LC13 Symptom Domains Across Study Groups

Domain	ANOVA p-value	η^2 (Effect size)	Interpretation
Q31 Coughing	<0.001	0.35	Large
Q32 Hemoptysis	<0.001	0.69	Very large
Q33 Dyspnea at rest	<0.001	0.3	Large
Q34 Dyspnea walking	<0.001	0.28	Large
Q35 Dyspnea stairs	<0.001	0.25	Large
Q36 Sore mouth	<0.001	0.72	Very large
Q37 Dysphagia	<0.001	0.61	Very large
Q38 Neuropathy	<0.001	0.57	Very large
Q39 Hair loss	<0.001	0.52	Very large
Q40 Chest pain	<0.001	0.22	Moderate to large
Q41 Arm/shoulder pain	0.005	0.17	Moderate
Q42 Other pain	<0.001	0.43	Large

Table 6. Multivariable Linear Regression Analysis of QLQ-LC13 Symptom Scores Across Treatment Groups (reference = chemotherapy group)

Domain	Atezolizumab β (95% CI)	p-value	Pembrolizumab β (95% CI)	p-value
Q31 Coughing	-9.95 (-15.02 to -4.87)	<0.001	-14.00 (-19.34 to -8.65)	<0.001
Q 32 Hemoptysis	-27.44 (-32.26 to -22.62)	<0.001	-11.03 (-16.10 to -5.96)	<0.001
Q33 Dyspnea at rest	-8.42 (-14.74 to -2.10)	0.005	-11.25 (-17.91 to -4.60)	<0.001
Q34 Dyspnea walking	-0.64 (-6.55 to 5.27)	1.000	-14.33 (-20.56 to -8.11)	<0.001
Q35 Dyspnea stairs	4.39 (-2.11 to 10.90)	0.311	-12.99 (-19.84 to -6.14)	<0.001
Q36 Sore mouth	-25.17 (-29.27 to -21.08)	<0.001	-15.07 (-19.39 to -10.76)	<0.001
Q37 Dysphagia	-23.09 (-27.96 to -18.21)	<0.001	-13.36 (-18.49 to -8.23)	<0.001
Q38 Neuropathy	-17.98 (-22.35 to -13.61)	<0.001	-11.65 (-16.26 to -7.05)	<0.001
Q 39Hair loss	-13.02 (-17.41 to -8.62)	<0.001	-14.93 (-19.55 to -10.30)	<0.001
Q40 Chest pain	-0.33 (-7.75 to 7.09)	1.000	-12.74 (-20.55 to -4.93)	<0.001
Q41 Arm/shoulder pain	-4.38 (-11.44 to 2.68)	0.404	-10.03 (-17.46 to -2.60)	0.004
Q42 Other pain	-15.48 (-21.20 to -9.77)	<0.001	-15.79 (-21.81 to -9.78)	<0.001

This may have contributed to an overestimation of HRQOL benefits observed in the immunotherapy groups. Additionally, the absence of key variables such as ECOG performance status, line of therapy, comorbidity burden, and COPD severity (GOLD classification) may have further influenced the observed associations.

COPD severity may also influence treatment selection in routine clinical practice, as patients with more advanced respiratory impairment may be less likely to receive certain systemic therapies.

In addition, different COPD phenotypes and degrees of pulmonary dysfunction may interact with treatment response to immune checkpoint inhibitors [30]. However, due to the lack of standardized COPD severity assessment (e.g., GOLD classification), this relationship could not be formally evaluated in the present study and should be explored in future research.

Among immunotherapy groups, pembrolizumab-treated patients showed the lowest symptom burden. While pembrolizumab demonstrated consistently lower symptom scores across most domains, atezolizumab showed significant improvements in several but not all domains after adjustment.

The observed variability in the atezolizumab group may reflect differences in real-world treatment allocation, including patient selection factors and PD-L1–driven prescribing patterns. In addition, residual confounding cannot be excluded, which may contribute to the less consistent associations observed compared with pembrolizumab [31].

Prior real-world and pooled analyses have reported favorable clinical and tolerability profiles with immune checkpoint inhibitors [32] which may be associated with improved patient-reported outcomes in routine practice.

These findings are particularly relevant in patients with coexisting COPD, who often present with increased baseline symptom burden and limited pulmonary reserve. COPD adversely affects functional status and overall quality of life [33] and chemotherapy-related pulmonary complications may further exacerbate respiratory symptoms [34].

The higher rates of mucositis, dysphagia, neuropathy, and alopecia observed in chemotherapy-treated patients are consistent with regional evidence suggesting a negative impact of cytotoxic therapy on HRQOL [35, 36].

From a clinical perspective, these results emphasize

the importance of incorporating patient-reported outcomes into therapeutic decision-making for patients with advanced NSCLC and COPD. Treatment strategies that minimize systemic toxicity while preserving pulmonary function may be associated with improved quality-of-life outcomes.

Nevertheless, residual confounding cannot be excluded, and the cross-sectional design limits causal inference. In addition, the non-randomized nature of treatment allocation and the inclusion of patients who completed at least six cycles of therapy may introduce selection and survivorship bias. Prospective longitudinal studies are needed to further clarify the relationship between treatment modality, pulmonary function, and HRQOL trajectories in this setting.

Strengths

This study represents one of the first multicenter real-world evaluations of HRQOL among patients with advanced NSCLC and coexisting COPD in Iraq. Inclusion of patients treated in routine clinical practice may improve the generalizability of the findings to similar real-world settings. The use of the validated EORTC QLQ-LC13 instrument supports the reliability and clinical relevance of patient-reported outcomes. Real-world data offer important insights into treatment tolerability in populations often underrepresented in randomized clinical trials [14].

Limitations

The cross-sectional design precludes assessment of longitudinal changes in HRQOL and limits causal inference. Baseline spirometry prior to treatment initiation was not uniformly available, preventing formal GOLD staging. In addition, the sample size may limit statistical power for subgroup analyses.

The inclusion of only patients who completed at least six cycles of therapy introduces potential survivorship bias, as patients with early disease progression or treatment intolerance were not captured. Furthermore, the observational nature of the study and the non-randomized allocation of treatment may result in residual confounding despite multivariable adjustment.

Baseline HRQOL was not assessed, limiting the ability to evaluate changes over time and potentially affecting the interpretation of between-group differences.

Both HRQOL and FEV1% were assessed after treatment completion, which introduces the possibility of post-treatment measurement bias. In addition, the cross-sectional design does not allow evaluation of longitudinal changes in HRQOL over time. Furthermore, the use of interview-administered questionnaires may introduce measurement bias compared with self-administered assessments.

Additionally, COPD diagnosis was based on physician documentation without standardized spirometric confirmation, which may introduce misclassification bias.

Future prospective studies incorporating baseline and follow-up HRQOL assessments are warranted to better characterize dynamic quality-of-life trajectories over time [37].

In conclusion, Immunotherapy, particularly pembrolizumab, was associated with more favorable HRQOL outcomes compared with chemotherapy among patients with advanced NSCLC and coexisting COPD in this real-world cohort.

These findings highlight the potential importance of incorporating patient-reported outcomes into treatment evaluation and clinical decision-making. However, given the observational cross-sectional design and potential sources of bias, these findings should be interpreted as associations rather than definitive evidence of treatment superiority. Prospective longitudinal studies are required to confirm these observations.

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