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Original Scientific Paper

STUDY HYPOTHESIS: AGE, GENDER, PRESENCE OF DIABETES MELLITUS OR HYPERTENSION, AND ANTI-HYPERTENSIVE DRUGS ARE INDEPENDENT RISK FACTORS FOR COVID-19 MORTALITY

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SUMMARY – We aimed to investigate the effects of comorbid diseases and antihypertensive drugs on the clinical outcome of hospitalized patients with COVID-19 infection. A total of 1045 patients whose data could be gathered and confirmed from both hospital files and Turkish National Health Network records were retrospectively screened, and 264 of 1045 patients were excluded because of having more than one comorbid disease. The study population consisted of a total of 781 patients, of which 482 had no comorbid disease, while the remaining 299 patients had only one comorbid disease. The mortality risk was 7.532 times higher in those over 65 years of age compared to cases younger than 30 years (OR: 7.532; 95% CI: 1.733-32.730); the risk of mortality in men was 2.131 times higher than in women (OR: 2.131; 95% CI: 1.230-3.693); and presence of diabetes mellitus (DM) increased mortality risk 2.784 times (OR: 2.784; 95% CI: 1.288-6.019). While hypertension was not found to be an independent risk factor for COVID-19 mortality, age, gender, and presence of DM were independent risk factors for COVID-19 mortality. There was no association between antihypertensive drugs and mortality. Accordingly, age (>65 years), gender (male), and presence of DM were independent risk factors for COVID-19 mortality, whereas hypertension and use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and their combinations with other antihypertensive drugs were not risk factors for COVID-19 mortality.

Keywords: *COVID-19; Hypertension; Diabetes mellitus; Angiotensin-converting enzyme inhibitor; Angiotensin II receptor blocker*

Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has recently become an international public health emergency. As of June 13, 2020, there have been 7,553,182 laboratory-confirmed cases and 423,349 deaths globally[1]. In Turkey, the first case was detected on March 11, 2020, and there have been 176,677 laboratory-confirmed cases and 4,792 deaths so far[2]. As of June 13, 2020, the mortality rate of 5.5% in the world and 2.71% in Turkey, with more than 10,000 cases detected in 59 countries, the ranking of Turkey regarding this ratio is 27 (lower ranking means lower ratio)[1-3].

The effect of patient comorbid disease(s) and/or its (their) related drug(s) use on the mortality of

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COVID-19 are study topics that attract attention of researchers. A meta-analysis of 6 studies that comprised 1558 patients revealed that, while there was no correlation between an increased risk of COVID-19 and renal disease, malignancy, or liver disease, a significant correlation was shown between the increased risk of COVID-19 and hypertension (HT), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), cardiovascular disease, and cerebrovascular disease[4]. Previous studies show that 20%-51% of COVID-19 patients were reported as having at least one comorbidity on admission[5-8]. Another study conducted in China showed that having at least one comorbidity increased mortality in COVID-19 patients, and a higher number of comorbidities also correlated with poorer clinical outcomes[9].

The angiotensin-converting enzyme 2 (ACE2) receptor, which is associated with the severity and risk of metastasis in some cancers, is also responsible for binding the SARS-CoV2 viral spike and causing COVID-19 infection[10,11]. Previous studies conducted in animals showed upregulated expression of ACE2 receptors when they were treated with angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II type receptor blockers (ARB)[12]. There is a worldwide debate regarding the use of the abovementioned medications in COVID-19 infected patients. The point of concern is that using these drugs and their combinations during the COVID-19 outbreak could upregulate the expression of ACE2 receptors and may worsen the prognosis of this infection[13].

To date, there is no study conducted on a Turkish population investigating the consequences of comorbid diseases and antihypertensive drugs (ACEi, ARB, other antihypertensive drugs, and their combinations) on the mortality of COVID-19 patients. Thus, in this study, we aimed to investigate the effects of comorbid diseases and antihypertensive drugs on the clinical outcome of hospitalized patients with COVID-19 infection. Also, because no multivariate adjustment was conducted in previously published studies regarding the effects of comorbid diseases on the mortality of COVID-19 patients, the question has been raised regarding the effect of potential confounders on the disease mortality. Unlike previous studies, in order to avoid selection bias, our study targeted only patients with a single comorbid disease and those with no comorbid disease, and therefore patients with more than one comorbid disease were excluded from the study.

Materials and Methods

Study design and patients

This was a population-based case-control study at a pandemic hospital in Turkey. A total of 1968 patients were hospitalized at Bakirkoy Dr. Sadi Konuk Education and Training Hospital in Istanbul, Turkey, due to COVID-19 pneumonia from March 15 to April 30, 2020; a total of 1045 patients whose data could be gathered and confirmed from both hospital files and Turkish National Health Network (NHN) records were retrospectively screened and evaluated for the study. As a result of retrospective evaluation, 264 of 1045 patients were further excluded because of having more than one comorbid disease. Our study population consisted of a total of 781 patients, of which 482 had no comorbid disease, while the remaining 299 patients had only one comorbid disease; the study flow is illustrated in Figure 1.

Patients who were pregnant, patients under age 18, and those whose hospital files or NHN records could not be accessed were excluded from the study. Patients who had more than one comorbid disease also were excluded from the study.

The Medical Research Ethics Committee of the Bakirkoy Dr. Sadi Konuk Education and Training Hospital approved the study. We were committed to protecting patient privacy and complying with the Helsinki Declaration (approval number: 2020/207)

Patient demographic data and clinical outcome

Data on comorbidities, medications used to treat hypertension, treatments received for COVID-19, clinical outcomes, and other demographics of the patients were obtained from the hospital medical records and NHN records. The clinical outcome of the patients was evaluated by overall survival.

Treatment

All patients received standard treatments according to the National Guideline for the Diagnosis and Treatment Protocol for COVID-19 (SARS-CoV-2 infection)[14], including hydroxychloroquine, favipiravir, azithromycin, low-molecular-weight heparin, methylprednisolone, other symptom relievers, and oxygen therapy.

Radiological evaluation

Whole-lung spiral computed tomography (CT) images of the patients (Somatom 64 Slice, Siemens

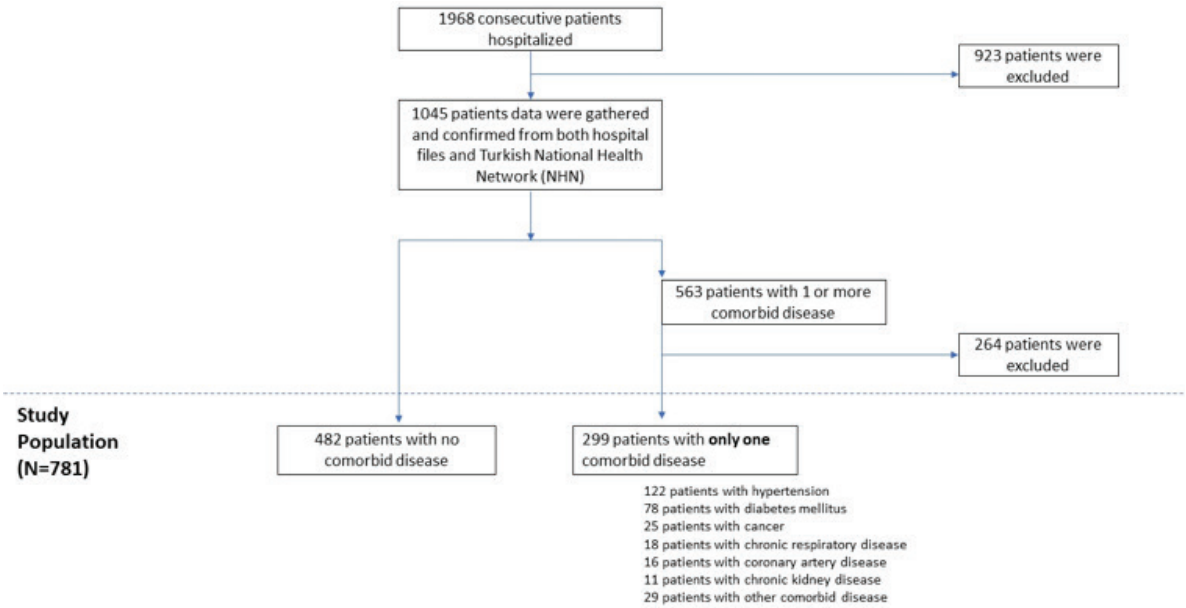

Fig. 1. Study flow chart.

Healthcare, Forchheim, Germany) were evaluated and reported by at least one radiologist. Radiological findings of COVID-19 pneumonia were classified into four types: mild, moderate, severe, atypical involvement, and no radiological findings.

Statistical analysis

The Number Cruncher Statistical System 2007 (NCSS, Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used when evaluating study data. The suitability of quantitative data for normal distribution was tested by the Shapiro-Wilk test and graphic evaluations. Mann Whitney U test was used for comparisons between two groups that did not show normal distribution. Fisher exact test and Fisher-Freeman-Halton test were used to compare qualitative data. Logistic regression analysis was used to evaluate risk factors affecting mortality. The level of statistical significance was set at $p<0.05$.

Results

As we mentioned above, the final analysis was done with a total of 781 patients. Of these 781 patients, 482 (61.7%) had no known comorbidities. The remaining 299 patients had only one comorbid disease. The distribution of comorbid diseases was as follows:

- hypertension (HT) 15.6% (n=122),
- diabetes mellitus (DM) 10.0% (n=78),
- chronic respiratory disease 2.3% (n=18),
- coronary artery disease (CAD) 2.0% (n=16),
- chronic kidney disease (CKD) 1.4% (n=11),
- malignancy 3.2% (n=25), and
- others 3.7% (n=29).

The study population consisted of 43.7% (n=341) of female and 56.3% (n=440) of male patients, age range 18-93 years, mean 53.40±15.76 years. Discharged were 94.4% (n=737) of the patients, and 5.6% (n=44) of them died. The length of hospital stay varied between 1 and 57 days, mean 9.31±5.99 days. Demographic data of the study population and distribution of antihypertensive drugs used by the patients with only hypertension are shown in Table 1.

When we evaluated the effect of demographic characteristics of patients without comorbid disease on mortality, a statistically significant difference was found between discharged and dead cases according to age ($p=0.001$), whereas there was no statistically significant difference according to gender, length of hospital stay, CT result, fever on admission, and systolic and diastolic blood pressure values between discharged and dead cases ($p>0.05$ all) (Table 2).

Table 1. Demographic data of patients

		n (%)
Age (years)	Minimum-maximum (median)	18-93 (54)
	Mean±SD	53.40±15.76
	<30	73 (9.3)
	30-65	577 (73.9)
	>65	131 (16.8)
Sex	Female	341 (43.7)
	Male	440 (56.3)
Outcome	Discharged	737 (94.4)
	Dead	44 (5.6)
Length of stay (days)	Minimum-maximum (median)	1-57 (7)
	Mean±SD	9.31±5.99
CT results	Normal	55 (7.0)
	Atypical	9 (1.1)
	Mild	252 (32.2)
	Moderate	310 (39.7)
	Severe	90 (11.5)
	Absent	65 (8.32)
Fever (°C) (n=647)	Minimum-maximum (median)	35.1-40 (36.5)
	Mean±SD	36.71±0.74
Systolic blood pressure (n=281)	Minimum-maximum (median)	62-238 (123)
	Mean±SD	128.19±25.48
Diastolic blood pressure (n=281)	Minimum-maximum (median)	36-147 (75)
	Mean±SD	76.57±13.56
Comorbidity:		
No known comorbid disease		482 (61.7)
Hypertension		122 (15.6)
Diabetes mellitus		78 (10)
Chronic respiratory disease		18 (2.3)
Coronary artery disease		16 (2.0)
Cancer		25 (3.2)
Chronic kidney disease		11 (1.4)
Other comorbid diseases		29 (3.7)
Anti-hypertensive drugs (n=122):		
ACEi		14 (11.4)
ACEi + thiazide		23 (18.8)
ACEi + CCB		12 (9.8)
ACEi + CCB + thiazide		1 (0.8)
Total patients using ACE and its combinations		50 (40.9)
ARB		13 (10.6)
ARB + thiazide		32 (26.2)
ARB + CCB		10 (8.2)
ARB + CCB + thiazide		0 (0)
Total patients using ARB and its combinations		55 (45)
Other antihypertensive drugs		17 (14)

SD = standard deviation; CT = computed tomography; ACEi = angiotensin-converting enzyme inhibitor; CCB = calcium channel blocker; ARB = angiotensin II receptor blocker

Table 2. Effect of demographic characteristics of patients without comorbid disease on mortality

Patients with no comorbid disease (n=482)		Outcome		p
		Discharged (n=468)	Dead (n=14)	
Age (years)	Minimum-maximum (median)	18-93 (46)	26-83 (59.5)	c0.001**
	Mean±SD	46.46±14.05	59.79±15.12	
	<30 years	59 (98.3)	1 (1.7)	
	30-65 years	366 (98.1)	7 (1.9)	
	>65 years	43 (87.8)	6 (12.2)	
Sex	Female	199 (98.0)	4 (2.0)	a0.413
	Male	269 (96.4)	10 (3.6)	
Length of stay (days)	Minimum-maximum (median)	1-35 (7)	2-36 (8.5)	c0.301
	Mean±SD	8.68±5.07	13.43±11.04	
CT results	Normal	32 (94.1)	2 (5.9)	b0.346
	Atypical	6 (100)	0 (0)	
	Mild	149 (96.8)	5 (3.2)	
	Moderate	193 (98.0)	4 (2.0)	
	Severe	46 (93.9)	3 (6.1)	
	Absent	42 (100)	0 (0)	
Fever (°C) (n=400)	Minimum-maximum (median)	35.1-40 (36.5)	36-38 (36.5)	c0.805
	Mean±SD	36.73±0.78	36.68±0.75	
Systolic blood pressure (n=157)	Minimum-maximum (median)	62-210 (120)	96-123 (108)	c0.119
	Mean±SD	122.43±20.42	108.75±11.18	
Diastolic blood pressure (n=157)	Minimum-maximum (median)	36-132 (74)	51-87 (68)	c0.277
	Mean±SD	75.12±11.74	68.50±14.8	

[a]Fisher exact test; [b]Fisher Freeman-Halton test; [c]Mann Whitney U test; *p<0.05; **p<0.01; SD = standard deviation; CT = computed tomography

Table 3. Effect of comorbid diseases on mortality

Comorbidity	Outcome, n (%)		[a]p	OR
	Discharged	Dead		95% CI
No comorbidity	468 (97.1)	14 (2.9)	0.031*	2.662
Hypertension	113 (92.6)	9 (7.4)		1.124-6.306
No comorbidity	468 (97.1)	14 (2.9)	0.001**	4.916
Diabetes mellitus	68 (87.2)	10 (12.8)		2.100-11.507

[a]Fisher exact test; *p<0.05; **p<0.01; OR = odds ratio; CI = confidence interval

Table 4. Logistic regression analysis of risk factors affecting mortality

	p	OR	95% CI	
			Lower	Upper
Age (<30 years)	0.000**			
30-65 years	0.585	1.504	0.348	6.504
>65 years	0.007**	7.532	1.733	32.730
Sex (male)	0.007**	2.131	1.230	3.693
Hypertension	0.649	1.198	0.551	2.604
Diabetes mellitus	0.009**	2.784	1.288	6.019

**p<0.01; OR = odds ratio; CI = confidence interval

We could not examine the effect of the diseases on mortality due to the low number of cases in the groups of patients with cancer, CKD, respiratory diseases, CAD, and other comorbid diseases. Therefore, only HT and DM were examined to evaluate the effect of COVID-19 disease on mortality.

The mortality rate in patients with HT was statistically significantly higher as compared with patients without comorbid disease (p=0.031). The presence of hypertension increased the mortality risk 2.662 times (OR: 2.662; 95% CI: 1.124-6.306).

In patients with DM, the mortality rate was found to be statistically significantly higher than in patients with no comorbid disease (p=0.001). The presence of DM increased mortality risk 4.916 times (OR: 4.916; 95% CI: 2.100-11.507) (Table 3).

When we evaluated the effect of the variables of age, gender, presence of hypertension, and presence of diabetes on mortality with logistic regression analysis, the coefficient of determination of the model was found to be 0.934. The mortality risk was 7.532 times higher in those over 65 years of age compared to cases younger than 30 years (OR: 7.532; 95% CI: 1.733-32.730). The risk of mortality in men was 2.131 times higher than in women (OR: 2.131; 95% CI: 1.230-3.693). The presence of DM increased mortality risk 2.784 times (OR: 2.784; 95% CI: 1.288-6.019). In the model, the presence of hypertension was not associated with increased mortality (p=0.649; OR: 1.198; 95% CI: 0.551-2.604), whereas age (>65 years), gender (male), and presence of DM were found to be independent risk factors for COVID-19 mortality (Table 4).

There was no association between antihypertensive drugs used during COVID-19 infection in hypertensive patients and their mortality (p>0.05 for all drugs) (Table 5).

Discussion

The first epidemiological studies that originated in China suggest that hypertension and diabetes are associated with mortality in COVID-19 patients. A previous study performed on 44,672 COVID-19 patients showed that the overall mortality rate was 2.3% and that it was elevated in certain comorbid diseases, such as cardiovascular disease (10.5%), DM (7.3%), chronic respiratory disease (6.3%), and hypertension (6%)[15].

Another two studies also showed that hypertension was the most common comorbid disease (15%) in both laboratory-confirmed COVID-19 outpatients and hospitalized patients, and hypertension was also more frequent in hospitalized patients who died compared with those who were discharged[16,17].

A systematic review and meta-analysis included 7 studies that were performed in a total of 46,248 infected patients found that the most prevalent comorbidity was hypertension (17±7%) and hypertension may be a risk factor in severe patients compared with non-severe patients[18].

As Sisnieguez *et al.*[19] report, although the results of previous studies seem to be similar and compatible, there was no multivariate adjustment in these studies, raising the question that the effect of hypertension on the severity or mortality of the disease may have been affected by potential confounders. It is now a well-known fact that hypertension, DM and cardiovascular disease frequently are coexistent diseases and these diseases are especially associated with advanced age and gender. When evaluating whether these risk factors

Table 5. Effect of antihypertensive drugs used by patients with hypertension and their demographic characteristics on mortality

Patients with only hypertension (n=122) Discharged (n=113)		Outcome		p
		Dead (n=9)		
Age (years)	Minimum-maximum (median)	22-91 (60)	58-82 (67)	[c]0.071
	Mean±SD	59.62±14.50	67.33±7.07	
	<30	5 (100)	0 (0)	
	30-65	70 (95.9)	3 (4.1)	
	>65	38 (86.4)	6 (13.6)	
Sex	Female	66 (94.3)	4 (5.7)	[a]0.494
	Male	47 (90.4)	5 (9.6)	
Length of stay (days)	Minimum-maximum (median)	1-26 (7)	3-33 (8)	[c]0.686
	Mean±SD	8.81±4.05	12.78±10.63	
Anti-hypertensive drugs:				
ACEi	Yes	100 (92.6)	8 (7.4)	[a]1.000
	No	13 (92.9)	1 (7.1)	
ACEi + thiazide	Yes	91 (91.9)	8 (8.1)	[a]1.000
	No	22 (95.7)	1 (4.3)	
ACEi + CCB	Yes	102 (92.7)	8 (7.3)	[a]1.000
	No	11 (91.7)	1 (8.3)	
ACEi + CCB + thiazide	Yes	112 (92.6)	9 (7.4)	[a]1.000
	No	1 (100)	0 (0)	
Total patients using ACE and its combinations	Yes	66 (91.7)	6 (8.3)	[a]0.736
	No	47 (94.0)	3 (6.0)	
ARB	Yes	100 (91.7)	9 (8.3)	[a]0.595
	No	13 (100)	0 (0)	
ARB + thiazide	Yes	85 (94.4)	5 (5.6)	[a]0.240
	No	28 (87.5)	4 (12.5)	
ARB + CCB	Yes	104 (92.9)	8 (7.1)	[a]0.550
	No	9 (90.0)	1 (10.0)	
ARB + CCB + thiazide	Yes	113 (92.6)	9 (7.4)	-
	No	-	-	
Total patients using ARB and its combinations	Yes	63 (94.0)	4 (6.0)	[a]0.730
	No	50 (90.9)	5 (9.1)	
Other antihypertensive drugs	Yes	97 (92.4)	8 (7.6)	[a]1.000
	No	16 (94.1)	1 (5.8)	

[a]Fisher exact test; [c]Mann Whitney U test; SD = standard deviation; CT = computed tomography; ACEi = angiotensin-converting enzyme inhibitor; CCB = calcium channel blocker; ARB = angiotensin II receptor blocker

are effective risk factors for mortality in COVID-19, studies focusing on the right patient selection and performing multivariate analysis are required rather than retrospective studies examining only patient characteristics[15-17].

To address this potential issue, our study targeted only patients with a single comorbid disease and those with no comorbid disease; thus, we excluded patients with more than one comorbid disease, and we evaluated the results by multivariate logistic regression analysis.

In our study, while the results before regression analysis were consistent with the results of previous studies, post-analysis results showed that hypertension alone was not a risk factor for mortality in COVID-19, but DM alone was a significant risk factor for mortality in COVID-19.

In our study, we also examined whether the use of ACEi, ARB, or their combinations with other antihypertensive drugs caused any increase in COVID-19 mortality in hypertensive patients, and we did not find a significant relationship for any of these parameters.

While some observational studies found no association between the use of ACEi and ARB and COVID-19 severity, a few studies found a significant reduction in the risk of death or severe disease, and one study found an increased risk of admission to the intensive care unit[19-25].

A recent meta-analysis included 10 observational studies that were performed on a total of 9890 hypertensive subjects and showed no significant increase in the risk of developing severe or fatal COVID-19 in the subjects treated with either ACEi or ARB. Our study result was consistent with the results of this meta-analysis[26].

Our study also showed that the mortality risk was 7.532 times higher in those over 65 years of age compared to cases younger than 30 years, and the risk of mortality in men was 2.131 times higher than in women. The presence of DM also increased mortality risk 2.784 times. In the model, age (>65 years), gender (male), and presence of DM were found to be independent risk factors for COVID-19 mortality. These results were consistent with previous studies[15,18,27]. We did not include the length of hospital stay in regression analysis, as previous studies have shown that prolonged hospitalization is not a risk factor for mortality[28].

In conclusion, in this population-based case-control study, we showed that while age (>65 years), gender (male), and DM alone were significant risk factors for COVID-19 mortality, HT alone was not a risk factor. We also showed that the use of ACEi, ARB or their combinations with other antihypertensive drugs did not cause any increase in COVID-19 mortality in hypertensive patients.

Limitations

First, by its nature as an observational study, no causal inference can be made and relationships should be interpreted as associations. Second, the use of ACEi, ARB, or their combinations with other antihypertensive drugs was defined by prescriptions, and actual drug consumption by the case patients could not be assessed. Furthermore, data were derived from a national sample of patients with COVID-19 but in a short time span. Hence, although the screening and treatment of patients COVID-19 has been determined according to national strategies, a change in screening and treatment approaches over time may have caused bias.

References

1. World Health Organization. Coronavirus disease (COVID-19) situation reports. Retrieved from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/ last accessed 13 June 2020.
2. Turkey Ministry of Health Daily Coronavirus Table. Retrieved from: https://covid19.saglik.gov.tr/last accessed: 13 June 2020 (in Turkish).
3. COVID-19 pandemic data. Retrieved from: https://en.wikipedia.org/wiki/Template:COVID-19_pandemic_data last accessed 13 June 2020.
4. Wang B, Li R, Lu Z, Huang Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. Aging. 2020;12(7):6049-57. doi: 10.18632/aging.103000.
5. 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(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5.
6. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13. doi: 10.1016/S0140-6736(20)30211-7.
7. 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(11):1061-9. doi: 10.1001/jama.2020.1585 [Epub ahead of print].
8. Zhang JJ, Dong X, Cao YY, Yuan Y, Yang YB, Yan YQ, *et al*. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75:1730-41.

9. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, *et al.* China Medical Treatment Expert Group for COVID-19 comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020 May;55(5):2000547. https://doi.org/10.1183/13993003.00547-2020.
10. Dolomatov S, Zukow W, Novikov N, Markaryan A, Eremeeva E. Expression of the renin-angiotensin system components in oncologic diseases. Acta Clin Croat. 2019;58(2):354-63. doi:10.20471/acc.2019.58.02.21.
11. Wu F, Zhao S, Yu B, *et al*. A new coronavirus associated with human respiratory disease in China. Nature. 2020 Mar;579(7798):265-9. doi: 10.1038/s41586-020-2008-3.
12. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, Diz DI, Gallagher PE. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation. 2005;111(20):2605-10. doi: 10.1161/CIRCULATIONAHA.104.510461.
13. Giavina-Bianchi P, Aun MV, Agondi RC, Kalil J. Debate on drugs that may aggravate COVID-19. J Allergy Clin ImmunolPract. 2020;8(7):2452-3. https://doi.org/10.1016/j.jaip.2020.04.037.
14. Republic of Turkey Ministry of Health. COVID-19 (SARS-CoV-2 Infection) Guide – Science Board Study. Available at: https://covid19bilgi.saglik.gov.tr/depo/rehberler/COVID-19_Rehberi.pdf?type=file. Accessed 05/07/2020.
15. 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(13):1239-42. doi:10.1001/jama.2020.2648.
16. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, *et al.* (2020). Clinical characteristics of coronavirus disease 2019 in China. NEngl J Med. 2020;382(18):1708-20.
17. Qiurong Ruan, Kun Yang, Wenxia Wang, Lingyu Jiang, Jianxin Song. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46:846-8. https://doi.org/10.1007/s00134-020-05991-x.
18. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, *et al*. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J InfectDis. 2020;94:91-5.
19. Sisnieguez CEL, Espeche WG, Salazar MR. Arterial hypertension and the risk of severity and mortality of COVID-19. Eur Respir J. 2020 Jun 11;55(6):2001148. doi: 10.1183/13993003.01148-2020.
20. de Abajo FJ, Rodríguez-Martín S, Lerma V, Mejía-Abril G, Aguilar M, García-Luque A, *et al*. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. Lancet. 2020;395:1705-14.
21. Giorgi Rossi P, Marino M, Formisano D, *et al.* Characteristics and outcomes of a cohort of SARS-CoV-2 patients in the province of Reggio Emilia, Italy. MedRxiv. 2020. doi: https://doi.org/10.1101/2020.04.13.20063545.
22. Liu Y, Huang F, Xu J, *et al*. Anti-hypertensive angiotensin II receptor blockers associated to mitigation of disease severity in elderly COVID-19 patients. MedRxiv. 2020.
23. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-angiotensin-aldosterone system blockers and the risk of COVID-19. NEngl J Med. 2020;382(25):2431-40. https://doi.org/10.1056/NEJMoa2006923.
24. Reynolds HR, Adhikari S, Pulgarin C, *et al*. Renin-angiotensin-aldosterone system inhibitors and risk of COVID-19. 2020 Jun 18;382(25):2441-8. doi: 10.1056/NEJMoa2008975. Epub 2020 May 1.
25. Tedeschi S, Giannella M, Bartoletti M, Trapani F, TadoliniM, Borghi C, *et al*. Clinical impact of renin-angiotensin system inhibitors on in-hospital mortality of patients with hypertension hospitalized for COVID-19. [published online ahead of print, 2020 Apr 27]. Clin Infect Dis. 2020 Jul 28;71(15):899-901. doi: 10.1093/cid/ciaa492.
26. Flacco ME, Acuti Martellucci C, Bravi F, Parruti G, Cappadona R, Mascitelli A, *et al*. Treatment with ACE inhibitors or ARBs and risk of severe/lethal COVID-19: a meta-analysis. Heart.2020;106(19). Published Online: July 1, 2020. doi: 10.1136/heartjnl-2020-317336.
27. Guo W, Li M, Dong Y, *et al*. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020;e3319. doi: 10.1002/dmrr.3319.
28. Štubljar D, Štefin M, Tacar MP, Cerović O, Grosek Š. Prolonged hospitalization is a risk factor for delirium onset: one-day prevalence study in Slovenian intensive care units. Acta Clin Croat. 2019;58(2):265-73. doi: 10.20471/acc.2019.58.02.09.

Sažetak

HIPOTEZA STUDIJE: DOB, SPOL, PRISUTNOST ŠEĆERNE BOLESTI ILI HIPERTENZIJE I ANTIHIPERTENZIVNI LIJEKOVI SU NEOVISNI ČIMBENICI RIZIKA ZA SMRTNOST KOD INFEKCIJE COVID-19

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Cilj istraživanja bio je ispitati učinak supostojećih bolesti i antihipertenzivnih lijekova na klinički ishod hospitaliziranih bolesnika s infekcijom COVID-19. Retrospektivnim probirom obuhvaćeno je ukupno 1045 bolesnika čije podatke smo mogli prikupiti i potvrditi iz bolničkih kartona i zapisa Turske nacionalne zdravstvene mreže; od tih bolesnika njih 264 je isključeno, jer su imali više od jedne supostojeće bolesti. Tako je u studiju uključen ukupno 781 bolesnik, od kojih njih 482 nisu imali nikakve supostojeće bolesti, dok je preostalih 299 imalo samo jednu supostojeću bolest. Rizik od smrtnog ishoda bio je 7,532 puta veći kod bolesnika starijih od 65 godina u usporedbi sa slučajevima mlađim od 30 godina (OR: 7,532; 95% CI: 1,733-32,730); rizik od smrtnog ishoda bio je 2,131 puta veći kod muškaraca u nego kod žena (OR: 2,131; 95% CI: 1,230-3,693); prisutnost dijabetes melitusa (DM) povećala je rizik od smrti 2,784 puta (OR: 2,784; 95% CI: 1,288-6,019). Hipertenzija nije utvrđena kao čimbenik rizika za smrtnost kod infekcije COVID-19, ali su se dob, spol i prisutnost DM pokazali neovisnim rizičnim čimbenicima za smrtnost kod infekcije COVID-19. Prema tome, dob (iznad 65 godina), spol (muški) i prisutnost DM utvrđeni su kao neovisni čimbenici rizika za smrtnost kod infekcije COVID-19, dok hipertenzija i uzimanje inhibitora angiotenzin-konvertirajućeg enzima, blokatora receptora angiotenzina i njihovih kombinacija s drugim antihipertenzivnim lijekovima nisu utvrđeni kao rizični čimbenici smrtnosti kod infekcije COVID-19.

Ključne riječi: *COVID-19; Hipertenzija; Dijabetes melitus; Inhibitor angiotenzin-konvertirajućeg enzima; Blokator receptora angiotenzina II.*