Fırat Tıp Dergisi 2026; 31(3): 241-245
Firat Med J 2026; 31(3): 241-245

RESEARCH ARTICLE

Does the History of Systemic Antihistamine and Nasal Steroid Use Have an Impact on the Severity of Covid-19?

Sistemik Antihistaminik ve Nazal Steroid Kullanım Öyküsünün Covid-19 Hastalık Şiddeti Üzerinde Etkisi Var mı?

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ABSTRACT

Objective: We aimed to investigate whether the usage history of systemic antihistamines, leukotriene antagonists, and nasal steroids before Covid-19 has an impact on the severity of the disease in patients with Covid-19.

Material and Method: This study was conducted by retrospectively scanning the data of 1592 patients between the ages of 18 and 65 who applied to Izmir Bakircay University Cigli Training and Research Hospital and were diagnosed with Covid-19.

Results: Of comorbid diseases, diabetes mellitus, chronic heart failure, coronary artery disease, hypothyroidism, and hypertension were observed significantly more in the severe disease group than in the mild disease group. Diabetes mellitus and hypertension were observed significantly more in the intensive care and died group. No relationship was found between the usage history of drugs, which was examined in our study, and the severity of the disease, intensive care need, or mortality rates.

Conclusion: Our study is one of the most comprehensive clinical studies conducted on the impact of usage history of antihistamines, leukotriene antagonists, and intranasal steroids on the course of Covid-19 disease. We found that the usage history of all these drugs has no impact on the course of Covid-19 disease, the need for intensive care, or mortality rates.

Keywords: Antihistamine, Intranasal Steroid, Leukotriene Antagonist, Covid-19, Severity.

ÖZET

Amaç: Covid-19 hastalığı öncesinde sistemik antihistaminik, lökotrien antagonisti ve nazal steroid tedavisi alma öyküsünün Covid-19 hastalarında hastalığın şiddeti üzerinde bir etkisi olup olmadığını araştırmayı amaçladık.

Gereç ve Yöntem: Bu çalışma, İzmir Bakırçay Üniversitesi Çiğli Eğitim ve Araştırma Hastanesi'ne başvuran ve Covid-19 tanısı konulan 18-65 yaş aralığındaki 1592 hastanın verilerinin retrospektif olarak taranmasıyla yürütüldü.

Bulgular: Eşlik eden hastalıklardan diabetes mellitus, kronik kalp yetmezliği, koroner arter hastalığı, hipotiroidizm ve hipertansiyon, Covid-19 şiddetli hastalık grubunda hafif hastalık geçiren gruba göre anlamlı olarak daha fazla gözlendi. Diabetes mellitus ve hipertansiyon, yoğun bakıma yatan hasta grubunda ve ölen hastalarda anlamlı olarak daha fazla gözlendi. Çalışmamızda incelenen ilaçların kullanım geçmişi ile hastalığın şiddeti, yoğun bakım ihtiyacı veya ölüm oranları arasında bir ilişki bulunmadı.

Sonuç: Çalışmamız, antihistaminikler, lökotrien antagonistleri ve intranazal steroidlerin kullanım geçmişinin Covid-19 hastalığının seyri üzerindeki etkisine ilişkin yürütülen en kapsamlı klinik çalışmalardan biridir. Tüm bu ilaçların kullanım geçmişinin Covid-19 hastalığının seyri, yoğun bakım ihtiyacı veya ölüm oranları üzerinde bir etkisi olmadığını bulduk.

Anahtar Sözcükler: Antihistaminik, İntranazal Steroid, Lökotrien Antagonisti, Covid-19, Şiddet.

Coronavirus disease (Covid-19) which is caused by Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2), emerged in Wuhan, China, in December 2019 and spread all over the world and

Gönderim Tarihi: 15.04.2025
Kabul Tarihi: 21.04.2025

became a pandemic(1). The virus attaches to the angiotensin converting enzyme 2 (ACE-2) receptor and infects the airway epithelium and endothelial cells(2). Covid-19 is not a simple respiratory tract disease, it causes deaths by causing acute respiratory distress syndrome (ARDS). The disease has a more severe course in older ages and in the presence of comorbidities(3). Cytokine storm with an uncontrolled inflammatory response of cells that are involved in the immune system is the most important cause of ARDS. T cells, macrophages, neutrophils, natural killers and mast cells - in other words, almost all immune response cells play a significant role in this uncontrolled inflammation in the development of ARDS. As a result of these uncontrolled cytokine storm, vital organs such as the lungs, heart and kidneys are damaged, and the direct cause of death is multiple organ failure(4).

Histamine is a molecule that plays an important role in immune response. The H1 receptor, one of the four G protein-dependent sub-receptors of histamine (H1R, H2R, H3R, H4R) plays a role in allergic reactions and inflammatory response. H2R plays a role in acid release in gastric mucosa. H3R is expressed in the central nervous system and plays a role in neurotransmitter regulation. H4R is related with in innate and adaptive immune response. H1 receptor is found in a wide variety of cells such as endothelium, muscle cells, monocytes, macrophages, neutrophils, and T cells. Immune response develops as a result of the increase in cytokine levels with the H1 receptor stimulation(5).

Leukotrienes are produced by mast cells, macrophages, and eosinophils, and they are also involved in allergic and immune response reactions. Leukotriene receptor antagonists and antihistamines are molecules that suppress this allergic reaction and immune responses(6). In a recent study that examined the molecular pathogenesis of Covid-19, it is recommended to try the use of leukotriene receptor antagonists to prevent the cytokine storm seen in severe disease(7). Nasal steroids also have a topical effect on the nasal mucosa and inhibit the immune response(8).

Antiviral efficacy of H1R antagonists against Sars-CoV-2 has been demonstrated in in vitro studies(9, 10). In addition, there are clinical studies showing that H1R and H2R antagonist treatment reduces the severity of Covid-19 disease and has positive results in the treatment of cytokine storm(11, 12).

In the light of these findings, we aimed to investigate whether the usage history of systemic antihistamines, leukotriene antagonists and nasal steroids before Covid-19 has an impact on the severity of the disease in patients with Covid-19.

MATERIAL AND METHOD

This study was conducted by retrospectively scanning the data of 1592 patients between the ages 18-65 who applied to Izmir Bakircay University Cigli Training and Research Hospital and were diagnosed with Covid-19 via real-time PCR tests on oropharyngeal and nasopharyngeal swabs. Ethical approval was obtained from the Izmir Bakircay University Ethics Committee(29.01.2021/156). Hospitalized patients were classified as severe, and patients who were outpatient or asymptomatic were classified as mild. After this classification, the demographic distribution of the patients, usage history of antihistamine, leukotriene antagonist or nasal steroid drugs, and comorbid diseases were investigated. All medications evaluated in this study (systemic antihistamines, leukotriene antagonists, and intranasal steroids) had been prescribed for pre-existing allergic conditions such as allergic rhinitis or asthma and were being used prior to the diagnosis of Covid-19. None of the patients in the cohort received these medications for the treatment of Covid-19. Patients were included in the study if they had used the relevant treatments intermittently or regularly during the three months preceding their Covid-19 diagnosis. The study population was categorized as follows: patients with milder allergic symptoms who were using antihistamines alone; patients with more severe allergic symptoms who were using a combination of antihistamines and montelukast; and patients presenting with mild rhinitis and nasal congestion who were using intranasal steroids. To prevent overlap between groups and to allow an accurate assessment of the differential effects of topical and systemic therapies, individuals who were using both antihistamines and intranasal steroids were excluded from the analysis.

In addition, patients who needed intensive care, recovered or died as a result of Covid-19 were examined in terms of all these parameters.

Statistical analyses

Data were analyzed using the SPSS version 21.0 software program (Statistical Package for Social Sciences v.21, IBM, Chicago, IL). The age of data was checked by the Shapiro-Wilk test for normal distributions and by the Levene test for homogeneity of variance. The Pearson Chi-Square test was used to investigate the association between categorical variables. The Student's t test was used to compare the age variables between groups. A p value < 0.05 was considered statistically significant.

RESULTS

In this study, there were 1592 patients who had Covid-19 via real-time PCR tests on oropharyngeal and nasopharyngeal swabs. The mean age of the

patients was found to be 48.91±11.63 (18-65) years. When the participants of the study are grouped as mild disease and severe disease, demographic distribution, comorbid diseases, and the presence of antihistamine use of the groups are shown in table 1.

Table 1. Characteristics of the patients in mild disease group and severe disease group.

	Mild disease	Severe disease	p value
Age, years, mean±SD	47.51±12.50	50.96±9.89	**<0.001**★
Sex			
Female, n	491	338	0.911★★
Male, n	454	309	
Comorbid diseases, n(%)			
Diabetes mellitus	208 (22%)	278 (43%)	**<0.001**★★
Chronic heart failure	10 (1.1%)	18 (2.8%)	**0.010**★★
Coronary artery disease	47 (5%)	52 (8%)	**0.013**★★
Hypothyroidism	57 (6%)	70 (10.8%)	**0.001**★★
Hypertansion disease	210 (22.2%)	263 (40.6%)	**<0.001**★★
Asthma	79 (8.4%)	49 (7.6%)	0. 571★★
Allergic rhinitis	95 (10.1%)	57 (8.8%)	0. 407★★
Drug uses			
Antihistamine use, n(%)	150 (%15.9)	90 (13.9)	0.282★★
Antihistamine+Montelukast use, n(%)	70 (7.4%)	40 (6.2%)	0.344★★
Nasal steroid spreys use, n(%)	56 (5.9%)	34 (5.3%)	0.569★★

★Student t test, ★★Pearson Chi-Square test, SD: standart deviation.

The mean age was significantly greater in the severe group than in the mild disease group. There was no difference between the groups in terms of the gender. Of comorbid diseases, diabetes mellitus, chronic heart failure, coronary artery disease, hypothyroidism, and hypertension were observed significantly more in the severe disease group than in the mild disease group. While there was no difference between the two groups in terms of asthma and allergic rhinitis, there was also no difference between the two groups in terms of antihistamine and nasal steroid use.

Table 2 demonstrates the demographic distribution, comorbid diseases, and presence of antihistamine use of the groups when the participants of the study are grouped by intensive care needs.

Table 2. Characteristics of the patients in terms of the need for intensive care unit care.

	Patients that did not need intensive care	Patients needed intensive care	p value
Age, years, mean±SD	48.74±11.75	52.18±8.25	**0.001**★
Sex			
Female, n	784	45	0.443★★
Male, n	728	35	
Comorbid diseases, n(%)			
Diabetes mellitus	438 (29%)	48 (60%)	**<0.001**★★
Chronic heart failure	25 (1.7%)	3 (3.8%)	0.164★★
Coronary artery disease	90 (6%)	9 (11.3%)	0.056★★
Hypothyroidism	120 (7.9%)	7 (8.8%)	0.794★★
Hypertansion disease	440 (29.1%)	33 (41.3%)	**0.020**★★
Asthma	125 (8.3%)	3 (3.8%)	0.148★★
Allergic rhinitis	142 (9.4%)	10 (12.5%)	0.357★★
Drug uses			
Antihistamine use, n(%)	228 (15.1%)	12 (15%)	0.985★★
Antihistamine+Montelukast use, n(%)	105 (6.9%)	5 (6.3%)	0.811★★
Nasal steroid spreys use, n(%)	87 (5.8%)	3 (3.8%)	0.449★★

★Student t test, ★★Pearson Chi-Square test, SD: standart deviation.

Mean age was significantly greater in the group that needed intensive care. There was no difference between the groups in terms of the gender. Of comorbid diseases, diabetes mellitus and hypertension

were observed significantly more in the intensive care unit group. There was no difference between the two groups in terms of chronic heart failure, coronary artery disease, hypothyroidism, asthma, and allergic rhinitis. There was no difference between the two groups in terms of antihistamine and nasal steroid use.

When the participants of the study are grouped as discharged or died, the demographic distribution, comorbid diseases, and presence of antihistamine use of the groups are shown in table 3.

Table 3. Characteristics of the patients in discharged and died group.

	Discharged group	Died group	p value
Age, years, mean±SD	48.68±11.67	57.73±4.68	**<0.001**★
Sex			
Female, n	804	25	0.248★★
Male, n	747	16	
Comorbid diseases, n(%)			
Diabetes mellitus	455 (29.3%)	31 (75.6%)	**<0.001**★★
Chronic heart failure	26 (1.7%)	2 (4.9%)	0.124★★
Coronary artery disease	96 (6.2%)	3 (7.3%)	0.768★★
Hypothyroidism	123 (7.9%)	4 (9.8%)	0.670★★
Hypertansion disease	450 (29%)	23 (56.1%)	**<0.001**★★
Asthma	126 (8.1%)	2 (4.9%)	0.451★★
Allergic rhinitis	145 (9.3%)	7 (17.1%)	0.097★★
Drug uses			
Antihistamine use, n(%)	233 (15%)	7 (17.1%)	0.717★★
Antihistamine+Montelukast use, n(%)	106 (6.8%)	4 (9.8%)	0.467★★
Nasal steroid spreys use, n(%)	88 (5.7%)	2 (4.9%)	0.828★★

★Student t test, ★★Pearson Chi-Square test, SD: standart deviation.

Mean age was significantly greater in the died group. There was no difference between the groups in terms of the gender. Diabetes mellitus and hypertension were observed significantly more in the dead group. There was no difference between the two groups in terms of chronic heart failure, coronary artery disease, hypothyroidism, asthma, and allergic rhinitis. There was also no difference between the two groups in terms of antihistamine and nasal steroid use.

DISCUSSION

In this study, there were 1592 patients who had Covid-19 via real-time PCR tests on oropharyngeal and nasopharyngeal swabs. The mean age of the patients was found to be 48.91±11.63 (18-65) years. When the participants of the study are grouped as mild disease and severe disease, demographic distribution, comorbid diseases, and the presence of antihistamine use of the groups are shown in Table 1. The mean age was significantly greater in the severe group than in the mild disease group. There was no difference between the groups in terms of the gender. Of comorbid diseases, diabetes mellitus, chronic heart failure, coronary artery disease, hypothyroidism, and hypertension were observed significantly more in the severe disease group than in the mild disease group. While there was no difference between the two groups in terms of asthma and allergic rhinitis, there was also no difference between the two groups in terms of antihistamine and nasal steroid use.

Table 2 demonstrates the demographic distribution, comorbid diseases, and presence of antihistamine use of the groups when the participants of the study are grouped by intensive care needs. Mean age was significantly greater in the group that needed intensive care. There was no difference between the groups in terms of the gender. Of comorbid diseases, diabetes mellitus and hypertension were observed significantly more in the intensive care unit group. There was no difference between the two groups in terms of chronic heart failure, coronary artery disease, hypothyroidism, asthma, and allergic rhinitis. There was no difference between the two groups in terms of antihistamine and nasal steroid use.

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