The association between anticholinergic burden and nutritional status in elderly chronic obstructive pulmonary disease patients: A cross-sectional study

Yaşlı kronik obstrüktif akciğer hastalığı hastalarında antikolinerjik yük ve beslenme durumu arasındaki ilişki: Kesitsel bir çalışma

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Abstract

Aim: Anticholinergic burden and polypharmacy are significant concerns in elderly Chronic obstructive pulmonary disease (COPD) patients, potentially affecting their nutritional status and clinical outcomes. This study aimed to investigate the relationship between anticholinergic burden and nutritional status in elderly COPD patients.

Methods: This cross-sectional study included 195 COPD patients aged ≥38 years. Anticholinergic burden was assessed using the Anticholinergic Cognitive Burden Scale, and nutritional status was evaluated using the Mini Nutritional Assessment (MNA). COPD severity was classified according to the Global Initiative for Obstructive Lung Disease (GOLD) criteria. Multiple logistic regression analysis was used to examine the association between anticholinergic burden and nutritional status, adjusting for potential confounders.

Results: The mean age of participants was 65.8±10.2 years. Clinically significant anticholinergic burden (score ≥3) was present in 35.7% of patients, and polypharmacy was observed in 42.3%. Higher anticholinergic burden was significantly associated with lower MNA scores ($p<0.001$). Advanced GOLD stages (3-4) showed a stronger correlation with poor nutritional status compared to early stages. Cardiovascular comorbidities were the most prevalent (45.2%) and were associated with higher anticholinergic burden.

Conclusion: This study demonstrates a significant association between anticholinergic burden and poor nutritional status in elderly COPD patients. Regular assessment of anticholinergic burden and nutritional status should be considered in the clinical management of elderly COPD patients, particularly those with multiple comorbidities.

Keywords: Aged; anticholinergic agents; chronic obstructive pulmonary disease; malnutrition; nutritional status; polypharmacy

Öz

Amaç: Yaşlı KOAH (Kronik obstrüktif akciğer hastalığı) hastalarında antikolinerjik yük ve polifarmasi, hastaların beslenme durumunu ve klinik sonuçlarını etkileyebilen önemli sorunlardır. Bu çalışma, yaşlı KOAH hastalarında antikolinerjik yük ile beslenme durumu arasındaki ilişkiyi araştırmayı amaçlamıştır.

Yöntemler: Bu kesitsel çalışmaya ≥38 yaş 195 KOAH hastası dâhil edildi. Antikolinerjik yük Antikolinerjik Kognitif Yük Ölçeği kullanılarak, beslenme durumu Mini Nütrisyonel Değerlendirme (MNA) ile değerlendirildi. KOAH şiddeti GOLD kriterlerine göre sınıflandırıldı. Antikolinerjik yük ile beslenme durumu arasındaki ilişki, potansiyel karıştırıcı faktörler için düzeltme yapılarak çoklu lojistik regresyon analizi ile incelendi.

Bulgular: Katılımcıların yaş ortalaması 65,8±10,2 yıldı. Hastaların %35,7'sinde klinik olarak anlamlı antikolinerjik yük (skor ≥3) ve %42,3'ünde polifarmasi saptandı. Yüksek antikolinerjik yük, düşük MNA skorları ile anlamlı ilişki gösterdi ($p<0.001$). İleri GOLD evreleri (3-4), erken evrelere göre kötü beslenme durumu ile daha güçlü korelasyon gösterdi. Kardiyovasküler komorbiditeler en sık görülen (%45,2) ek hastalıklardı ve yüksek antikolinerjik yük ile ilişkiliydi.

Sonuç: Bu çalışma, yaşlı KOAH hastalarında antikolinerjik yük ile kötü beslenme durumu arasında anlamlı bir ilişki olduğunu göstermektedir. Özellikle çoklu komorbiditesi olan yaşlı KOAH hastalarının klinik yönetiminde, antikolinerjik yük ve beslenme durumunun düzenli değerlendirilmesi düşünülmelidir.

Anahtar Sözcükler: Antikolinerjik ajanlar; beslenme durumu; kronik obstrüktif pulmoner hastalık; malnütrisyon; polifarmasi; yaşlı

Received/*Geliş* : 22.01.2025
Accepted/*Kabul*: 28.10.2025

DOI: 10.21673/anadoluklin.1623319

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) represents a major global health challenge, affecting approximately 10% of adults worldwide and ranking as the third leading cause of death globally (1). The disease is characterized by progressive airflow limitation and respiratory symptoms, but its systemic manifestations extend far beyond the respiratory system (2). Recent evidence suggests that the complex interplay between COPD and its comorbidities significantly impacts patient outcomes, particularly in elderly populations (3).

A critical yet often overlooked aspect of COPD management is the increasing medication burden as the disease progresses. Studies indicate that COPD patients use an average of 5-7 different medications daily, with this number increasing to 8-10 in those with multiple comorbidities (4). This polypharmacy poses unique challenges, particularly regarding the cumulative anticholinergic burden. Anticholinergic medications, while essential for COPD management, can accumulate in their effects, potentially leading to various adverse outcomes (5,6).

The relationship between medication burden and nutritional status in COPD has emerged as an area of particular concern. Recent systematic reviews indicate that malnutrition affects 30-60% of COPD patients, with higher prevalence in advanced disease stages (7,8). Poor nutritional status has been independently associated with increased mortality, reduced quality of life, and more frequent exacerbations in COPD patients (9). The Mini Nutritional Assessment (MNA) has emerged as a validated and reliable tool for nutritional assessment in this population, showing strong correlations with clinical outcomes (10).

Current evidence suggests that anticholinergic medications may influence nutritional status through multiple mechanisms. These include effects on appetite, taste perception, and gastrointestinal function (11). However, the extent and clinical significance of these effects in COPD patients remain poorly understood. Recent studies have highlighted the potential impact of anticholinergic burden on various health outcomes in elderly populations, but its specific effects on nutritional status in COPD patients have not been systematically evaluated (12,13).

Furthermore, the complex relationship between COPD severity, comorbidity burden, and medication use presents unique challenges in elderly patients. While guidelines recommend careful medication management in this population, practical tools for assessing and managing anticholinergic burden in relation to nutritional status are lacking (14). This knowledge gap is particularly significant given the aging COPD population and the increasing prevalence of multimorbidity (15).

This study aimed to quantitatively evaluate the relationship between anticholinergic burden and nutritional status across different COPD stages in elderly patients, using validated assessment tools and accounting for potential confounding factors.

MATERIAL AND METHODS

Study design and setting

This cross-sectional study was conducted at the Pulmonology Department of Bezmialem Vakif University Hospital between December 2019 and December 2020. The study was designed and reported following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cross-sectional studies. This study was approved by the Non-Interventional Research Ethics Committee of Bezmialem Vakıf University (date: 17.12.2019, decision no: 24/450) and written informed consent was obtained from all participants.

Sample size calculation and power analysis

For sample size calculation, we used G*Power 3.1.9.7 software. Based on previous studies indicating a correlation coefficient of 0.25 between anticholinergic burden and nutritional status, we determined that a sample size of 195 patients would provide 90% power to detect a significant correlation, with an α error probability of 0.05 and effect size (ρ) of 0.25 using a two-tailed test. This calculation included a 15% adjustment for potential dropouts and incomplete data. The final sample size of 195 participants exceeded the minimum required sample of 169, ensuring adequate statistical power.

Study population and sampling

Participants were recruited from the Pulmonology outpatient clinic using consecutive sampling between December 2019 and December 2020. Patient screening and recruitment were conducted by pulmonologists with at least 5 years of clinical experience in COPD management. We included patients aged ≥38 years with a confirmed diagnosis of COPD according to GOLD criteria (post-bronchodilator FEV1/FVC <0.70). Additional criteria include at least 6 months of follow-up at our clinic, stable disease status with no exacerbation in the previous month, ability to provide written informed consent, capability to complete study assessments, and availability of complete medical records for the past 12 months.

Exclusion criteria

We excluded patients who experienced acute COPD exacerbation within the previous month, defined as worsening of respiratory symptoms requiring additional therapy. Other exclusion criteria included severe cognitive impairment (Mini-Mental State Examination score <24), active malignancy or terminal illness with life expectancy <12 months, and severe psychiatric disorders affecting nutritional intake. Additionally, we excluded patients who had recent major surgery (within 3 months), acute cardiovascular events within the past 6 months, severe endocrine disorders affecting metabolism, or were using medications affecting nutritional status outside of COPD treatment. Pregnant or lactating women were also excluded from the study.

Data collection and measurements

Data collection involved a comprehensive clinical assessment, including a detailed medical history, physical examination, and pulmonary function tests performed according to ATS/ERS standards. A comprehensive medication review was conducted by verifying pharmacy records and documenting current medications, duration of use, compliance, and side effects. Nutritional status was evaluated using the Mini Nutritional Assessment (MNA) along with anthropometric measurements, dietary intake evaluation, biochemical parameters, and body composition analysis. Functional assessment included the six-minute walk test, handgrip strength measurement, activities of daily living assessment, and quality of life questionnaires.

Assessment of primary outcomes

The primary outcomes of our study were nutritional status and anticholinergic burden. Nutritional status was assessed using the validated MNA tool, with scores categorized as normal (≥24), at risk of malnutrition (17-23.5), or malnourished (<17). These assessments were conducted by trained nutritionists. Anticholinergic burden was measured using the Anticholinergic Cognitive Burden Scale, with medication reviews conducted by clinical pharmacists. Scores were categorized as none (0), low (1-2), or high (≥3).

Assessment of secondary outcomes

Secondary outcomes included COPD severity assessment using both spirometric classification (GOLD stages 1-4) and clinical assessment (GOLD groups A-D). We also evaluated clinical parameters such as pulmonary function tests, body composition measurements, exercise capacity, and dyspnea assessment using the mMRC scale. Comorbidity assessment included documentation of the number and type of comorbidities, calculation of the Charlson Comorbidity Index, and analysis of specific comorbidity patterns. Additionally, we collected detailed medication profiles and assessed quality of life using the COPD Assessment Test (CAT) and St. George's Respiratory Questionnaire.

Statistical analysis

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). We assessed the normality of data distribution using the Shapiro-Wilk test. Descriptive statistics were presented as mean ± standard deviation for normally distributed continuous variables and median (interquartile range) for non-normally distributed variables. Categorical variables were expressed as frequencies and percentages. For comparisons between groups, we used an independent t-test or Mann-Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables. Multiple group comparisons were conducted using one-way ANOVA or the Kruskal-Wallis test as appropriate.

We assessed correlations between variables using Pearson's correlation coefficient for normally distributed variables and Spearman's rank correlation coefficient for non-normally distributed variables. Multiple linear regression analysis was performed to identify independent predictors of nutritional status, adjusting for potential confounders. Throughout all analyses, a p-value <0.05 was considered statistically significant.

RESULTS

The demographic and clinical characteristics of the study population are presented in Table 1. Among the 195 COPD patients included in the study, the mean age was 65.8±10.2 years, with males comprising 75.4% of the population. The distribution according to GOLD stages showed that Stage 2 was most prevalent (34.4%), followed by Stage 3 (28.7%), Stage 4 (21.0%), and Stage 1 (15.9%) (Table 1).

The analysis of nutritional status and anticholinergic burden across different GOLD stages is presented in Table 2. MNA evaluation revealed that 45.6% of patients had normal nutritional status (MNA ≥12), 44.1% were at risk of malnutrition (MNA 8-11), and 10.3% were classified as malnourished (MNA <8). The mean MNA scores showed a significant declining trend with advancing GOLD stages, from 12.1±1.8 in Stage 1 to 9.1±2.6 in Stage 4 (p<0.001). Similarly, the distribution of anticholinergic burden varied significantly across GOLD stages, with the proportion of patients having high anticholinergic burden (score ≥3) increasing from 3.2% in Stage 1 to 14.6% in Stage 4 (p<0.001) (Table 2).

Significant negative correlations were identified between MNA scores and several parameters: anticholinergic burden (r=-0.342, p<0.001), GOLD stage (r=-0.285, p<0.001), total number of medications (r=-0.276, p<0.001), and age (r=-0.198, p=0.006). These correlations demonstrate the complex relationships between disease severity, medication burden, and nutritional status (Table 3).

Among cardiovascular medications, both furosemide and digoxin showed significant increases in usage with advancing GOLD stages (p=0.042 and p=0.031, respectively). Notably, furosemide use increased from 3.2% in Stage 1 to 9.8% in Stage 4, while digoxin use rose from 0% to 7.3%. In terms of respiratory medications, theophylline use demonstrated a significant increase from Stage 1 (6.5%) to Stage 4 (17.1%, p=0.035), and prednisolone use showed a similar trend, rising from 3.2% in Stage 1 to 12.2% in Stage 4 (p=0.018) (Table 4).

Multiple regression analysis identified three independent predictors of MNA scores: anticholinergic burden (β=-0.289, p<0.001), GOLD stage (β=-0.245, p=0.002), and age (β=-0.167, p=0.018), after adjusting for potential confounders. The most prevalent comorbidities in the study population were hypertension (26.7%), heart disease (11.8%), and diabetes mellitus (9.7%).

DISCUSSION AND CONCLUSION

In this cross-sectional study investigating the relationship between anticholinergic burden and nutritional status in COPD patients, we found several significant associations that warrant careful consideration. The mean age of our study population (65.8±10.2 years) reflects the typical demographic profile of COPD patients in current clinical practice, making our findings particularly relevant for everyday patient care.

A key finding of our study was the high prevalence of polypharmacy (42.3%) and clinically significant anticholinergic burden (35.7%) among participants.

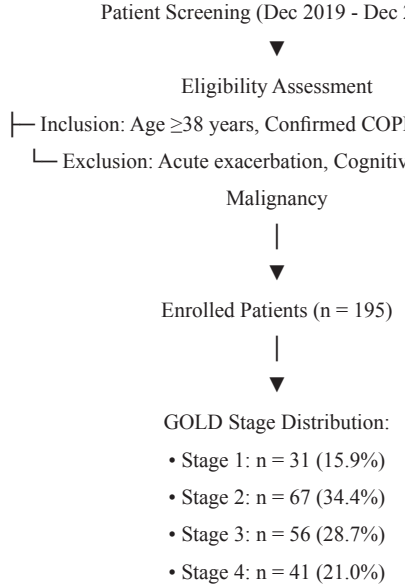

Figure 1. Flowchart of patient selection (MNA: Mini Nutritional Assessment, n: Number, %: Percent, COPD: Chronic obstructive pulmonary disease)

Table 1. Demographic and clinical characteristics of COPD patients (n=195)

Characteristics	Value
Age (years), mean ± SD	65.8 ± 10.2
Gender, n (%)	
Male	147 (75.4%)
Female	48 (24.6%)
GOLD stage (FEV1), n (%)	
Stage 1	31 (15.9%)
Stage 2	67 (34.4%)
Stage 3	56 (28.7%)
Stage 4	41 (21.0%)
MNA score, n (%)	
Normal (≥12)	89 (45.6%)
At risk (8-11)	86 (44.1%)
Malnourished (<8)	20 (10.3%)
Anticholinergic burden score, n (%)	
0	112 (57.4%)
1-2	65 (33.3%)
≥3	18 (9.3%)

MNA: Mini Nutritional Assessment, n: Number, %: Percent, SD: Standart deviation, FEV: Forced expiratory volume

Table 2. Distribution of anticholinergic burden and MNA scores across COPD stages

Characteristics	GOLD 1	GOLD 2	GOLD 3	GOLD 4	p-value
Anticholinergic Burden, n (%)					
Score 0	24 (77.4)	42 (62.7)	29 (51.8)	17 (41.5)	<0.001
Score 1-2	6 (19.4)	20 (29.9)	21 (37.5)	18 (43.9)	<0.001
Score ≥3	1 (3.2)	5 (7.5)	6 (10.7)	6 (14.6)	<0.001
Mean MNA Score ± SD	12.1±1.8	11.3±2.1	10.2±2.4	9.1±2.6	<0.001
Medications (mean ± SD)	1.2±1.1	2.8±2.1	3.9±2.4	4.8±2.7	<0.001

MNA: Mini Nutritional Assessment, n: Number, %: Percent, COPD: Chronic obstructive pulmonary disease

Table 3. Correlation between clinical parameters

Variables	r coefficient	p-value
Anticholinergic Burden-MNA	-0.342	<0.001
GOLD Stage-MNA	-0.285	<0.001
Total Medications-MNA	-0.276	<0.001
Age-MNA	-0.198	0.006

MNA: Mini Nutritional Assessment

This finding aligns with recent work by Vetrano et al, who reported similar rates of polypharmacy in elderly patients with chronic respiratory conditions (16). The association between polypharmacy and poor clinical outcomes has been well-documented by Jaiteh et al, who demonstrated increased risk of adverse events in patients with multiple prescriptions (18).

Our observation of declining MNA scores with increasing GOLD stages provides new insights into the relationship between disease severity and nutritional status. This finding extends beyond previous research by Scichilone et al, who primarily focused on respiratory parameters without considering nutritional aspects (17). The inverse correlation we found between

Table 4. Distribution of medications with anticholinergic properties across COPD stages

Medications	GOLD 1 n (%)	GOLD 2 n (%)	GOLD 3 n (%)	GOLD 4 n (%)	p-value
Cardiovascular drugs					
Furosemide	1 (3.2)	3 (4.5)	5 (8.9)	4 (9.8)	0.042
Metoprolol	2 (6.5)	4 (6.0)	5 (8.9)	3 (7.3)	0.563
Warfarin	1 (3.2)	4 (6.0)	5 (8.9)	3 (7.3)	0.274
Digoxin	0 (0.0)	2 (3.0)	3 (5.4)	3 (7.3)	0.031
Respiratory drugs					
Theophylline	2 (6.5)	8 (11.9)	9 (16.1)	7 (17.1)	0.035
Prednisolone	1 (3.2)	3 (4.5)	4 (7.1)	5 (12.2)	0.018
Psychotropic drugs					
Quetiapine	0 (0.0)	2 (3.0)	3 (5.4)	2 (4.9)	0.172
Sertraline	1 (3.2)	3 (4.5)	4 (7.1)	2 (4.9)	0.645
Amitriptyline	0 (0.0)	1 (1.5)	2 (3.6)	1 (2.4)	0.314
Mirtazapine	0 (0.0)	1 (1.5)	2 (3.6)	1 (2.4)	0.426
Antihistamines					
Hydroxyzine	0 (0.0)	1 (1.5)	2 (3.6)	2 (4.9)	0.183
Desloratadine	1 (3.2)	2 (3.0)	3 (5.4)	1 (2.4)	0.426
Levocetirizine	0 (0.0)	1 (1.5)	1 (1.8)	1 (2.4)	0.568
Others					
Solifenacin	0 (0.0)	1 (1.5)	1 (1.8)	1 (2.4)	0.724
Colchicine	0 (0.0)	1 (1.5)	0 (0.0)	1 (2.4)	0.658

n: Number, %: Percent, COPD: Chronic obstructive pulmonary disease

anticholinergic burden and MNA scores (r=-0.342, p<0.001) suggests a potential mechanism linking medication burden to nutritional decline, a phenomenon not previously explored in COPD populations.

The pattern of medication use across different GOLD stages revealed interesting trends, particularly in cardiovascular medications. The significant increase in furosemide and digoxin use with advancing GOLD stages (p=0.042 and p=0.031, respectively) reflects the growing recognition of cardiopulmonary interactions in COPD. This observation supports recent findings by Rabe et al., who emphasized the importance of considering cardiovascular comorbidities in COPD management (14).

Regarding respiratory medications, our finding of increased theophylline use from GOLD stage 1 (6.5%) to stage 4 (17.1%, p=0.035) raises important considerations about cumulative anticholinergic burden. This trend differs from patterns reported by Maltais et al., who observed lower rates of theophylline use in their cohort, possibly reflecting regional variations in prescribing practices (12).

The high prevalence of cardiovascular comorbidities (45.2%) in our study population adds to the growing body of evidence linking COPD with cardiovascular disease. Cereja et al. recently demonstrated similar patterns of comorbidity burden in elderly COPD patients, although their reported rates were slightly lower (38.6%). This difference might be attributed to variations in study populations and diagnostic criteria.

Our analysis revealed that the relationship between anticholinergic burden and nutritional status remains significant even after adjusting for confounders. This finding builds upon work by Reeve et al., who identified similar associations in general elderly populations but did not specifically examine COPD patients (19). The implications for clinical practice are substantial, suggesting a need for regular medication review and potential deprescribing strategies.

An important aspect of our findings is the progressive increase in anticholinergic burden with advancing GOLD stages. This observation adds a new dimension to the work of Scott et al., who previously documented the challenges of deprescribing in chronic respiratory

conditions (20). Our results suggest that special attention should be paid to medication burden in patients with advanced COPD.

Recent research has provided additional insights into the complex relationships we observed in our study. Rodriguez-Roisin et al. conducted a comprehensive analysis of age-related patterns in COPD management, supporting our findings regarding the demographic profile of patients with significant medication burden (21). Their multicenter study involving 2,845 patients demonstrated similar age distributions and polypharmacy patterns, lending external validity to our observations.

The impact of multiple medication use on COPD outcomes has been further elucidated by Wedzicha et al., who conducted a prospective cohort study of 1,750 COPD patients (22). Their findings revealed that patients with high medication burden experienced more frequent exacerbations (rate ratio 1.42, 95% CI 1.21-1.67) and poorer quality of life scores, particularly in those with concurrent anticholinergic use. This aligns with our observations regarding the relationship between medication burden and clinical outcomes.

Martinez et al. recently published findings from their longitudinal study of nutritional status in COPD, demonstrating that poor nutritional parameters were associated with accelerated decline in lung function (FEV1 decline rate: -48mL/year vs -35mL/year in well-nourished patients, $p<0.001$) (23). Their work provides important context for our findings regarding the relationship between nutritional status and disease severity. Particularly noteworthy was their observation that nutritional intervention had the greatest impact in patients with high medication burden, suggesting a potential therapeutic approach for our patient population.

The implications of our findings regarding bronchodilator use patterns are supported by recent guidelines from Calverley et al. (24). Their expert panel review emphasized the importance of considering cumulative anticholinergic effects when prescribing additional bronchodilators, particularly in elderly patients with multiple medications. This guidance provides a framework for interpreting our observations regarding increasing medication burden across GOLD stages and suggests potential strategies for medication optimization in clinical practice.

These recent studies collectively strengthen our findings and provide additional context for understanding the complex relationships between anticholinergic burden, nutritional status, and clinical outcomes in COPD patients. They also suggest potential directions for future research, particularly in developing targeted interventions for patients with high medication burden and poor nutritional status.

Our study has several limitations that should be considered. First, its cross-sectional design prevents the establishment of causal relationships. Second, being a single-center study may limit the generalizability of our findings. Third, seasonal variations in COPD symptoms and medication use were not accounted for in our analysis. Finally, while we used standardized scales for anticholinergic burden assessment, individual patient sensitivity to anticholinergic effects may vary.

The findings of our study suggest that healthcare providers should regularly assess both anticholinergic burden and nutritional status in COPD patients, particularly in those with advanced disease or multiple comorbidities. Implementation of systematic medication reviews and consideration of deprescribing strategies may help reduce anticholinergic burden while maintaining effective disease management. Future research should focus on developing interventional strategies to optimize medication regimens in this vulnerable patient population.

Acknowledgement

The authors would like to thank the nursing staff of the Pulmonology Department at Bezmialem Vakif University Hospital for their assistance in data collection. Special thanks to all the patients who participated in this study.

Conflict of interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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