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The association between polypharmacy, anticholinergic burden, comorbidities, and hospital length of stay in geriatric patients

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Abstract

We aimed to evaluate the association between polypharmacy, anticholinergic burden, comorbidities, and hospital length of stay in older adults. We analyzed 213 older in-patient data retrospectively. Demographic data, comorbidities, length of stay, medication use, and laboratory results at admission were extracted from electronic medical records. We used a calculator to work out Anticholinergic Burden (ACB). The use of five or more drugs was considered polypharmacy. The mean age was 78±7.3 years; 54.5% of patients were female. The mean length of stay of patients was 20.7±13.8 days. The prevalence of polypharmacy was 66.2% (n:141), and 182 (85.4%) of the patients were treated with anticholinergic medications. 52.6% had high ACB scores (ACB score 3 and more). The most used drugs with anticholinergic potential were metoprolol (40.4%) and metformin (32.4%). Polypharmacy was identified as a risk factor for the presence of high ACB with 86% sensitivity and 55% specificity. (OR 0.758 95% CI: 0.692-0.824, p: <0.001). High ACB score was an independent risk factor for the presence of length of stay (OR: 1.19, 95% CI: 1.10-1.29, p: <0.001), diabetes mellitus (OR: 3.15, 95% CI: 1.08-9.18, p=0.035), coronary artery disease (OR: 5.32, 95% CI: 1.65-17.11, p=0.005), atrial fibrillation (OR: 4.94, 95% CI: 1.30-18.83, p=0.019), depression (OR: 10.96, 95% CI: 3.28-36.58, p: <0.001), psychotic disorder (OR: 80.53, 95% CI: 4.72-1372.05, p=0.002), Parkinson's disease (OR: 3.65, 95% CI: 1.21-11.01, p=0.021), and rheumatological illness (OR: 5.89, 95% CI: 1.20-28.97, p=0.029). Polypharmacy, length of stay, and comorbidities such as cardiometabolic diseases (diabetes mellitus, coronary artery disease, atrial fibrillation), psychiatric and neurological disorders (depression, psychotic disorder, Parkinson's), and rheumatological illness are significantly associated with ACB. It is crucial to be aware of the ACB for rational drug use and optimum treatment of comorbidities to prevent adverse outcomes in older patients.

Keywords: Anticholinergic burden score, polypharmacy, comorbidities, length of stay, older adults

Introduction

The geriatric population is increasing worldwide [1]. With the increase in the aging population and comorbid conditions, using multiple drugs, defined as polypharmacy, is becoming a current issue [2]. Older adults have a high incidence of polypharmacy, a geriatric syndrome, and many of these drugs have anticholinergic effects. As a result of the anticholinergic effect, symptoms such as constipation, blurred vision, urinary retention, and balance disorder may occur [3]. It is well known that these side effects increase in older age. At the same time, it is associated with cognitive impairment, falls, frailty, morbidity, and mortality [4-6]. These increased side effects in older adults are thought to be related with reduction in cholinergic activity in the brain, decreasing in hepatic metabolism and kidney functions, and increasing in blood-brain barrier permeability by

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aging [7]. Exposure to anticholinergic agents increases getting older [8]. Anticholinergic Burden Score (ACB) scales were developed to identify drugs with anticholinergic activity to detect current risks [9]. There are some scales developed to calculate the ADB. Some of them are Anticholinergic Activity Scale (AAS); Anticholinergic Burden Classification (ABC) scale; Anticholinergic Cognitive Burden (ACB) scale; Anticholinergic Drug Scale (ADS) [10].

Some previous studies have addressed associations between anticholinergic and sedative drugs and hospitalizations. Anticholinergic drug load was significantly associated with age, comorbidities, and polypharmacy in hospitalized geriatric patients [11,12]. In another study conducted on hospitalized geriatric patients, a high ACB score was related to increased 1-year mortality in geriatric patients after discharge [13].

In this study, we aimed to investigate the association between the anticholinergic drug burden, polypharmacy, comorbidities, and length of stay in the geriatric clinic of our hospital. More studies are needed to examine various aspects of anticholinergic drugs.

Material and Metods

We retrospectively evaluated the data from hospitalized patients over the age of 65 in the Istanbul University-Cerrahpasa inpatient unit between March 2021 to January 2023. We excluded patients with incomplete data (n:10) and under age 65 (n:16). Overall, 213 patients were included in the study. Demographic features, comorbidities, length of stay, medication use, and laboratory results at admission were obtained from electronic medical records. Polypharmacy was accepted as the use of 5 or more medications [14]. We used a calculator, a combination of the German Anticholinergic Burden scores and the Anticholinergic Cognitive Burden Scale, to work out the ACB for patients. In this calculator, the anticholinergic effects of drugs are on a score of 0 to 3. Drugs with no known anticholinergic activity are given a score of 0; drugs with potential anticholinergic effects based on receptor binding studies are given a score of 1, drugs with reported anticholinergic adverse events, usually in overdoses, are given a score of 2; and drugs with profound anticholinergic properties are given a score of 3. A score of 3 and more is defined as high risk [15,16].

Ethical approval was obtained from the ethics committee of Istanbul Cerrahpasa University Faculty of Medicine (Ethics committee number: 672244-25.04.2023) for the study.

Statistical analysis

We analyzed data by package program called SPSS for Windows, v21.0; IBM Corp. Armonk, NY, USA. Data were shown as mean and standard deviation (SD) for continuous variables and counts and frequencies for categorical variables. The chi-square test or Fisher's exact test was used for the comparison of categorical variables between the groups. Student's t-test for normally distributed and Mann-Whitney U test for non-normally distributed were used to compare differences in continuous variables between the two groups. Pearson correlation analysis was performed between the Anticholinergic Burden Score and associated parameters. Multivariable regression modeling was used to explore independent risk factors for ACB score. Receiver Operating Characteristic (ROC) curve analysis was performed to show the relationship between the number of drugs and the ACB score. A p value less than 0.05 was considered statistically significant.

Results

Of the 213 hospitalized patients over 65, they were mainly female (54.5%), the mean age was 78±7.3, and the mean length of stay was 20.7±13.8 days. The mean number of chronic disease was 3.8±2.1. The most prevalent comorbidities were hypertension (80.3%) and diabetes mellitus (49.3%). The mean number of drugs was 6.5±3.9. The prevalence of polypharmacy was 66.2% (n:141). The mean ACB score of the patients was 3.4±2.6. Eighty-five percent of the patients were treated with drugs with anticholinergic effects (n:182). Of these, 112 (52.6%) had high ACB scores (ACB score 3 and above).

The baseline characteristics of the patients according to the ACB score are shown in Table 1. Patients with higher ACB scores were older (mean age: 78.1±7.3). Length of stay in hospital, the number of chronic diease, the number of drugs was significantly associated with higher ACB score ($p<0.001$, for all). Patients with higher ACB scores had more prevalence of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, atrial fibrillation, cognitive impairment, depression, psychotic disorder, Parkinson's disease, rheumatological illness, malignancy, and urinary incontinence when compared with those not. Among these comorbidities, diabetes mellitus, hyperlipidemia, coronary artery disease, depression, psychotic disorder, and urinary incontinence were strongly significantly associated with higher ACB scores ($p<0.001$ for all).

The correlation analysis between the Anticholinergic Burden Score and associated parameters is given in Table 2. There was a strong correlation between ACB score with hospital length of stay, number of chronic diseases, and number of drugs ($p<0.001$, for all).

The top 10 most commonly used anticholinergic drugs in hospitalized patients are shown in Table 3, respectively. The three most commonly used drugs with anticholinergic potential were metoprolol (n: 86), metformin (n: 69), and furosemide (n: 50). Among the drugs with high anticholinergic potential (ACB score 3≤), quetiapine 20, olanzapine 8, solifenacin 8, propiverine 4, fesoterodine 4, tolterodine 4, trospium 3, paroxetine 2, trifluoperazine 1, clozapine 1, darifenacin 1 were used regularly by the patient.

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Table 1. Demographic and clinical characteristics of the patients according to the anticholinergic burden score

Characteristics	Low risk (ACB score 0-2) (n=101)	High risk (ACB score 3≤) (n=112)	p value
Age (years), mean±SD	77.9±7.4	78.1±7.3	0.816
Age, n (%)			
65-74	32 (47.1%)	36 (52.9%)	0.966
75-84	44 (46.8%)	50 (53.2%)	
≥85	25 (49.0%)	26 (51.0%)	
Hospital length of stay, days, mean±SD	12.6±5.8	28.2±14.8	**<0.001**
Gender, n (%)			
Female	53 (45.7%)	63 (54.3%)	0.581
Male	48 (49.5%)	49 (50.5%)	
The number of chronic diseases, n (%)			
1	56 (87.5%)	8 (12.5%)	**<0.001**
2	41 (39.8%)	62 (60.2%)	
3≤	4 (8.7%)	42 (91.3%)	
The number of drugs, n (%)			
<5	56 (77.8%)	16 (22.2%)	**<0.001**
5≤	45 (31.9%)	96 (68.1%)	
The number of drugs, mean±SD	4.8±3.5	8.0±3.5	**<0.001**
Comorbidity, n (%)			
Hypertension	72 (42.1%)	99 (57.9%)	**0.002**
Diabetes mellitus	35 (33.3%)	70 (66.7%)	**<0.001**
Hyperlipidemia	13 (24.5%)	40 (75.5%)	**<0.001**
Coronary artery disease	19 (26.0%)	54 (74.0%)	**<0.001**
Congestive heart failure	13 (27.1%)	35 (72.9%)	**0.001**
Atrial fibrillation	16 (30.2%)	37 (69.8%)	**0.004**
Chronic kidney disease	18 (40.0%)	27 (60.0%)	0.262
Cognitive impairment	13 (32.5%)	27 (67.5%)	**0.036**
Depression	15 (18.8%)	65 (81.3%)	**<0.001**
Psychotic disorder	0 (0%)	21 (100%)	**<0.001**
Parkinson's disease	3 (20.0%)	12 (80.0%)	**0.027**
Cerebrovascular disease	9 (33.3%)	18 (66.7%)	0.117
Chronic obstructive pulmonary disease	20 (37.7%)	33 (62.3%)	0.103
Thyroid disease	5 (35.7%)	9 (64.3%)	0.364
Rheumatological illness	5 (23.8%)	16 (76.2%)	**0.022**
Malignancy	7 (26.9%)	19 (73.1%)	**0.026**
Urinary incontinance, n(%)	6 (16.7%)	30 (83.3%)	**<0.001**
Laboratory results at admission, mean±SD			
Wbc	7.6±2.9	7.4±2.6	0.586
Hgb (g/dL)	11.1±2.1	10.7±1.6	0.097
Serum urea (mg/dL)	46.6±23.2	51.7±26.1	0.140
Serum creatinine (mg/dL)	1.07±0.52	1.06±0.57	0.575
ALT	19.6±25.6	18.8±21.8	0.793
AST	23.4±15.4	24.2±25.4	0.778
CRP	27.4±41.4	23.9±35.1	0.507

Significant p values are bolded. p<0.05 was considered statistically significant
ACB: anticholinergic burden, Wbc: white blood count, Hgb: hemoglobin, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C-reactive protein

Table 2. Correlation between Anticholinergic Burden Score and associated parameters

	ACB score	
	r	**p**
Age	-0.038	0.580
Hospital length of stay	**0.585**	**<0.001**
Number of chronic diseases	**0.573**	**<0.001**
Number of drugs	**0.524**	**<0.001**

Significant p values are bolded. p<0.05 was considered statistically significant

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Table 3. The top 10 most commonly used anticholinergic drugs in hospitalized patients

Drugs	ACB score	Risk	Number of patients using these drug	%
Metoprolol	1	Low	86	40.4
Metformin	1	Low	69	32.4
Furosemide	1	Low	50	23.5
Ipratropium	1	Low	36	16.9
Escitalopram	1	Low	26	12.2
Lansoprazole	1	Low	22	10.3
Isosorbide mononitrate	1	Low	21	9.9
Quetiapine	3	High	20	9.4
Sertraline	1	Low	19	8.9
Warfarin	1	Low	16	7.5

The multivariate regression analysis of associated risk factors for ACB Score was perfomed in Table 4. We showed that hospital length of stay (OR: 1.19, 95% CI: 1.10-1.29, p: <0.001), diabetes mellitus (OR: 3.15, 95% CI: 1.08-9.18, p=0.035), coronary artery disease (OR: 5.32, 95% CI: 1.65-17.11, p=0.005), atrial fibrillation (OR: 4.94, 95% CI: 1.30-18.83, p=0.019), depression (OR: 10.96, 95% CI: 3.28-36.58, p: <0.001), psychotic disorder (OR: 80.53, 95% CI: 4.72-1372.05, p=0.002), parkinson's disease (OR: 3.65, 95% CI: 1.21-11.01, p=0.021), and rheumatological illness (OR: 5.89, 95% CI: 1.20-28.97, p=0.029) were independently associated with ACB score.

Table 4. Multivariate regression analysis of associated risk factors for ACB score

	Odds ratio (95% CI)	p value
Age	0.97 (0.91-1.05)	0.585
Hospital length of stay	1.19 (1.10-1.29)	**<0.001**
Hypertension	1.16 (0.31-4.34)	0.825
Diabetes mellitus	3.15 (1.08-9.18)	**0.035**
Hyperlipidemia	1.55 (0.42-5.65)	0.505
Coronary artery disease	5.32 (1.65-17.11)	**0.005**
Congestive heart failure	2.31 (0.65-8.17)	0.193
Atrial fibrillation	4.94 (1.30-18.83)	**0.019**
Cognitive impairment	0.44 (0.10-1.92)	0.277
Depression	10.96 (3.28-36.58)	**<0.001**
Psychotic disorder	80.53 (4.72-1372.05)	**0.002**
Parkinson's disease	3.65 (1.21-11.01)	**0.021**
Rheumatological illness	5.89 (1.20-28.97)	**0.029**
Malignancy	4.53 (0.80-25.64)	0.087
Urinary incontinance	2.87 (0.59-13.81)	0.188

Significant p values are bolded. p<0.05 was considered statistically significant
ACB: anticholinergic burden

The relationship between hospital length of stay and ACB score is shown in Figure 1. In addition, the ROC analysis shows the relationship between the number of drugs and the ACB score in Figure 2. The cut-off point for polypharmacy was determined to be five drugs, with 86% sensitivity and 55% specificity. The area under the curve was 0.758 (p: <0.001, 95% confidence interval (CI): 0.692-0.824).

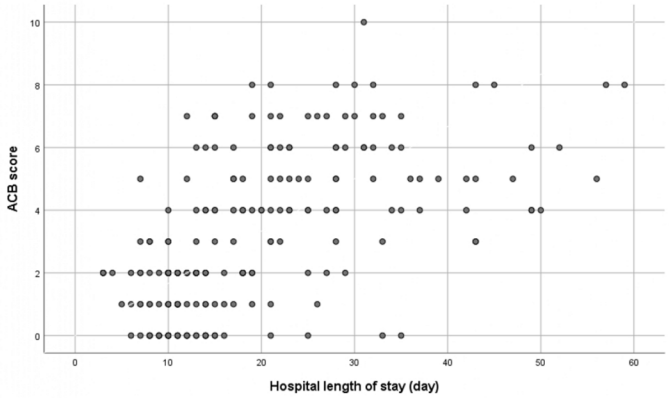

Figure 1. The relationship between hospital length of stay and ACB score

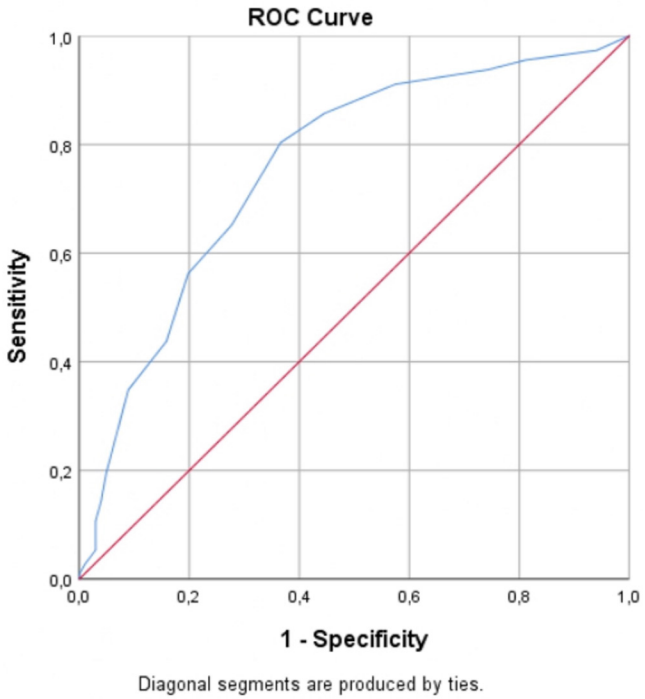

Figure 2. ROC (receiver operating characteristic) curve based on a univariate model showing the number of drugs used to predict patients' risk of high anticholinergic burden. The area under the curve was 0.758 (P<0.001, 95% CI: 0.692-0.824), with a sensitivity of 86%, specificity of 55%

Discussion

In the present study, we revealed the highest relationship between anticholinergic burden score and polypharmacy, comorbidities, and hospital stay length in geriatric patients.

As a known geriatric syndrome, polypharmacy is closely related to many geriatric syndromes like falls, cognitive impairment, functional decline, urinary incontinence, and hospitalization [17]. Polypharmacy is prevalent in older ambulatory care, hospital, and nursing home patients. Our study identified polypharmacy, the use of 5 or more medications, as a risk factor for increased anticholinergic burden, and that is well-known both conditions are related to the negative health outcomes of older adults [18-21].

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Most older people are exposed to medications with anticholinergic effects with multiple comorbidities. As we demonstrated, patients with many chronic conditions were exposed to ACB. Patients with psychiatric and neurological disorders, urinary incontinence, cardiovascular disease, and rheumatological diseases are high-risk groups exposed to anticholinergic medications. Multiple chronic diseases are a risk factor for anticholinergic medications and polypharmacy [22]. Similarly, Jun K et al. found that older age, female gender, polypharmacy, and comorbidities such as depression, schizophrenia, Parkinson's disease, and urinary incontinence were associated with high ACB [23]. Oral antipsychotics, antidepressants, and drugs for treating urinary incontinence have higher anticholinergic effects. For example, quetiapine, olanzapine, clozapine, paroxetine, darifenacin, trospium, tolterodine, solifenacin, propiverine, fesoterodine were reported as having high anticholinergic activity. We checked these drugs use among our patients, and they were at high risk because of increased over treatment. The ACB score in patients with depression, psychotic disorders, and urinary incontinence was significantly higher. In regression analysis, depression and psychotic disorders were independently associated with ACB.

As known, a high proportion of Parkinson's patients are at high risk because of treated with antiparkinsonian, urological, antipsychotic, and anticholinergic medications. In a study, the prevalence of taking medications with anticholinergic properties was 31.5 to 53.63% in Parkinson's patients [24]. In our present study, the ACB score in Parkinson's patients was significantly high, and a high proportion of Parkinson's (80%) were at increased risk.

Although these drugs have low-risk anticholinergic effects and concomitant use due to multimorbidity, we found a significant association between diabetes mellitus, coronary artery disease, atrial fibrillation, and ACB score because of over-treatment with metoprolol, metformin, nitrate, and warfarin drugs, among the top 10 most commonly used anticholinergic drugs in patients.

Most patients with rheumatological illness are managed with cholinergic antagonist drugs, prednisolone, codeine, and/or combinations. In a study, 5.7% of patients with sjögren syndrome were found to receive prednisolone [25]. Similarly, we found that seven percent of patients were treated with prednisolone.

In present study, there was an increasing analgesic use in older patients. It was found that 15 percent of the patients used regular analgesics, including fentanyl (n:15), tramadol (n:7), oxycodone (n:6), and morphine (n:4). We can attribute this result to our patients' high prevalence of cancer (12.2%) and rheumatological illness (9.9%). In older patients with cancer, high ACB indicated worsening clinical outcomes and high mortality [26].

High scores of Anticholinergic burden were a risk factor for long hospitalization. In the literature, some studies found that ACB was associated with an increased hospital stay in older adults [27,28]. Our present study confirmed these findings.

The strength of our study is that it is a rare study to assess the relationship between ACB and length of hospital stay. We suggest that ACB may be a risk factor for the length of hospital stay in the geriatric population. Multicomorbidities are especially associated with ACB. Moreover, we highlight that it is crucial to be aware of the anticholinergic burden for rational drug use and optimum treatment of comorbidities to prevent adverse outcomes in older adults.

This study has several limitations. Falls, delirium, geriatric evaluation tests could not be extracted from the patient's files.

Conclusion

Our study has identified that polypharmacy, hospital length of stay and comorbidities such as cardiometabolic diseases (diabetes mellitus, coronary artery disease, atrial fibrillation), psychiatric and neurological disorders (depression, psychotic disorder, Parkinson's disease), and rheumatological illness are significantly associated with the anticholinergic burden. We demostrated polypharmacy, the use of 5 or more medications, as a risk factor for high ACB, and that is well-known both conditions are related to the adverse health outcomes of older adults. It is crucial to be aware of the ACB for rational drug use and optimum treatment of comorbidities to prevent adverse outcomes in older patients.

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

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
Ethical approval was obtained from the ethics committee of Istanbul Cerrahpasa University Faculty of Medicine (Ethics committee number: 672244-25.04.2023) for the study.

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