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Effects of previous exposure to different medications on the clinical course of COVID-19 patients in Istanbul, Turkey

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Ethics Committee Approval
This study was approved by Clinical Research Ethics Committee of Marmara University Faculty of Medicine (May 8, 2020, protocol code: 09.2020.552). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Multiple studies have investigated the effects of drugs that alter ACE2 expression, such as renin-angiotensin system inhibitors, non-steroidal anti-inflammatory drugs, and thiazolidinediones, on the clinical course of coronavirus disease-2019 (COVID-19). But a consensus has not yet been reached, and it has been stated that they do not have any effect. There are publications in which metformin is associated with low mortality and insulin with high mortality. Data from different parts of the world are important given that the rate of spread of COVID-19 may be related to the expression status of ACE2 or TMPRSS2 receptors or some other unknown genetic factors. This study aims to examine the effects of medications used chronically in the last 6 months before contracting COVID-19 on the clinical course of COVID-19 in a sample of Istanbul, Turkey.

Methods: In this retrospective cohort study, which included 525 patients diagnosed with COVID-19 between March and November 2020 from four family health centers in Istanbul, the records of the patients were retrospectively analyzed. In addition to demographic information, all medications chronically used by the patients in the last 6 months before the diagnosis of COVID-19 were noted. The effects of demographic data and medications on the three main endpoints of the study, which were hospitalization, intensive care unit (ICU) admission, and mortality, were analyzed using logistic regression models.

Results: Of the 525 COVID-19 patients included in the study, 109 (20.8%) were hospitalized, 18 (3.4%) were treated in ICU, and 11 (2.1%) patients died. Increasing age is associated with hospitalization, ICU admission and mortality. Also, the presence of COVID-19 thoracic computed tomography (CT) findings and polypharmacy was associated with increased hospitalization. Living alone and the presence of COVID-19 thoracic CT findings was associated with increased ICU admission. When adjusted for age and comorbidity, logistic regression models revealed that medications for diabetes mellitus (DM) increased the probability of hospitalization (OR: 3.9, 95% CI 1.2-13.0), and calcium channel blockers (CCBs) increased the probability of ICU admission (OR: 15.8, 95% CI 2.1–120.2) and mortality (OR: 295.1, 95% CI 4.6–18946.6).

Conclusion: Previous use of DM medications and CCBs may negatively affect the clinical course of COVID-19.

Keywords: COVID-19, SARS-CoV-2, epidemiology, pharmacoepidemiology, hypoglycemic agents, calcium channel blockers

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Introduction

The pandemic caused by the coronavirus disease-2019 (COVID-19) has caused millions of people's death since December 2019 and continues to do so. Although an effective drug treatment has not yet been found, vaccines developed against COVID-19 have been applied worldwide since the last months of 2020. On the other hand, studies on which factors affect the severity of the disease are continuing. Studies indicate that age is the primary risk factor for COVID-19-related hospitalization and/or death. In addition, it has been revealed that the clinical course of COVID-19 is more severe in patients with chronic diseases, such as hypertension (HT), cardiovascular diseases (CVD), diabetes mellitus (DM), obesity, chronic kidney failure, and cancer [1-4].

The cellular structure and receptors of the severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) that causes COVID-19 were found in March 2020. It was determined that the virus entered the cell with the angiotensin-converting enzyme-2 (ACE2) receptor, and the transmembrane protease serine 2 (TMPRSS2) receptor facilitated the entry of the virus into the cell [5]. Since then, the use of drug groups, such as ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) [6–8], ibuprofen, and other non-steroidal anti-inflammatory drugs (NSAIDs) [9,10], and thiazolidinediones [11], which may cause an increase or decrease in ACE2 expression, has been investigated in large-scale studies during the COVID-19 pandemic.

In general, it has been demonstrated that these drugs do not affect the severity or mortality of COVID-19. Besides, some studies have reported that metformin was associated with decreased mortality and insulin was associated with increased mortality [11–14]. Dipeptidyl peptidase-4 (DPP4) inhibitors have been reported to be associated with the good or poor clinical course of COVID-19 [11,15,16].

Considering that the rate of spread of COVID-19 may be related to the expression status of ACE2 or TMPRSS2 receptors [17,18] or to some other genetic factors that are not yet known, data in different parts of the world are important. With this study, we aimed to examine the effects of previous drug utilization in the last 6 months before contracting COVID-19 on the clinical course of COVID-19 by presenting data from Istanbul, Turkey.

Materials and methods

This retrospective cohort-type study started in May 2020 under the direction of the Marmara University Health Sciences Institute Medical Pharmacology Department and was carried out between May 2020 and October 2021. Patients registered at Istanbul Uskudar Zeynep Kamil Family Health Center (FHC), Sultanbeyli Jandarma Ustegmen Rahim Celik FHC, Beyoglu 6th FHC, and Eyup Islambey FHC were included in the study. Those diagnosed with COVID-19 between 11 March 2020 and 30 November 2020 constituted the study population.

Inclusion criteria were to be a patient enrolled in the FHCs mentioned above and to have a positive COVID-19 PCR test between 11 March 2020 and 30 November 2020 or positive COVID-19 thoracic CT findings despite a negative test. The exclusion criterion from the study was the inability to access the medical information of the included patients via *e-nabiz* (an application that Turkish citizens and health professionals can access health data collected from health institutions via the internet and mobile devices).

The records of the patients included in the study were scanned retrospectively. Data scanning was performed via family medicine information systems and *e-nabiz*. The patients' data were collected by the researcher working in the relevant FHC and participating in the study. The information obtained from the patient files were as follows: patient's age, gender, marital status, education level, employment status, occupation, smoking habit, date of the first diagnosis, first application complaint, COVID-19 PCR test result, presence of COVID-19 findings in thoracic CT, received COVID-19 pharmacological treatment, presence of comorbidity, and medications chronically used in the previous 6 months. Chronic drugs were prescribed to be taken daily for ≥ 30 days. Using five or more different drugs for more than 6 months was considered polypharmacy. The medications utilized in the previous 6 months were recorded according to the Anatomic Therapeutic Chemical (ATC) 5 classification. It was then further grouped according to ATC 3. These data were compared with the three main endpoints of the study, namely, the need for hospitalization, an intensive care unit (ICU), and mortality in comparative analyses.

We did not perform sample size calculation because all COVID-19 patients registered to the FHCs included in the study during the first wave of the COVID-19 pandemic were involved. Therefore, we avoided selection bias.

To obtain study data from family medicine information systems and *e-nabiz*, permission was obtained from the Turkish Republic Ministry of Health General Directorate of Health Services Scientific Research Platform on 29.04.2020. Before collecting the study data, an application was made for the approval of the Marmara University Faculty of Medicine Clinical Research Ethics Committee, and the ethics committee approval was obtained on 08.05.2020 with the protocol code 09.2020.552. The study was carried out following the principles in the Declaration of Helsinki.

Statistical analysis

SPSS 21.0 was used for statistical analysis. Frequency analysis was performed by specifying numbers and percentages for categorical variables. Normal distribution was tested using the Kolmogorov-Smirnov test. Mean and standard deviation were used for continuous variables, and median and range of values were used for non-parametric variables as measures of central tendency and dispersion, respectively. Logistic regression was used to compare the independent variables with the three dependent variables. Correlation analysis and the Pearson Chi-square test confirmed the direction of the comparisons. All logistic regression models were adjusted for age and comorbid conditions. Demographic data were also compared between outpatients, hospitalization, ICU admission, and mortality using the Pearson-chi square test and Fisher's exact test, when needed. For parameters with non-normal distribution, ranks were compared using the Kruskal-Wallis test. For normally distributed parameters, means were compared using a one-way analysis of

variance (ANOVA) test. In the presence of significant variables, Tukey's post hoc test was performed after the ANOVA test, the Dunn test was performed after the Kruskal-Wallis test, and Pearson chi-square or Fisher's exact test in pairs was performed after the Pearson chi-square or Fisher's exact test. *P*-values <0.05 were considered statistically significant.

Results

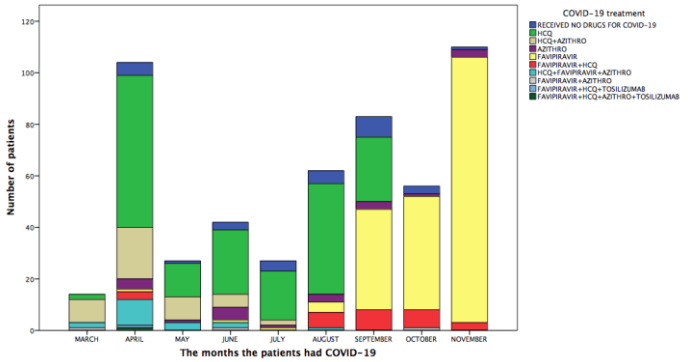
Between March 2020 and November 2020, a total of 525 patients with COVID-19 PCR positive (n=504; 96.0%) or PCR negative and CT positive (n=21; 4.0%) were included in the study from the previously determined FHCs. Demographic and baseline characteristics were compared between outpatient, hospitalized, ICU, and dead patients (Table 1). While the most common complaint in outpatients was fatigue, the most common complaint in patients admitted to the hospital or ICU or who died was cough. Cough, fever, and shortness of breath were more common in hospitalized patients in the ICU or who died than outpatients (*P*=0.008) (Table 1). Education level, employment status and occupation data were not included in the analyses because the relevant data were unavailable for the study population.

Table 1: Demographic and other characteristics of patients

	Total	Outpatient	Hospitalization	Admission to the ICU	Mortality	*P*-value
Gender, n (%)						0.30[F]
Female	260 (49.5)	210 (50.6)	49 (45.0)	8 (44.4)	7 (63.6)	
Male	265 (50.5)	205 (49.4)	60 (55.0)	10 (55.6)	4 (36.4)	
Age [a], median (min-max)	41 (0.5-94)	36 (0.5-80)	57 (11-90)	69.5 (38-88)	72 (42-94)	0.01[K]
Marital status [b], n (%)						0.02[F]
Married	333 (63.4)	253 (61.0)	80 (73.4)	10 (55.6)	5 (45.5)	
Alone	192 (36.6)	162 (39.0)	29 (26.6)	8 (44.4)	6 (54.5)	
Presence of complaints [c], n (%)						0.01[F]
Asymptomatic	143 (27.4)	133 (32.0)	10 (9.2)	1 (5.6)	1 (9.1)	
Symptomatic	382 (72.6)	282 (68.0)	99 (90.8)	17 (94.4)	10 (90.9)	
Weakness	141 (26.9)	108 (26.0)	33 (30.3)	4 (22.2)	1 (9.1)	0.32[A]
Cough [d]	129 (24.6)	79 (19.0)	50 (45.9)	10 (55.6)	7 (63.6)	0.01[A]
Fever [c]	96 (18.3)	56 (13.5)	40 (36.7)	5 (27.8)	2 (18.2)	0.01[A]
Headache	58 (11.0)	50 (12.0)	8 (7.3)	1 (5.6)	0	0.42[A]
Throat ache [e]	48 (9.1)	38 (9.2)	10 (9.2)	3 (16.7)	0	0.03[A]
Back pain	45 (8.6)	38 (9.2)	7 (6.4)	0	0	0.56[A]
Loss of taste and smell	37 (7.0)	35 (8.4)	2 (1.8)	0	0	0.12[A]
Shortness of breath [a]	33 (6.3)	8 (1.9)	24 (22.0)	7 (38.9)	5 (45.5)	0.01[A]
Rhinorrhea	8 (1.5)	8 (1.9)	0	0	0	0.54[A]
Diarrhea	4 (0.8)	4 (1.0)	7 (6.4)	0	0	0.79[A]
Sputum	3 (0.6)	3 (0.7)	0	0	0	0.85[A]
PCR positivity [a], n (%)						0.01[F]
PCR positive	504 (96.0)	410 (98.8)	93 (85.3)	13 (72.2)	9 (81.8)	
PCR negative, BT positive	21 (4.0)	5 (1.2)	16 (14.7)	5 (27.8)	2 (18.2)	
CT findings [a], n (%)						0.01[F]
Positive	165 (31.4)	69 (16.6)	95 (87.2)	17 (94.4)	10 (90.9)	
Negative	360 (68.6)	346 (83.4)	14 (12.8)	1 (5.6)	1 (9.1)	
Smoking, n (%)						0.12[K]
Smoker	77 (14.7)	64 (15.4)	13 (11.9)	0	0	
Quit	50 (9.5)	31 (7.5)	19 (17.4)	3 (16.7)	0	
Non-smoker	398 (75.8)	320 (77.1)	77 (70.6)	15 (83.3)	11 (100.0)	
Comorbidity [a], n (%)						0.01[F]
Not present	299 (57.0)	266 (64.1)	33 (30.3)	2 (11.1)	1 (9.1)	
Present	226 (43.0)	149 (35.9)	76 (69.7)	16 (88.9)	10 (90.9)	
HT [c]	125 (23.8)	73 (17.6)	52 (47.7)	8 (44.4)	5 (45.5)	0.01[A]
DM [c]	73 (13.9)	42 (10.1)	31 (28.4)	7 (38.9)	4 (36.4)	0.01[A]
HL [c]	49 (9.3)	27 (6.5)	21 (19.3)	4 (22.2)	3 (27.3)	0.01[A]
Asthma/COPD [d]	48 (9.1)	26 (6.3)	22 (20.2)	6 (33.3)	4 (36.4)	0.01[A]
CVD [c]	34 (6.5)	17 (4.1)	17 (15.6)	4 (22.2)	2 (18.2)	0.01[A]
Kidney diseases [f]	10 (1.9)	4 (1.0)	6 (5.5)	2 (11.1)	2 (18.2)	0.01[A]
CVO [a]	8 (1.5)	1 (0.2)	6 (5.5)	2 (11.1)	2 (18.2)	0.01[A]
Drug utilization [d], n (%)						0.01[F]
No	176 (33.5)	161 (38.8)	15 (13.8)	1 (5.6)	0	
Yes	349 (66.5)	254 (61.2)	94 (86.2)	17 (94.4)	11 (100.0)	
Medications (ATC codes)						
Drugs for acid rel. dis. [1] (A02)	110 (21.0)	72 (17.3)	38 (34.9)	6 (33.3)	2 (18.2)	
Drugs used in diabetes (A10)	64 (12.2)	34 (8.2)	30 (27.5)	7 (38.9)	4 (36.4)	
Antithrombotic agents (B01)	43 (8.2)	21 (5.1)	22 (20.2)	5 (27.8)	3 (27.3)	
Cardiac therapy (C01)	12 (2.3)	3 (0.7)	9 (8.3)	2 (11.1)	1 (9.1)	
Diuretics (C03)	10 (1.9)	6 (1.4)	4 (3.7)	1 (5.6)	1 (9.1)	
Beta blocking agents (C07)	42 (8.0)	22 (5.3)	20 (18.3)	4 (22.2)	1 (9.1)	
CCBs [2] (C08)	28 (5.3)	12 (2.9)	16 (14.7)	5 (27.8)	4 (36.4)	
Agents acting on RAS [3] (C09)	82 (15.6)	46 (11.1)	36 (33.0)	7 (38.9)	3 (27.3)	
Lipid modifying agents (C10)	31 (5.9)	13 (3.1)	18 (16.5)	4 (22.2)	2 (18.2)	
Endocrine drugs [4] (H)	27 (5.1)	19 (4.6)	8 (7.3)	0	0	
Nervous system (N)	150 (28.6)	104 (25.1)	46 (42.2)	7 (38.9)	3 (27.3)	
Drugs for obst. air. dis. [5] (R03)	50 (9.5)	32 (7.7)	18 (16.5)	5 (27.8)	3 (27.3)	
Antihistamines for systemic use (R06)	42 (8.0)	31 (7.5)	11 (10.1)	2 (11.1)	1 (9.1)	
Polypharmacy [a], n (%)						0.01[F]
No	465 (88.6)	390 (94.0)	74 (67.9)	12 (66.7)	8 (72.7)	
Yes	60 (11.4)	25 (6.0)	35 (32.1)	6 (33.3)	3 (27.3)	
Total, n (%)	525 (100.0)	415 (100.0)	109 (100.0)	18 (100.0)	11 (100.0)	

ATC: Anatomical Therapeutic Chemical Classification System, [a] The differences between outpatient and hospitalization, outpatient and ICU, outpatient and mortality are statistically significant. [b] The differences between outpatient and hospitalization, hospitalization and mortality are statistically significant. [c] The difference between outpatient and hospitalization is statistically significant. [d] The differences between outpatient and hospitalization, outpatient and mortality are statistically significant. [e] The differences between outpatient and ICU, hospitalization and ICU, mortality, and ICU are statistically significant. [f] The differences between mortality and outpatient, mortality and hospitalization, mortality, and ICU are statistically significant. [1] Drugs for acid-related disorders, [2] Calcium channel blockers, [3] Renin-angiotensin system, [4] Systemic hormonal preparations, excluding sex hormones and insulins, [5] Drugs for obstructive airway diseases, [F] Fisher's exact test, [K] Kruskal-Wallis test, [A] One-way analysis of variance (ANOVA)

Figure 1: Treatment change according to the months of COVID-19.



HCQ: hydroxychloroquine, AZITHRO: azithromycin

The COVID-19 treatment approach varied from March 2020 to November 2020 (Figure 1). While in April 2020, the predominant treatment was hydroxychloroquine, by November 2020, the predominant treatment was favipiravir according to guidelines of the Turkish Ministry of Health. Considering the mortality, ICU admission and hospitalization rates by month, the highest mortality rate was seen in June 2020 at 4.8%. The highest hospitalization and ICU admission rate was seen in March 2020, 92.9% and 14.3%, respectively (Table 2).

Table 2: Hospitalization, ICU admission, and survival rates by month.

	Hospitalization, n (%)		ICU admission, n (%)		Survival, n (%)	
	Yes	No	Yes	No	Exitus	Alive
March 2020	13 (92.9)	1 (7.1)	2 (14.3)	12 (85.7)	0	14 (100.0)
April 2020	36 (34.6)	68 (65.4)	3 (2.9)	101 (97.1)	1 (1.0)	103 (99.0)
May 2020	11 (40.7)	16 (59.3)	2 (7.4)	25 (92.6)	1 (3.7)	26 (96.3)
June 2020	15 (35.7)	27 (64.3)	3 (7.1)	39 (92.9)	2 (4.8)	40 (95.2)
July 2020	5 (18.5)	22 (81.5)	0	27 (100.0)	0	27 (100.0)
August 2020	7 (11.3)	55 (88.7)	2 (3.2)	60 (96.8)	1 (1.6)	61 (98.4)
September 2020	8 (9.6)	75 (90.4)	0	83 (100.0)	0	83 (100.0)
October 2020	6 (10.7)	50 (89.3)	2 (3.6)	54 (96.4)	2 (3.6)	54 (96.4)
November 2020	8 (7.3)	102 (92.7)	4 (3.6)	106 (96.4)	4 (3.6)	106 (96.4)
Total	109 (20.8)	416 (79.2)	18 (3.4)	507 (96.6)	11 (2.1)	514 (97.9)

Increasing age was associated with an increased probability of hospitalization, mortality (P=0.01), and ICU admission (P=0.04). In addition, the presence of thoracic CT findings increased the probability of hospitalization 21 times (P<0.001), and polypharmacy increased the probability of hospitalization by two times (P=0.03). Those with thoracic CT findings were 18 times more likely to be admitted to the ICU than those without (P=0.01). Being married was associated with a reduced probability of ICU admission (P=0.02) (Table 3).

Table 3: Effects of demographic and other characteristics of patients on hospitalization, ICU admission, and mortality.

	Hospitalization		ICU admission		Mortality	
	OR (%95 CI)	*P*-value*	OR (%95 CI)	*P*-value*	OR (%95 CI)	*P*-value*
Age	1.0 (1.0-1.1)	0.01	1.0 (1.0-1.1)	0.04	1.1 (1.0-1.2)	0.01
Gender (Male)	1.7 (0.9-3.1)	0.11	3.2 (0.9-11.7)	0.07	1.6 (0.3-8.8)	0.58
Marital status (Alone)	0.6 (0.3-1.2)	0.15	0.2 (0.1-0.8)	0.02	0.2 (0.0-1.3)	0.10
Smoking	0.7 (0.3-1.7)	0.46	NA	1.00	NA	1.00
Being symptomatic	2.0 (0.9-4.7)	0.10	1.4 (0.2-12.7)	0.76	0.6 (0.1-6.4)	0.66
Thorax CT finding positivity	21.4 (11.0-41.6)	<0.001	18.6 (2.2-158.0)	0.01	7.0 (0.8-64.3)	0.08
Presence of comorbidity	1.0 (0.5-2.2)	0.98	2.6 (0.3-21.3)	0.37	0.7 (0.1-9.2)	0.81
Drug use	1.4 (0.6-3.3)	0.39	1.6 (0.1-23.8)	0.75	NA	1.00
Polypharmacy	2.7 (1.1-6.3)	0.03	0.8 (0.2 – 2.7)	0.72	0.4 (0.1-2.0)	0.29

NA: not applicable, *Logistic regression

The number of patients with asthma/chronic obstructive pulmonary disease (COPD) was 48 (Table 1). In 62.5% of these patients, COVID-19 thoracic CT findings were positive. Asthma/COPD was associated with developing thoracic CT findings; $x^2(1)=23.667$; P=0.007.

There was no statistically significant difference in developing COVID-19 thoracic CT findings between never smoked/quit smoking and being a smoker (P=0.13). The same was true when non-smokers were compared with quitting/smoking (P=0.25). The effects of medications chronically used in the previous 6 months before contracting COVID-19 on hospitalization, ICU admission, and death were analyzed using the logistic regression models adjusted for age and comorbidity. DM medications increased the probability of hospitalization by three times (P=0.03) (Table 4), while CCBs increased the probability of admission to the ICU 15 times (P=0.01) (Table 5) and the probability of mortality 295 times (P=0.01) (Table 6). When DM drugs are subdivided into metformin, sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors, GLP-1 agonists, DPP4 inhibitors, SGLT-2 inhibitors, and insulin, in the logistic regression model adjusted for age and comorbidity, there was no statistically significant difference between the subgroups of DM medications in terms of effects on hospitalization, ICU admission, or mortality (P>0.05).

Table 4: Effects of medications utilized in the last six months before contracting COVID-19 on hospitalization.

	Hospitalization			
	OR	%95 CI		*P*-value*
Medications (ATC codes) [1]				
Drugs for acid related disorders (A02)	1.0	0.5	1.8	0.96
Drugs used in diabetes (A10)	3.9	1.2	13.0	0.03
Antithrombotic agents (B01)	1.4	0.5	3.9	0.52
Cardiac therapy (C01)	3.0	0.5	18.3	0.24
Diuretics (C03)	0.9	0.1	5.3	0.89
Beta blocking agents (C07)	1.2	0.4	3.4	0.78
Calcium channel blockers (C08)	1.5	0.6	4.1	0.41
Agents acting on renin-angiotensin system (C09)	0.9	0.4	2.3	0.86
Lipid modifying agents (C10)	2.8	0.7	11.6	0.16
Endocrine system agents [2] (H)	0.5	0.2	1.4	0.19
Nervous system (N)	1.5	0.9	2.6	0.15
Drugs for obstructive airway diseases (R03)	0.6	0.2	1.6	0.33
Antihistamines for systemic use (R06)	1.0	0.4	2.5	0.96
Covariates				
Age	1.1	1.0	1.1	<0.001
Hypertension	0.9	0.3	2.2	0.77
Cardiovascular disease	0.7	0.2	2.5	0.56
Cerebrovascular disease	1.2	0.2	9.5	0.83
Asthma/COPD [3]	2.4	0.9	6.2	0.07
Chronic kidney disease	1.5	0.3	6.9	0.62
Hyperlipidemia	0.4	0.1	1.3	0.12
Diabetes	0.5	0.2	1.7	0.28

[1]Anatomical Therapeutic Chemical Classification System, [2]Systemic hormonal preparations, excluding sex hormones and insulins, [3]COPD: chronic obstructive pulmonary disease, *Logistic regression

Table 5: Effects of medications utilized in the last 6 months before contracting COVID-19 on ICU admission.

	ICU admission			
	OR	%95 CI		*P*-value*
Medications (ATC codes) [1]				
Drugs for acid related disorders (A02)	0.3	0.1	1.9	0.22
Drugs used in diabetes (A10)	5.8	0.4	87.9	0.21
Antithrombotic agents (B01)	1.6	0.2	14.4	0.67
Cardiac therapy (C01)	0.6	0.0	15.6	0.79
Diuretics (C03)	0.2	0.0	6.2	0.34
Beta blocking agents (C07)	1.2	0.1	21.2	0.91
Calcium channel blockers (C08)	15.8	2.1	120.2	0.01
Agents acting on renin-angiotensin system (C09)	2.2	0.2	21.5	0.49
Lipid modifying agents (C10)	3.8	0.1	131.1	0.46
Endocrine system agents [2] (H)	0.0	0.0	NA[4]	1.00
Nervous system (N)	1.0	0.3	3.7	0.94
Drugs for obstructive airway diseases (R03)	0.9	0.1	7.6	0.90
Antihistamines for systemic use (R06)	1.0	0.1	8.2	0.98
Covariates				
Age	1.1	1.0	1.1	<0.001
Hypertension	0.0	0.0	0.6	0.02
Cardiovascular disease	3.5	0.4	33.8	0.28
Cerebrovascular disease	2.2	0.1	59.2	0.63
Asthma/COPD [3]	6.8	0.8	56.0	0.08
Chronic kidney disease	2.4	0.2	28.5	0.49
Hyperlipidemia	0.1	0.0	4.0	0.23
Diabetes	0.6	0.0	9,2	0.71

[1] Anatomical Therapeutic Chemical Classification System, [2] Systemic hormonal preparations, excluding sex hormones and insulins, [3] COPD: chronic obstructive pulmonary disease, [4] NA: not applicable, * Logistic regression.

Table 6: Effects of medications utilized in the last 6 months before contracting COVID-19 on mortality.

	Mortality			
	OR	**%95 CI**		***P*-value***
Medications (ATC codes) [1]				
Drugs for acid related disorders (A02)	0.0	0.0	1.7	0.08
Drugs used in diabetes (A10)	14.8	0.1	3929.6	0.34
Antithrombotic agents (B01)	11.8	0.6	245.0	0.11
Cardiac therapy (C01)	8.5	0.0	11943.9	0.56
Diuretics (C03)	0.0	0.0	2.2	0.09
Beta blocking agents (C07)	0.0	0.0	NA[4]	1.00
Calcium channel blockers (C08)	295.1	4.6	18946.6	0.01
Agents acting on renin-angiotensin system (C09)	0.5	0.0	12.8	0.68
Lipid modifying agents (C10)	114.4	0.0	NA[4]	0.36
Endocrine system agents [2] (H)	0.0	0.0	NA[4]	1.00
Nervous system (N)	0.1	0.0	1.9	0.14
Drugs for obstructive airway diseases (R03)	1.3	0.0	46.5	0.90
Antihistamines for systemic use (R06)	0.5	0.0	33.9	0.73
Covariates				
Age	1.1	1.0	1.3	<0.001
Hypertension	0.0	0.0	1.4	0.08
Cardiovascular disease	73.9	2.1	2622.5	0.02
Cerebrovascular disease	NA[4]	0.0	NA[4]	1.00
Asthma/COPD [3]	13.4	0.4	426.4	0.14
Chronic kidney disease	9.5	0.1	867.2	0.33
Hyperlipidemia	0.0	0.0	22.5	0.17
Diabetes	0.7	0.0	158.5	0.91

[1] Anatomical Therapeutic Chemical Classification System, [2] Systemic hormonal preparations, excluding sex hormones and insulins, [3] COPD: chronic obstructive pulmonary disease, [4] NA: not applicable, * Logistic regression.

Regarding COVID-19 pharmacological treatments, according to the Chi-square analysis that included only hospitalized patients, different COVID-19 pharmacological treatments were not associated with ICU admission and mortality (P>0.05).

Discussion

In this study, carried out in the first wave of COVID-19, the effects of demographic data and drugs chronically utilized in the last 6 months before contracting COVID-19 on the probability of hospitalization, ICU admission, and mortality were examined in primary care. Increasing age was associated with all three main endpoints of the study. In addition, the presence of COVID-19 thoracic CT findings and polypharmacy were associated with an increased probability of hospitalization while being alone, and the presence of COVID-19 thoracic CT findings was associated with an increased probability of ICU admission. Regarding drugs, DM medications increased the probability of hospitalization, and CCBs increased the probability of ICU admission and mortality.

Increasing age and comorbidity are important risk factors for the severe clinical course of COVID-19 since the beginning of the COVID-19 pandemic [1,2,4]. We also obtained similar results in our study; HT, DM, hyperlipidemia, asthma/COPD, cardiovascular, kidney, and cerebrovascular diseases were associated with the clinical course of COVID-19. It was observed that HT increased the probability of ICU admission, while CVD increased the probability of mortality 73 times.

Since the beginning of the pandemic, numerous studies have shown that ACEI/ARBs are associated with COVID-19 in harmful or protective ways. According to data from most large-scale studies and meta-analyses, RAS blockers do not change the clinical course of COVID-19 [7,19,20]. Similar findings were obtained in our study; it was observed that ACEI and ARBs did not affect the clinical course of COVID-19.

In our study, it was also observed that DM medications increased the probability of hospitalization 3-fold. However, it did not affect ICU admission and mortality. In the logistic regression analysis, DM medications were divided into metformin, sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors, GLP-1 agonists, DPP4 inhibitors, SGLT-2 inhibitors, and insulin; no significant difference was observed between the drug groups in terms of their effects on hospitalization. However, a Chi-square analysis revealed that all DM drug subgroups were associated with hospitalization, and SGLT-2 inhibitors were associated with mortality and admission to the ICU. In the literature, it is stated that the use of metformin is generally associated with a decrease in mortality due to COVID-19, while the use of insulin is associated with an increase [11,12,21].

Regarding other DM drug groups, some publications show different results from each other. In a study involving 2.85 million patients with type 2 DM in the UK, statistical evidence was presented that patients receiving metformin, SGLT2 inhibitors, and sulfonylurea treatments had a lower risk of death than those who did not take these drugs. The same study determined that the risk of death was higher in those given insulin and DPP-4 inhibitors than in those who did not [11].

According to Yang et al.'s [12] meta-analysis, which included 17 studies and analyzed data from approximately 21,000 patients, metformin was associated with significantly reduced mortality in COVID-19 patients with DM. Regarding insulin therapy, in Yu et al.'s study, in addition to matching other medical characteristics, propensity score matching was applied to HbA1c levels, and insulin therapy was associated with increased mortality. It has been stated that insulin therapy at a more advanced stage in type 2 DM may be a residual confounding factor, although pairings have been made [21]. Unfortunately, we could not make a match based on the clinical level of DM in the case of DM drugs. In our study, which included 525 COVID-19 patients, 64 were diagnosed with DM and 64 received DM medication. When DM medications were divided into subgroups, there was no difference in their effects on the three main endpoints of this study, which may be due to the small patient groups. Regarding DPP4 inhibitors, a meta-analysis stated that they were associated with higher mortality in COVID-19 patients [11], whereas another stated the opposite [15]. In Hariyanto et al.'s [16] study, DPP-4 inhibitors did not change the severity of COVID-19.

In our study, CCBs are closely related to ICU admission and increased mortality. Studies were showing parallel findings [22,23]. In Mendez et al.'s [22] study, including 245 HT patients hospitalized due to COVID-19, 75 patients using CCBs and 175 patients not using CCBs were compared. CCB group had a significantly increased risk of intubation or death. In Jackson et al.'s [23] study, the need for mechanical ventilation and mortality were investigated in 297 hospitalized COVID-19 patients; prior ARB or CCB use was found to double the probability of mortality. According to a population case-control study, the risk of developing COVID-19 symptoms in people with HT who received CCBs was significantly increased, and disease risk was significantly lower in ARB and diuretic users [24].

On the other hand, studies indicating that CCBs reduce the mortality of COVID-19 or the possibility of serious illness

have also been published [25,26]. A study by Chouchana et al. [26], which included 3686 patients with HT hospitalized for COVID-19, demonstrated that CCBs reduced the probability of mortality [25]. In a meta-analysis, there was a significant reduction in all-cause mortality and disease severity in CCB users.

Considering why CCBs may worsen the COVID-19 clinic, as in our study, CCBs can inhibit type II pneumocyte secretion, leading to alveolar collapse [27]. In addition, precapillary vasodilation due to CCBs may cause alveolar edema [28–31]. Another reason may be that CCBs may cause hypoxic pulmonary vasoconstriction in patients with pulmonary disease, leading to profound hypoxemia [22,32–35]. On the other hand, the reason why CCBs may improve the clinical course of COVID-19 is that calcium is necessary for the virus's life cycle, so CCBs cause depletion in intracellular calcium, interfering negatively with the life cycle process [36,37]. *In vitro* studies suggest that CCBs can be used in therapy by reducing intracellular calcium levels, which provide the environment for virus entry [38]. Additionally, some studies have demonstrated the anti-inflammatory and anticoagulant effects of CCBs [37,39].

When we examined the effect of marital status on the clinical course of COVID-19, we found that being married reduced the possibility of ICU admission. In the literature, we could not find any other study examining the effect of marital status on the clinical course of COVID-19. In addition, publications are investigating the relationship between being married or living alone with the frequency of anxiety and depression during the COVID-19 pandemic; in these studies, it was stated that the frequency of depression was higher in the COVID-19 pandemic in those who were single [40,41]. This may lead to suppression of the immune system and be associated with a worse clinical course of COVID-19. It needs to be confirmed by larger studies.

Strengths and limitations

This study is the first study in Turkey investigating the relationship between drug utilization in chronic diseases and COVID-19 clinical course using primary care data. In the study by Senkal et al. [42], 611 hospitalized COVID-19 patients were included in the study, and they aimed to reveal the possibility of severe COVID-19 clinics in patients under ACEI or ARB treatment. It was concluded that chronic ACEI exposure was associated with a reduced likelihood of serious disease. Since our study presented primary care data, we had the opportunity to compare the effects of chronically used drugs on the clinical course of COVID-19 between outpatients diagnosed with COVID-19 and patients admitted to the hospital, ICU, or death. It is known that some genetic and ethnic factors under investigation, especially ACE2 and TMPRSS2 expression, may predispose to COVID-19. Accordingly, it has been reported that some patients might experience the disease more severely or mildly [17,18]. In this context, studies conducted in different countries that reveal the factors affecting the clinical course of COVID-19 gain importance.

One of the limitations of our study is that it was impossible to exclude all confounders since this study was retrospective. For example, since the anthropometrics of the patients were not known, the presence of overweight status was unknown if the obesity diagnosis was not stated in the patient records. Other than that, when the study population of 525 was subdivided, there was a small number of patients for comparison. Regarding CCBs, although the established logistic regression models have been adjusted for age and comorbidity, it should be considered that they are mostly used in the elderly hypertensive population.

Conclusion

We have demonstrated that increasing age, HT, and CVD are associated with the severe clinical course of COVID-19; being married reduces the probability of ICU admission due to COVID-19. Concerning drugs, DM medications increased the probability of hospitalization 3-fold, while CCBs increased the probability of ICU admission 155-fold and mortality 295-fold. On the other hand, it was observed that RAS blockers (ACEIs and ARBs) did not affect the clinical course of COVID-19. Larger cohort studies and meta-analyses, as with ACEI and ARBs, are needed for CCBs and DM medications.

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