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ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

Comparison of hypertension prevalence and the use of renin-angiotensin-aldosterone system blockers in hospitalized patients with COVID-19 and non-COVID-19 viral pneumonia

Hipertansiyon prevalansı ve renin-anjiyotensin-aldosteron sistemi blokerleri kullanımının COVID-19 ve COVID-19 dışı viral pnömoni hastalarında karşılaştırılması

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ABSTRACT

Objective: To compare the prevalence of hypertension and pre-existing use of renin-angiotensin-aldosterone system blockers in patients with coronavirus disease (COVID-19) and non-COVID-19 viral pneumonias.

Methods: Real-time polymerase chain reaction confirmed COVID-19 and non-COVID-19 pneumonia patients were retrospectively analyzed. The presence of hypertension, coronary artery disease (CAD), and pre-existing use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) were compared between the groups.

Results: A total of 103 COVID-19 and 91 non-COVID-19 hospitalized viral pneumonia patients were enrolled. Hypertension and CAD were more common in patients with non-COVID-19 viral pneumonia than in patients with COVID-19 (39.6% vs 22.3%, respectively, p=0.012 and 24.2% vs 4.9%, respectively, p<0.001). In our study, 2.9% and 6.8% of patients with COVID-19 were on ACEIs and ARBs, respectively, whereas 13.2% and 19.8% of patients with non-COVID-19 viral pneumonia were on ACEIs and ARBs, respectively (p=0.009 and p=0.013). Neutrophil-to-lymphocyte ratio (p<0.001) was prominent in patients with non-COVID-19 viral pneumonia compared with patients with COVID-19.

Conclusion: Our study results indicate that hypertension and CAD are more common among patients with non-COVID-19 viral pneumonia than patients with COVID-19. The prevalence of ACEIs and ARBs use was not higher in patients with COVID-19. Our results support that the use of ACEIs and ARBs do not play a specific role in patients with COVID-19.

ÖZET

Amaç: COVID-19 ve COVID-19 dışı viral pnömoni hastalarında hipertansiyon prevalansı ve önceden renin-anjiyotensin-aldosteron blokeri kullanımının karşılaştırılmasıdır.

Yöntemler: Gerçek-zamanlı polimeraz zincir reaksiyonu (RT-PCR) ile doğrulanmış COVID-19 pnömoni hastaları ile COVID-19 dışı viral pnömoni hastaları retrospektif olarak incelendi. Gruplar arasında hipertansiyon ve koroner arter hastalığı (KAH) varlığı ile önceden anjiyotensin dönüştürücü enzim inhibitörü (ADEİ) ve anjiyotensin reseptör blokeri (ARB) kullanımları karşılaştırıldı.

Bulgular: Çalışmaya hastanede yatarak tedavi gören 103 COVID-19 ve 91 COVID-19 dışı viral pnömoni hastası dahil edildi. Hipertansiyon ve KAH, COVID-19 dışı viral pnömoni hastalarında daha sıktı (%39.6'ya karşılık %22.3, sırasıyla, p=0.012 ve %24.2'ye karşılık %4.9, sırasıyla, p<0.001). COVID-19 hastalarının %2.9'u ADEİ ve %6.8'i ARB kullanmaktaydı. Buna karşılık COVID-19 dışı viral pnömoni hastalarının sırasıyla %13.2'si ve %19.8'i ADEİ ve ARB kullanmaktaydı (p=0.009 ve p=0.013). Nötrofil/lenfosit oranı (NLR) COVID-19 dışı viral pnömoni hastalarında belirgin olarak daha yüksekti (p<0.001).

Sonuç: Çalışmamız hipertansiyon ve KAH sıklığının COVID-19 dışı viral pnömonili hastalarında COVID-19 hastalarına kıyasla daha fazla olduğuna işaret etmektedir. COVID-19 hastalarında ADEİ ve ARB kullanım prevalansı COVID-19 dışı pnömonili hastalardan daha yüksek değildi. Çalışmamızın sonuçları ADEİ ve ARB kullanımının COVID-19 hastalarında özel bir rol oynamadığını desteklemektedir.

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Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a single-stranded RNA virus which was first identified in late December, as the cause of a pneumonia outbreak, in Wuhan, China.[1-3] The World Health Organization (WHO) termed the SARS-CoV-2 infection as coronavirus disease (COVID-19) and declared it as pandemic owing to its rapid and global spread on March 11, 2020.[4,5]

Preliminary reports have shown that hypertension, coronary artery disease (CAD), diabetes mellitus (DM), chronic respiratory diseases (i.e. chronic obstructive pulmonary disease [COPD]), and malignancy can be defined as pre-existing comorbidities especially in patients with severe COVID-19 and essential hypertension may be a risk factor for the severity of disease and mortality in hospitalized patients with COVID-19.[6-8] The cell entry mechanism of SARS-CoV-2 requires binding of the viral spike protein to the target cells via angiotensin-converting enzyme 2 (ACE2) receptors expressed by particularly type II alveolar cells in lungs, heart, intestine, kidney, and blood vessels.[9] Therefore, some researchers have postulated that patients with CAD, hypertension, or DM treated with drugs which increase ACE2 receptors, such as angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), are at a higher risk for severe COVID-19 infection.[10,11] However, most recent studies have demonstrated that taking ACEIs/ARBs during the pandemic is not associated with mortality and severity of COVID-19, while hypertension doubles the risk of dying from COVID-19.[12,13]

Nevertheless, it is still unclear whether hypertension and pre-existing use of ACEIs/ARBs is more common among patients with COVID-19 than in patients with non-COVID-19 viral pneumonia. Their association with viral pneumonia caused by agents other than SARS-CoV-2 itself remains to be elucidated. Furthermore, there is no study comparing the prevalence of pre-existing ACEIs/ARBs use among hospitalized patients with COVID-19 and non-COVID-19 viral pneumonia. Therefore, in the present study we aimed to compare the prevalence of hypertension and pre-existing use of ACEIs/ARBs between hospitalized patients with COVID-19 and non-COVID viral pneumonia.

METHODS

Study design and study population

This multi-center, observational, retrospective study was conducted in 4 hospitals in Istanbul. Adult consecutive patients with COVID-19 as confirmed by real-time polymerase chain reaction (RT-PCR) were retrospectively enrolled in the study between March 2020 and April 2020. COVID-19 diagnosis was made according to the WHO interim guidance[14] and confirmed by RT-PCR in the Republic of Turkey, Ministry of Health Clinical Laboratory. Inclusion criteria were as follows: aged 18 years or older, having COVID-19-associated respiratory tract infection (pneumonia), presence of dyspnea, and/or decreased oxygen saturation. Patients under the age of 18 years, with missed medical data, and pregnant patients were excluded. Patients who were receiving antihypertensive therapy with the diagnosis of hypertension at the time of enrollment were accepted as hypertensives. All patients were allowed to receive their medication as previously prescribed, including ACEIs and ARBs, and no adjustment was made in their routine treatment regimens during their hospital stay. Clinical data and laboratory parameters of previously diagnosed (from May 2017 until August 2019) consecutive patients with non-COVID-19 viral pneumonia were used for comparative study. Aforementioned exclusion criteria were also applied to patients with non-COVID-19 pneumonia. The diagnosis of non-COVID-19 viral pneumonia was confirmed by a combination of viral antigen detection tests from nasopharyngeal secretions and thoracic computed tomography (CT) images. Need of mechanical ventilation, septic shock, tachypnea (respiratory rate > 30/min), SpO_2 <90% or <70 mmHg (in room air without response to nasal oxygen up to 12 L/min with reservoir), progressive dyspnea and increased work of breathing, lactate level of >2 mmol/L, hypotension (systolic blood pressure <90 mmHg), and organ dysfunction (confusion, renal failure, liver dysfunction, elevated troponin I) were accepted as criteria for therapy in intensive care unit.[15]

Abbreviations:

ACE2	*Angiotensin-converting enzyme 2*
ACEIs	*Angiotensin converting enzyme inhibitors*
ARBS	*Angiotensin receptor blockers*
CAD	*Coronary artery disease*
CAP	*Community acquired pneumonia*
COPD	*Chronic obstructive pulmonary disease*
COVID-19	*Coronavirus disease 2019*
CRP	*C-reactive protein*
CT	*Computed tomography*
DM	*Diabetes mellitus*
ICU	*Intensive care unit*
NLR	*Neutrophil-to-lymphocyte ratio*
RSV-A	*Respiratory syncytial virus A RT-PCR Real-time polymerase chain reaction*
SARS-CoV-2	*Severe acute respiratory syndrome coronavirus-2*
WHO	*World Health Organization*

Data collection

Demographic data including age and gender; medical history; cigarette smoking; current medications; comorbidities such as hypertension, DM, CAD, or COPD; clinical symptoms (e.g., fever, cough, vomiting or nausea); laboratory parameters (e.g., neutrophil-to-lymphocyte ratio [NLR], C-reactive protein [CRP], and creatinine level); and imaging study findings including chest X-ray and/or thoracic CT were collected and analyzed in a common electronic medical system designed for all participant centers. The time of admission to the intensive care unit (ICU) was also recorded.

Ethical Committee of Acıbadem Mehmet Ali Aydınlar University and the local government health authority (2020-05-02T19_38_13) approved the study protocol (ATADEK 2020-08/27). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

Statistical analyses were performed with the commercially available software SPSS version 25.0 (IBM Corp.; Armonk, NY, USA). Normal and non-normal distributed quantitative variables were compared using the student *t*-test and Mann-Whitney U test. Categorical variables were compared by chi-square test. To verify the association of categorical variables in the study groups, we applied the Pearson's chi-square test or the Fisher's exact test, when the conditions for using the chi-square test were not been verified. Descriptive data were presented as median and interquartile range (IQR, values at the 25th and 75th percentiles were provided) and number and frequency, where applicable. A p value of <0.05 was considered statistically significant. GraphPad Prism software v8.0 (GraphPad Software Incorporation; CA, USA) was used for the figures.

RESULTS

The COVID-19 group was consisted of 103 patients (53 women) with a median age of 45 (IQR, 39 to 52) years. The non-COVID-19 viral pneumonia group was consisted of 91 patients (46 women) with a median age of 42 (IQR, 32 to 58) years. Baseline characteristics of the patients are shown in Table 1. Patients had similar symptoms including fever, cough, dyspnea, nausea, vomiting, and diarrhea in both groups. Smoking status (current and recent cigarette smoking), CAD, COPD, the use of antihypertensive drugs (i.e., ARBs, ACEIs and diuretics), and hypertensive status were significantly different between the groups (p<0.05 for all, respectively) (Table 1 and Figure 1).

Table 1. Baseline demographic and clinical characteristics of patients

Variable	COVID-19 (n=103)	Non-COVID-19 (n=91)	*p*
Age, median (IQR), yr	45 (39-52)	42 (32-58)	0.957
Female gender, n (%)	53 (51.5)	46 (50.5)	>0.999
Comorbidity, n (%)			
DM	6 (5.8)	9 (9.9)	0.420
Hypertension	23 (22.3)	36 (39.6)	0.012
CAD	5 (4.9)	22 (24.2)	<0.001
COPD	5 (4.9)	12 (13.2)	0.036
Smoking status, n (%)			
Current smoker	19 (18.4)	21 (25)	<0.001
Ex-smoker	0 (0)	12 (14.3)	
Symptoms, n (%)			
Fever	85 (82.5)	68 (81.9)	0.999
Cough	79 (76.7)	73 (88)	0.057
Shortness of breath	35 (34)	40 (48.2)	0.053
Fatigue	69 (67)	70 (87.5)	0.002
Myalgia	39 (37.9)	17 (20.5)	0.011
Nausea	5 (4.9)	10 (12)	0.103
Vomiting	11 (10.7)	6 (7.2)	0.455
Diarrhea	7 (6.8)	7 (8.4)	0.782
ICU requirement, n (%)	16 (15.7)	6 (7.3)	0.109
Use of antihypertensive drugs, n (%)			
ARB	7 (6.8)	18 (19.8)	0.009
ACE	3 (2.9)	12 (13.2)	0.013
Beta-blockers	9 (8.7)	6 (6.6)	0.604
Alpha-blockers	1 (1)	3 (3.3)	0.343
Diuretics	2 (1.9)	9 (9.9)	0.026
Calcium channel blockers	7 (6.8)	8 (8.8)	0.789

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; ICU: intensive care unit; IQR: interquartile range (values at 25th and 75th percentiles are presented); yr: years.
In all cases, differences were considered significant at p<0.05.

In our study 2.9% and 6.8% of patients with COVID-19 were on ACEIs and ARBs, respectively. However, ACEIs and ARBs were in use more frequently at statistically significant level among pa-

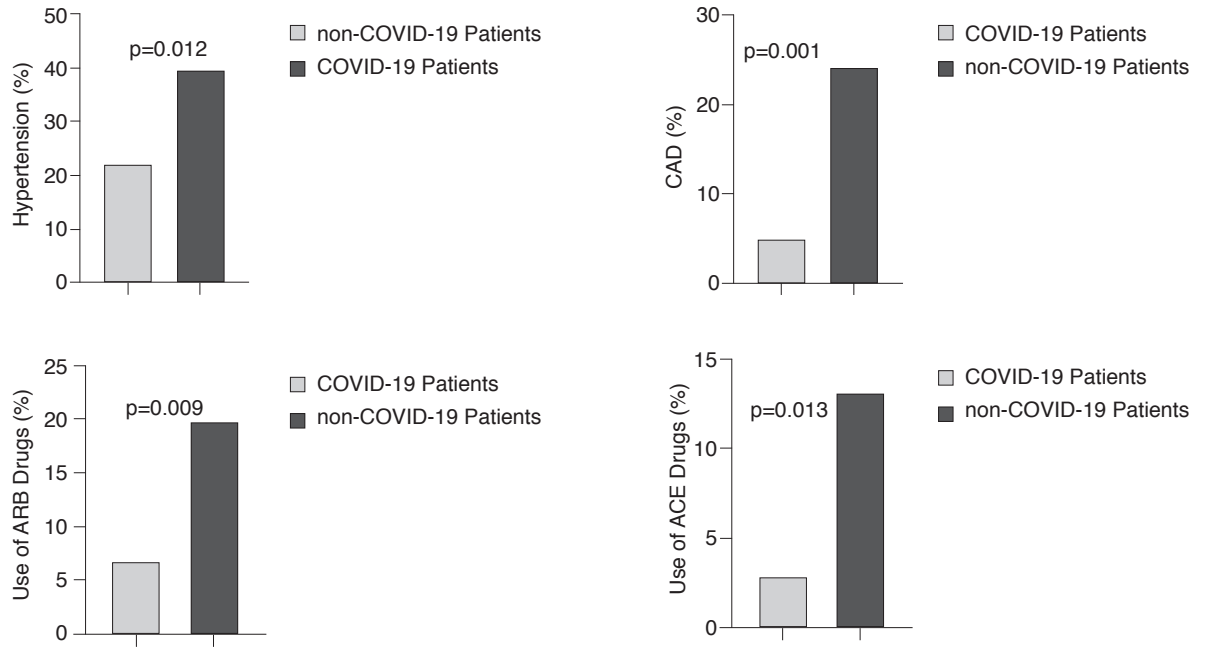

Figure 1. Distribution of comorbidities and use of antihypertensive drugs.
ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blockers; CAD: coronary artery disease. Differences between groups were significant. The values are calculated using chi-square test and the data are given in percentage.

Table 2. Laboratory findings of patients

Variable	COVID-19 (n=103)	Non-COVID-19 (n=91)	*p*
CRP (mg/L) median (IQR)	3.1 (1.9-4.7)	4.1 (2.5-6.4)	<0.001
NLR median (IQR)	3.1 (2.2-4.5)	4.5 (3.1-7.7)	<0.001
ALT (IU/L) median (IQR)	32.5 (26.0-49.2)	28.3 (25.7-49.0)	0.455
AST (IU/L) median (IQR)	28 (23.0-45.0)	31 (25.9-42.3)	0.702
Creatinine (mg/dL) median (IQR)	0.8 (0.6-1.0)	1.1 (0.8-1.5)	<0.001
Sodium (mmol/L) median (IQR)	138 (136-140)	136 (133.2-138.9)	0.005
Potassium (mmol/L) median (IQR)	3.9 (3.7-4.19)	4.1 (3.6-4.4)	0.354

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; IQR: interquartile range (values at the 25th and 75th percentiles are presented); NLR: neutrophil-to-lymphocyte ratio.
In all cases, differences were considered significant at p<0.05.

tients with non-COVID-19 viral pneumonia, whereas 13.2% and 19.8% of patients with non-COVID-19 viral pneumonia were on ACEIs and ARBs, respectively (p=0.009 and p=0.013).

Cigarette smoking (24.4% vs. 12%, respectively, p<0.001) and ICU requirement (7.3% vs. 22.4%, respectively, p=0.044) were significantly different between male patients with non-COVID-19 pneumonia and COVID-19.

The laboratory parameters of the groups are shown in Table 2. We found that CRP levels, creatinine levels, and NLR measurements on admission were statistically higher in patients with non-COVID-19 pneumonia than their counterparts. A list of viral agents detected in patients with non-COVID-19 viral pneumonia is given in Table 3.

DISCUSSION

In the current study, we compared the prevalence of hypertension and pre-existing use of ACEIs and ARBs in patients with COVID-19 and non-COVID viral pneumonia. Our study results demonstrated that the prevalence of hypertension, CAD, and antihypertensive therapy with ACEIs and ARBs were not high among patients with COVID-19, compared with viral pneumonia caused by other viral pathogens. At the beginning of the COVID-19 pandemic, the researchers indicated that hypertension and the use of

Table 3. Study groups and specific viral agents detected in patients

Patients with COVID-19 viral pneumonia (n=103)	Patients with non-COVID-19 viral pneumonia* (n=91)
RT-PCR confirmed COVID-19 patients	Human respiratory syncytial virus A (n=26)
	Parvovirus (n=2)
	Influenza A (n=2)
	Human rhinovirus A/B (n=17)
	Human metapneumovirus (n=9)
	Human coronavirus 229E/NL63 (n=5)
	Human coronavirus OC43/HKU1 (n=4)
	Human parainfluenza virus 1 (n=3)
	Human parainfluenza virus 2 (n=7)
	Human parainfluenza virus 3 (n=5)
	Human respiratory syncytial virus B (n=5)
	Human adenovirus (n=6)

CT: computed tomography; RT-PCR: real-time polymerase chain reaction.
*Combination of viral antigen detection tests from nasopharyngeal secretions and thoracic CT images confirmed viral pneumonia patients.

ACEIs or ARBs might increase the susceptibility to the SARS-CoV-2 infection, resulting in poor clinical outcomes. However, recent studies have not proven this preliminary hypothesis.[12,13] Furthermore, there is no head-to-head study available comparing SARS-CoV-2 and other agents associated viral pneumonia. To the best of our knowledge, our study is the first study to compare characteristics, prevalence of hypertension and other comorbidities, and pre-existing use of ACEIs and ARBs in both COVID-19 and other viral agents-associated pneumonia in hospitalized patients.

Viral pneumonia is very common worldwide and nearly 200 million cases of viral community acquired pneumonia (CAP) are reported every year.[16] Common risk factors for CAP include age, recent respiratory system disease, immune disorders, cardiovascular diseases, and DM. There are more than 20 viruses associated with CAP and, among adults, viral pneumonia accounts for one-third of all CAP cases, particularly influenza viruses, rhinoviruses, and coronaviruses being the leading causes.[16] These types of pneumonia are clinically and radiologically similar, and differential diagnosis can be made with laboratory confirmation of the specific viral nuclear material by RT-PCR.[17] In our study, the most common viral agent in the non-COVID-19 group was the respiratory syncytial virus A (RSV-A) (n=26) and human rhinovirus A and B (n=17).

From the beginning of the COVID-19 pandemic, hypertension and prescribed anti-hypertensives, particularly ACEIs and ARBs, were accused to contribute to the pathogenesis of pneumonia via increase of ACE2 expression. When the researchers discovered that SARS-CoV-2 performed an interaction with ACE2 receptors to enter to the cells,[18] hypertension, ACEIs, and ARBs therapies attracted a high interest for the researchers, and there are currently several studies investigating whether they increase susceptibility to the SARS-CoV-2 infection or play a role in clinical outcomes.

Previous studies have demonstrated that ACE2 deficiency may play an important role in the pathogenesis of SARS-CoV-2 infection.[9,19-20] Viral invasion causes a downregulation of ACE2, which seems to be important for patients with baseline ACE2 deficiency caused by advanced age, DM, hypertension, and heart failure. Furthermore, it is known that coronavirus species other than SARS-CoV-2 also uses ACE2 for cellular entry.[9] Despite all these controversies, the prevalence of ACEIs and ARBs use revealed in our study was not higher in patients with COVID-19, which indicates that ACE2 may not have a pathophysiological role specific to COVID-19.

In our study, we compared patients with COVID-19 and non-COVID-19 viral pneumonia for their recent medical history of hypertension, CAD, and antihypertensive medications. Interest-

ingly, patients with non-COVID-19 viral pneumonia had a higher prevalence of hypertension, CAD, and COPD than patients with COVID-19. Unexpectedly, the NLR was found increased in patients with non-COVID-19 viral pneumonia compared with patients with COVID-19. We assume that the nature of the pandemic and contagiousness of SARS-CoV-2 might have influenced the results. For instance, during the pandemic, younger individuals and those without any risk factors or affinity to CAP were easily infected with SARS-CoV-2, but non-COVID-19 viral agents did not cause CAP among patients at an increased risk for respiratory infections. The latter was usually observed in patients with chronic heart disease and/or hypertension. These results indicate that comorbidities such as hypertension, CAD, and use of ACEIs/ARBs are not specifically high in patients with COVID-19 compared with patients with non-COVID-19 viral pneumonia.

In contrast, patients with non-COVID-19 viral pneumonia more frequently had hypertension, CAD, and COPD when compared with patients with COVID-19. We think that various factors might have influence on this finding. For instance, non-COVID-19 viral pneumonia agents are frequently causing sporadic cases of viral pneumonia in susceptible subjects however COVID-19 is a pandemic caused by a very contagious virus and it is affecting almost the entire population.

Limitations

There are some limitations to our study. The relatively small sample size and retrospective design are the main limitations. In our study, the median age of the hospitalized patients was younger than some of previous studies but it was in concordance with large preliminary series.[21-22] We think that strict lockdown policies that were in practice for senior patients from the beginning of the pandemic have protected, at least in part, seniors from contact with patients with COVID-19 and have also limited contamination with SARS-CoV-2. Another potential reason of relatively younger patients with COVID-19 reported in our study might be associated with socio-economic conditions. The majority of patient population of the participating centers are consisted from relatively young or middle aged, actively working patients. However, no patient with mild to moderate pneumonia was accepted to the ICU and the ICU admission criteria and ICU requirement ratios were similar to previously reported data.[15,21-22] Of note, the median age in both groups was also similar. In addition, some of the participants might have both SARS-CoV-2 and coinfection with other viral agents. However, we were unable to perform respiratory viral panel test for every patient in the COVID-19 group owing to its high cost. Ideally, further large-scale, prospective studies examining almost all agents associated with viral pneumonia in both group of patients would provide more precise data.

Conclusion

Our study results indicate that hypertension, CAD, and pre-existing use of ACEIs and ARBs are not more common among hospitalized patients with COVID-19 compared with other patients with CAP. NLR levels were more prominently increased in patients with non-COVID-19 viral pneumonia. Our results support the finding that the use of ACEIs and ARBs does not play a specific role in patients with COVID-19. This is the first study which showed remarkable comparison between hospitalized patients with COVID-19 and non-COVID viral pneumonia in terms of hypertension prevalence and the use of renin-angiotensin-aldosterone system blockers.

The visual summary of the article can be seen in the Appendix 1

Ethics Committee Approval: Ethics committee approval was received for this study from the Acıbadem Mehmet Ali Aydınlar University Ethical Committee (ATADEK 2020-08/27) and Turkish Minstry of Health (2020-05-02 T19_38_13)

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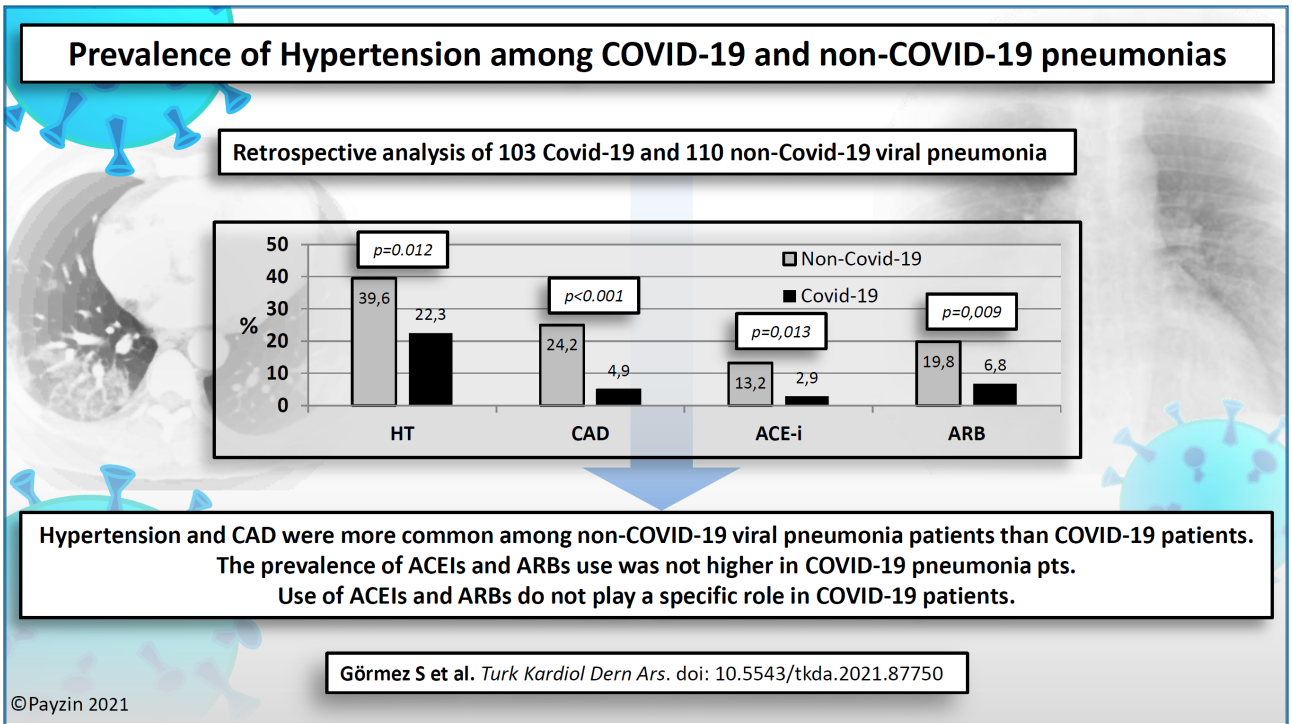
REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506. [Crossref]

2. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? Lancet 2020;395:1225- 8. [Crossref]
3. Bernard Stoecklin S, Rolland P, Silue Y, Mailles A, Campese C, Simondon A, et al. First cases of coronavirus disease 2019 (COVID-19) in France: surveillance, investigations and control measures, January 2020. Euro Surveill 2020;25:pii=2000094. [Crossref]
4. World Health Organization. Available at: https://www.who.int/dg/speeches/detail/who-director-generals-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020 (Accessed February 12, 2020).
5. WHO Director-General's opening remarks at the media briefing on COVID-19: 11 March 2020. March 11, 2020. Available at: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-themedia-briefing-on-covid-19---11-march-2020 (Accessed March 30, 2020).
6. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180:934-43. [Crossref]
7. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel Coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061-9. [Crossref]
8. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. China Medical Treatment Expert Group for Covid-19. clinical characteristics of Coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.
9. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271-80. [Crossref]
10. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020;8:e21. [Crossref]
11. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020;17:259-60. [Crossref]
12. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. N Engl J Med 2020;382:2431-40. [Crossref]
13. Gao C, Cai Y, Zhang K, Zhou L, Zhang Y, Zhang X, et al. Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. Eur Heart J 2020;41:2058-66. [Crossref]
14. Clinical management of COVID-19. Interim guidance. Available at: https://www.who.int/publications/i/item/clinical-management-of-covid-19. (Accessed May 27, 2020).
15. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community acquired pneumonia in adults. Clin Infect Dis 2007;44:27-72.
16. Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. Lancet 2011;377:1264-75. [Crossref]
17. Dandachi D, Rodriguez-Barradas MC. Viral pneumonia: etiologies and treatment. J Investig Med 2018;66:957-965. [Crossref]
18. Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci 2020;63:457-60. [Crossref]
19. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 2020;181:281-92.e6. [Crossref]
20. Verdecchia P, Cavallini C, Spanevello A, Angeli F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. Eur J Intern Med 2020;76:14-20. [Crossref]
21. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. Vital surveillances: the epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)-China, 2020. China CDC Weekly 2020;2:113-22. [Crossref]
22. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. JAMA 2020;323:1239-42. [Crossref]

Keywords: COVID-19; viral pneumonia; hypertension; angiotensin-converting enzyme inhibitors; angiotensin II type 2 receptor blockers

Anahtar Kelimeler: COVID-19; viral pnömoni; hipertansiyon; anjiyotensin-dönüştürücü enzim inhibitörleri; anjiyotensin II tip 2 reseptör blokerleri



Appendix 1. Visual summary of the article.