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

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Abstract

Aim: To examine the effects of drug use in the last 6 months before contracting coronavirus disease-2019 (COVID-19) on the clinical course of COVID-19. Methods: In this retrospective cohort study, which included 525 patients diagnosed with COVID-19 between March and November 2020 from four different family health centers in Istanbul, the records of the patients were retrospectively analyzed. In addition to demographic information, all medications 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 by 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. While increasing age is associated with hospitalization, ICU admission and mortality; also, the presence of COVID-19 thoracic computed tomography (CT) findings and polypharmacy were associated with an increased hospitalization; living alone and the presence of COVID-19 thoracic CT findings were associated with an 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: Previously utilization of DM medications and CCBs may have negative effects on the clinical course of COVID-19.

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Running head: Chronic drug utilization and COVID-19

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The authors confirm that the principal investigator for this study is Dr. Ülkü Sur Ünal, and that she had direct clinical responsibility for patients.

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What is already known about this subject:

1. A complete consensus has not yet been reached on the effect of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the COVID-19 clinical course.
2. Metformin and insulin are associated with better and poor COVID-19 clinical course, respectively.
3. There are inconclusive results about calcium-channel blockers on COVID-19 clinical course.

What this study adds:

1. Diabetes mellitus drugs increase the likelihood of hospitalization due to COVID-19.
2. Calcium-channel blockers increase the probability of ICU hospitalization and mortality due to COVID-19.
3. No effect of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on COVID-19 clinical course was detected.

Abstract

Aim: To examine the effects of drug use in the last 6 months before contracting coronavirus disease-2019 (COVID-19) on the clinical course of COVID-19.

Methods: In this retrospective cohort study, which included 525 patients diagnosed with COVID-19 between March and November 2020 from four different family health centers in Istanbul, the records of the patients were retrospectively analyzed. In addition to demographic information, all medications 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 by 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. While increasing age is associated with hospitalization, ICU

admission and mortality; also, the presence of COVID-19 thoracic computed tomography (CT) findings and polypharmacy were associated with an increased hospitalization; living alone and the presence of COVID-19 thoracic CT findings were associated with an 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: Previously utilization of DM medications and CCBs may have negative effects on the clinical course of COVID-19.

Inroduction

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 all over the world since the last months of 2020. On the other hand, studies on which factors affect the severity of the disease are still continuing. Studies to date 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 was 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], 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, studies in which metformin was associated with decreased mortality and insulin was associated with increased mortality were published [11–14]. Regarding dipeptidyl peptidase-4 (DPP4) inhibitors, results have been reported that they are associated with 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.

Methods

The study, which is a retrospective cohort type, started in May 2020 under the direction of 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. Of these patients, those who were diagnosed with COVID-19 between March 11, 2020 - November 30, 2020, constituted the population of the study.

Inclusion criteria were to be a patient enrolled in the above-mentioned FHCs 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 data of the patients were collected by the resear-

cher 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 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 used in the previous 6 months. 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, the need for intensive care unit (ICU), and mortality in comparative analyses.

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 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. The direction of the comparisons was confirmed by correlation analysis and Pearson chi-square test. All logistic regression models were adjusted for age and comorbid conditions. Demographic data were also compared between outpatients, hospitalization, ICU admission and mortality using Pearson-chi square test, when needed Fisher's exact test. For parameters with nonnormal distribution, ranks were compared using Kruskal–Wallis test. For normally distributed parameters, means were compared using one-way analysis of variance (ANOVA) test. In the presence of significant variables Tukey's post hoc test was performed after ANOVA test, Dunn test was performed after Kruskal-Wallis test and Pearson chi-square or Fisher's exact test in pairs were performed after Pearson chi-square or Fisher's exact test.

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 starting to collect 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 in accordance with the principles in the Declaration of Helsinki.

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 patients who were hospitalized or in the ICU or who died compared to outpatients ($p < 0.01$) (Table 1). Education level, employment status and occupation data were not included in the analyzes because the relevant data were not available for all of the study population.

The COVID-19 treatment approach varied in time 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 Turkish Ministry of Health. Considering the mortality, ICU admission and hospitalization rates by month, the highest mortality rate was seen in June 2020 with 4.8%. The highest rate of hospitalization and ICU admission was seen in March 2020; 92.9% and 14.3%, respectively (Table 2).

Increasing age was associated with an increased probability of hospitalization ($p<0.05$), ICU admission, and mortality ($p<0.01$). In addition, the presence of thoracic CT findings increased the probability of hospitalization 21 times ($p<0.01$), polypharmacy increased the probability of hospitalization by two times ($p<0.05$). 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 ($p<0.05$) (Table 3).

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; $x^2(1) = 23.667$; $p<0.01$.

There was no statistically significant difference in developing COVID-19 thoracic CT findings between never smoked/quit smoking and being a smoker ($p>0.05$). The same was true when non-smokers were compared with quitting/smoking ($p>0.05$).

The effects of medications used in the previous 6 months before contracting COVID-19 on hospitalization, ICU admission or dead were analyzed using the logistic regression models adjusted for age and comorbidity. DM medications increased the probability of hospitalization 3 times ($p<0.05$) (Table 4), while CCBs increased the probability of admission in the ICU 155 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 subgorups of DM medications in terms of effects on hospitalization, ICU admission or mortality ($p>0.05$).

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, which was carried out in the first wave of COVID-19, the effects of demographic data and drugs utilized in the last 6 months before contracting COVID-19 on the probability of hospitalization, ICU admission or mortality were examined. Increasing age was associated with all three main endpoints of the study, which were listed as hospitalization, ICU admission, and mortality. In addition, the presence of COVID-19 thoracic CT findings and polypharmacy was associated with an increased probability of hospitalization and being alone and the presence of COVID-19 thoracic CT findings were associated with an increased probability of ICU admission. When the effects of drugs used in the last 6 months before contracting COVID-19 were examined, it was seen that DM medications increased the probability of hospitalization, and CCBs increased the probability of ICU admission and mortality.

Increasing age and the presence of comorbidity have been shown to be an important risk factor 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 (Table 5), while CVD increased the probability of mortality 73 times (Table 6).

Numerous studies have been conducted since the beginning of the pandemic 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 had no effect on the clinical course of COVID-19.

In our study, it was also observed that DM medications increased the probability of hospitalization three fold (Table 4). However, it had no effect on ICU admission and mortality. In the logistic regression analysis when DM medications were divided into subgroups as 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, chi-square analysis revealed that all DM drug subgroups were associated with hospitalization, and SGLT-2 inhibitors were also associated with mortality and admission in the ICU. In the literature, it is stated that the use of metformin is generally associated with a decrease, while the use of insulin is associated with an

increase in mortality due to COVID-19 [11,12,21]. Regarding other DM drug groups, there are publications that 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 [11]. In the same study, it was determined that the risk of death was higher in those whose given insulin and DPP-4 inhibitors than those who did not [11].

According to the results of Yang et al.'s meta-analysis, which included 17 studies and analyzed data from a total of approximately 21.000 patients, metformin was associated with significantly reduced mortality in COVID-19 patients with DM [12]. 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 the use of insulin therapy at a more advanced stage in type 2 DM may be a residual confounding factor, although pairings have been made [21]. Although age and comorbidity were added to the logistic regression models as confounding factors when analyzing the effects of chronically used drugs on hospitalization, ICU admission, and mortality, 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 in total, 64 of these patients were diagnosed with DM and 64 were receiving DM medication. When divided DM medications into subgroups, there was no difference between the subgroups in terms of their effects on the three main endpoints of this study, which may due to the small patient groups. According to two meta-analyses examining the relationship between DPP4-inhibitors and mortality due to COVID-19, contrary to the results of Khunti et al.'s study on DPP4-inhibitors [11], Rakhmat et al. stated in their study that the use of DPP-4 inhibitors was associated with lower mortality in COVID-19 patients [15]. In the study by Hariyanto et al., they stated that DPP-4 inhibitors did not change the results of COVID-19 [16].

According to the results of our study, CCB use is closely related to ICU admission and increased mortality. There were studies showing parallel findings with our study regarding CCBs [22,23]. In the study of Mendez et al., 245 patients hospitalized due to COVID-19 and diagnosed with HT were included; the data of 75 patients using CCBs and 175 patients not using CCBs were compared. Those who received dihydropyridine group CCBs had a significantly increased risk of intubation or death compared to those who did not [22]. In the study conducted by Jackson et al., which included 297 patients, the need for mechanical ventilation and mortality were investigated in patients hospitalized with the diagnosis of COVID-19. ARB or CCB use before hospitalization for COVID-19 was found to double the probability of death (aORs, 2.02 [95% CI, 1.03-3.96] and 1.91 [95% CI, 1.03-3, 55]) [23]. According to a population case-control study examining the development of symptoms and contracting COVID-19 with chronically used drugs, the risk of developing COVID-19 symptoms in people with HT who received CCBs was significantly increased (OR) = 1.73; 95% CI 1.2–2.3), disease risk was significantly lower in ARB and diuretic users (OR = 0.22; 95% CI 0.15–0.30, and OR = 0.30; 95% CI, respectively). 0.19-0.58) [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]. In a study by Chouchana et al., which included 3686 patients with HT hospitalized for COVID-19, demonstrated that CCBs reduced the probability of mortality [25]. In a meta-analysis, it was stated that there was a significant reduction in all-cause mortality and disease severity in CCB users [26].

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, when we evaluate why CCBs may improve the clinical course of COVID-19; since calcium is necessary for virus penetration into the cell, viral gene expression, processing of viral proteins, and viral maturation and extracellular release, CCBs cause depletion in intracellular calcemia, thus negatively interfering with the life cycle of the virus. CCBs can inhibit viral replication by reducing intracellular calcium levels [36,37]. On the other hand, 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].

Thiazolidinediones, aspirin and famotidine, which are among the medications whose effects on the clinical course of COVID-19 were examined in previous studies, were included in the logistic regression models within their main groups (diuretics, anticoagulants, stomach drugs; respectively) in our study. However, they were found to have no effect on all three study endpoints. A meta-analysis of aspirin suggests that aspirin use is associated with a lower risk of death from COVID-19 [40]. In a case-control study, however, aspirin had no effect on the COVID-19 clinic [41]. Regarding famotidine, in the study of Yeramaneni et al., 7158 patients were included and it was stated that famotidine had no effect on mortality due to COVID-19 [42].

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, there are publications 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 [43,44]. 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.

As far as we know, our study was 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., 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 [45]. 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 who were admitted to the hospital, ICU or dead. It is known that some genetic and ethnic factors under investigation, especially ACE2 and TMPRSS2 expression, may predispose to COVID-19. Accordingly, it had been reported that some patients may experience the disease more severely or mildly [17,18,46–49]. 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 not possible to exclude all confounders, since this study was retrospective. For example, since the antropometrics 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.

To conclude, 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. In addition, DM medications increased the probability of hospitalization three fold; while CCBs increased the probability of ICU admission 155 fold and the probability of 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. In conclusion, larger cohort studies and meta-analyses as with ACEI and ARBs, are needed for CCBs and DM medications.

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Contributors

Ü.S.Ü and A.K. proposed the concept, involved in the design of the study and preparation of the manuscript. Ü.S.Ü was the principal investigator for the study. Ü.S.Ü, Y.D.K., M.K. and F.G. collected the data. Ü.S.Ü, H.R.Y. and Ö.K.Ü. involved in the analysis and interpretation of data. A.K. and H.R.Y. revised the manuscript. All authors reviewed and approved the final manuscript.

Conflict of interest statement

None of the other authors declared any competing financial interests.

Availability of data

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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