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Original Article

Association of Cardiovascular Disease, Respiratory Diseases, and Diabetes Treatment With COVID-19 Mortality in Hospitalized Patients

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Abstract

Background: The prevalence of the coronavirus disease 2019 (COVID-19) in patients with preexisting non-communicable disease was high, and there was a question regarding the effect of the usage of medications on COVID-19 outcomes in these patients. Therefore, this study investigated the outcome of patients with different cardiovascular diseases (CVDs), respiratory diseases, and diabetes drug use.

Methods: In this analytical longitudinal study, information was collected on clinical laboratory data, COVID-19 severity, comorbidities, and drug use. The follow-up time was from enrollment to discharge or death.

Results: A total of 1046 hospitalized patients with COVID-19 participated in this analytical longitudinal study. The most commonly used drugs were CVD drugs (39.4%) and diabetes drugs (19.7%). The frequency of drug use was statistically similar between survivors and non-survivors except for diabetic drug use which was significantly higher in non-survivors ($P=0.04$). Patients who used the diabetic drugs were more likely to die (odds ratio [OR]: 1.41, 95% CI: 1.008-1.97). Moreover, the association was not significant after adjusting to confounding factors, and there was no significant association between other drug use and death in patients with COVID-19.

Conclusion: The result of the present study showed that antihypertensive treatments, antidiabetic, and respiratory disease drugs were not associated with higher deaths in hospitalized patients with COVID-19.

Keywords: COVID-19, Non-communicable diseases, Drug, Mortality

Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory infectious disease that started the pandemic in March 2020.[1] Since the beginning of this article, more than 692 million cases and six million deaths have been officially reported.[2]

Considering the high mortality rate associated with COVID-19, the factors associated with death were investigated in different studies. The presence of preexisting comorbidities was one of the main reasons for higher mortality in these patients.[3-7] Instead, the association between medication use and the risk of mortality in COVID-19 patients was investigated in various studies. For example, some studies suggested that since antihypertensive drugs increase Angiotensin-converting enzyme 2 (ACE2) expression,[8-11] they could worsen the prognosis of COVID-19. However, some other investigations suggested that the use of antihypertensive medications has a protective effect on acute lung injury.[12]

In terms of diabetes, earlier studies showed that the severity and odds of mortality are significantly higher in patients with poorly controlled glycemia compared to people with well-controlled glycemia. However, the results of studies regarding the effect of anti-diabetic agents[13] and respiratory medication[14] on COVID-19 outcomes were inconclusive.

Considering the high prevalence of COVID-19 in patients with preexisting non-communicable diseases, the usage of drugs warrants great concern. Indeed, controversy remains regarding the usage of these medications on the vulnerable population. Owing to the fact that Iran is amongst the countries with a high prevalence of non-communicable diseases and accordingly the drug treatment,[15] we hypothesized that medication use may be an important factor in the high rate of COVID-19 mortality in Iran. Therefore, we aimed to investigate the outcome of patients with different cardiovascular diseases (CVDs), respiratory, and diabetes drug use.

Methods

In this analytical longitudinal study, we used the data of hospitalized patients with COVID-19 in Imam-Reza Hospital, the main referral hospital for COVID-19 patients in East Azerbaijan. The inclusion criteria were the affirmation of COVID-19 by reverse transcription-polymerase chain reaction (RT-PCR) test or lung imaging features.

For obtaining demographic features and smoking status, the author-designed questionnaires were used, and for recording the laboratory data, the patient's medical reports were used. On admission, the nurses recorded the information regarding the patient's comorbidities and current drug use.

CVD was defined as having hypertension, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, or heart failure. Diabetes includes both type I diabetes and type II diabetes. This information was gathered from the patient or primary next of kin. For assessing COVID-19 severity, quick sequential organ failure assessment (qSOFA) score and confusion, urea, respiratory rate, blood pressure, and 65 years of age or older (CURB-65) scores were used. In this regard, information regarding the Glasgow Coma Scale, respiratory rate, blood pressure, blood urea nitrogen, and age were obtained. The severe COVID-19 was defined as qSOFA scores ≥ 2 or CURB-65 scores ≥ 3.[16,17] The follow-up time was from enrollment until discharge or death.

Statistical Analysis

We used SPSS version 25 for data analysis. The Kolmogorov-Smirnov test was applied to test if the data comes from the normal distribution., and the descriptive statistics were presented as mean and standard deviations for numeric variables and as frequency (%) for categorical and nominal data. Then, the between-group comparisons were done using an independent t-test, and chi-square test, with Fisher's exact test as necessary. Logistic regression analysis in both crude and adjusted models (adjusted for age, sex, smoking, COVID-19 severity, and comorbidities) was applied to evaluate an association between different drug category use and mortality. Furthermore, the significance level was set at 0.05.

Results

A total of 1046 hospitalized patients with COVID-19 participated in this longitudinal study. The patients' mean age was 63.48 ± 17.06 (95% confidence interval [CI]: 62.58-64.38) years, and 54.6% of them were male. Overall, 18.20% of patients were died.

As can be seen in Table 1, the survivors were significantly younger than non-survivors ($P < 0.001$). Being a smoker ($P = 0.005$) and non-survivor was significantly more diabetic than being a survivor ($P = 0.003$).

As presented in Table 2, the most common drugs used were CVD drugs (45.7%) and diabetes drugs (19.7%). There were no significant differences between survivors and non-survivors regarding drug use except for diabetic agent use which was significantly higher in non-survivors ($P = 0.04$).

As can be inferred from Table 3, patients who used diabetic drugs were more likely to die (Odds ratio [OR]: 1.41, 95% CI: 1.008-1.97). This association was not significant when adjusted for demographic characteristics, disease severity, and comorbidities. Moreover, there was no significant association between other drug use and death in patients with COVID-19 in both adjusted and non-adjusted models ($P > 0.05$).

Table 1. The Baseline Characteristics of Patients

Demographic Variables	Total (n = 1406)	Non-survivors (n = 256)	Survivors (n = 1150)	*P* Value
Age (y), Mean ± SD	63.48 ± 17.06	69.13 ± 14.17	62.21 ± 17.28	< 0.001 [a]
Gender, Males, n (%)	769 (54.6)	149 (58.2)	620 (53.9)	0.2 [b]
Smoking, n (%)	77 (5.4)	21 (8.2)	56 (4.8)	0.005 [b]
Comorbidities, n (%)				
CVD	643 (45.7)	121 (47.2)	521 (45.3)	0.09 [b]
Respiratory diseases	183 (13.01)	39 (15.2)	144 (12.5)	0.7 [b]
Urologic diseases	127 (9.03)	25 (9.7)	101 (8.7)	0.24 [b]
Diabetes	324 (23.04)	72 (28.2)	252 (21.9)	0.003 [b]
Carcinoma	64 (4.5)	13 (5.07)	51 (4.4)	0.45 [b]
Obesity	312 (22.1)	53 (20.7)	259 (22.5)	0.52 [b]
BMI (kg/m^2) Mean ± SD	27.49 ± 5.04	27.51 ± 5.20	27.49 ± 5.01	0.97 [a]

Note. CVD: Cardiovascular disease; BMI: Body mass index; SD: Standard deviation.
[a] *P* value of independent t-test; [b] *P* value of chi-square.

Table 2. Comparison of the Different Drug Category Use between COVID-19 Survivors and Non-survivors

Drug Categories	Total (n = 1406)	Non-survivors (n = 256)	Survivors (n = 1150)	*P* Value
CVD drugs, n (%)	554 (39.4)	107 (41.79)	447 (38.8)	0.14
Respiratory drugs, n (%)	164 (11.6)	34 (13.2)	130 (11.3)	0.19
Diabetic drugs, n (%)	277 (19.7)	58 (22.6)	219 (19.04)	0.04
CVD and respiratory drugs, n (%)	105 (7.4)	22 (8.6)	83 (7.2)	0.32
CVD and diabetic drugs, n (%)	175 (12.4)	38 (14.8)	137 (11.9)	0.10
Respiratory and diabetic drugs, n (%)	42 (2.9)	8 (3.1)	34 (2.9)	0.77
CVD, diabetic, and respiratory drugs, n (%)	31 (2.2)	6 (2.3)	25 (2.17)	0.74

Note. CVD: Cardiovascular disease.

Discussion

Previously, different studies demonstrated that pre-existing non-communicable diseases were accompanied by higher mortality in patients with COVID-19.[18,19] However, few studies have been dedicated to the association between

Table 3. Logistic Regression Analysis of the Association Between Different Drug Category Use and COVID-19 Mortality

Variables	Crude Model			Multivariate Model[a]		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
CVD drugs	1.24	0.93-1.65	0.14	1.75	0.77-3.94	0.17
Respiratory drugs	1.31	0.87-1.97	0.19	1.02	0.15-6.78	0.98
Diabetic drugs	1.41	1.008-1.97	0.04	1.76	0.27-11.36	0.55
CVD and respiratory drugs	1.28	0.78-2.09	0.32	0.81	0.36-1.83	0.61
CVD and diabetic drugs	1.37	0.93-2.03	0.10	0.94	0.5-1.76	0.85
Respiratory and diabetic drugs	1.21	0.51-2.45	0.77	0.71	0.29-2.22	0.56
CVD, diabetic, and respiratory drugs	1.61	0.47-2.89	0.34	0.63	0.2-1.96	0.42

Note. CVD: Cardiovascular disease; OR: Odds ratio; CI: Confidence interval.
[a] Multivariate model was adjusted for age, gender, smoking, COVID-19 severity, and comorbidities.

non-communicable disease treatment and COVID-19 outcomes. In this study, we found that CVD drug use was not related to higher death in hospitalized patients with COVID-19. Some studies suggested that antihypertensive medications may increase ACE2 expression[20-22] and accordingly may be associated with the increased risk of incidence and severity of COVID-19. However, others showed no changes,[23,24] so, the effect of these drugs on ACE2 expression was inconclusive. A recent meta-analysis of 53 studies also showed no evidence of the association between antihypertensive medications and hospitalization, severity, and mortality of COVID-19.[25] Therefore, based on these findings, the antihypertensive medications should not be discontinued when patients already taken them.

In addition, the result of the present study indicated that the mortality risk was not significantly higher in patients who took respiratory medication. Some previous studies suggested that inhaled corticosteroids might decrease the severity of COVID-19. Studies revealed that adding steroids and β-agonists in cell lines decreases coronavirus replication and cytokine production.[26-28] However, in infected respiratory diseases other than COVID-19, inhaled corticosteroids are associated with an increased risk of severity.[29] A cohort study showed a higher mortality rate in patients prescribed inhaled corticosteroids.[14] The authors postulated that the observed result may be due to the presence of risk factors not recorded in the available data. In a systematic review, Cheng et al indicated that the use of inhaled corticosteroids in COVID-19 patients decreased the disease severity and hospital stay but did not have any significant impact on intensive care unit need and or death.[30]

We illustrated that antidiabetic drug use is significantly linked with death from COVID-19. However, after adjustment for covariates, this significant association was no longer observed. Since multiple treatments were used in diabetic patients, the results of previous studies were mixed. A recent meta-analysis study showed that diabetic patients who used metformin, sodium-glucose cotransporter-2 inhibitors, and glucagon-like peptide-1 receptor agonists have lower mortality rates than non-users. However, the patients who used insulin had a higher mortality rate than non-users.[31] Furthermore, metformin had anti-inflammatory effects and was associated with lower serum inflammatory biomarkers. This could positively affect disease severity and death in COVID-19 patients.[32] In previous systematic reviews, insulin therapy was significantly related to higher COVID-19 deaths.[31,33,34] Although insulin has anti-inflammatory and antioxidant effects, it may have pro-inflammation effects on the lungs, as shown in animal studies.[35] Moreover, studies displayed that insulin users on hospital admission have higher inflammatory markers, more coexisting disease, and lower lymphocyte counts compared to non-users which may predispose them to more severe COVID-19.[36]

This study had some limitations that may affect the generalizability of findings. It was a single-center study. However, Imam Reza hospital is the main referral hospital for COVID-19 in East Azerbaijan Province, Iran. Moreover, we only included the hospitalized patients. In addition, we did not record the names of drugs and just recorded the drug categories.

Conclusion

In conclusion, the results of the present study showed that after adjusting for demographic and lifestyle factors, COVID-19 severity and comorbidities, antihypertensive treatments, antidiabetic, and respiratory disease drugs were not accompanied by higher death in hospitalized patients with COVID-19. However, considering the limitations of the study, more prospective studies considering the exact name of medications not just their class are needed to confirm these findings.

Ethics statement

Before participation, all patients gave informed consent, and the Ethics Committee of Tabriz University of Medical Sciences approved the study (Ethics code: IR.TBZMED.REC.1398.1274).

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Conflict of interests declaration

None.

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References

1. Esakandari H, Nabi-Afjadi M, Fakkari-Afjadi J, Farahmandian N, Miresmaeili SM, Bahreini E. A comprehensive review of COVID-19 characteristics. Biol Proced Online. 2020;22:19. doi: 10.1186/s12575-020-00128-2.
2. Coronavirus Update. https://www.worldometers.info/coronavirus/.
3. Faghih Dinevari M, Somi MH, Sadeghi Majd E, Fattahzadeh A, Nikniaz Z. elevated liver aminotransferases level and COVID-19 prognosis in hospitalized patients: a prospective study from Iran. Middle East J Dig Dis. 2022;14(1):64-9. doi: 10.34172/mejdd.2022.257.
4. Faghih Dinevari M, Somi MH, Sadeghi Majd E, Abbasalizad Farhangi M, Nikniaz Z. Anemia predicts poor outcomes of COVID-19 in hospitalized patients: a prospective study in Iran. BMC Infect Dis. 2021;21(1):170. doi: 10.1186/s12879-021-05868-4.
5. Nikniaz Z, Somi MH, Faghih Dinevari M, Taghizadieh A, Mokhtari L. Diabesity associates with poor COVID-19 outcomes among hospitalized patients. J Obes Metab Syndr. 2021;30(2):149-54. doi: 10.7570/jomes20121.
6. Adab P, Haroon S, O'Hara ME, Jordan RE. Comorbidities and COVID-19. BMJ. 2022;377:o1431. doi: 10.1136/bmj.o1431.
7. Russell CD, Lone NI, Baillie JK. Comorbidities, multimorbidity and COVID-19. Nat Med. 2023;29(2):334-43. doi: 10.1038/s41591-022-02156-9.
8. 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(4):e21. doi: 10.1016/s2213-2600(20)30116-8 .
9. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, et al. 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.
10. Ishiyama Y, Gallagher PE, Averill DB, Tallant EA, Brosnihan KB, Ferrario CM. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. Hypertension. 2004;43(5):970-6. doi: 10.1161/01.HYP.0000124667.34652.1a .
11. Nicin L, Abplanalp WT, Mellentin H, Kattih B, Tombor L, John D, et al. Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts. Eur Heart J. 2020;41(19):1804-6. doi: 10.1093/eurheartj/ehaa311.
12. Rastkar M, Nikniaz L, Abbasalizad Farhangi M, Nikniaz Z. Circulating chemerin level and the risk of nonalcoholic fatty liver disease: a systematic review and meta-analysis. J Diabetes Metab Disord. 2023;22(1):83-95. doi: 10.1007/s40200-023-01187-4.
13. Nguyen NN, Ho DS, Nguyen HS, Ho DKN, Li HY, Lin CY, et al. Preadmission use of antidiabetic medications and mortality among patients with COVID-19 having type 2 diabetes: a meta-analysis. Metabolism. 2022;131:155196. doi: 10.1016/j.metabol.2022.155196.
14. Schultze A, Walker AJ, MacKenna B, Morton CE, Bhaskaran K, Brown JP, et al. Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an observational cohort study using the OpenSAFELY platform. Lancet Respir Med. 2020;8(11):1106-20. doi: 10.1016/s2213-2600(20)30415-x.
15. Esteghamati A, Meysamie A, Khalilzadeh O, Rashidi A, Haghazali M, Asgari F, et al. Third national Surveillance of Risk Factors of Non-Communicable Diseases (SuRFNCD-2007) in Iran: methods and results on prevalence of diabetes, hypertension, obesity, central obesity, and dyslipidemia. BMC Public Health. 2009;9:167. doi: 10.1186/1471-2458-9-167.
16. Chang CL, Sullivan GD, Karalus NC, Mills GD, McLachlan JD, Hancox RJ. Predicting early mortality in acute exacerbation of chronic obstructive pulmonary disease using the CURB65 score. Respirology. 2011;16(1):146-51. doi: 10.1111/j.1440-1843.2010.01866.x.
17. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of clinical criteria for sepsis: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):762-74. doi: 10.1001/jama.2016.0288.
18. Chudasama YV, Gillies CL, Appiah K, Zaccardi F, Razieh C, Davies MJ, et al. Multimorbidity and SARS-CoV-2 infection in UK Biobank. Diabetes Metab Syndr. 2020;14(5):775-6. doi: 10.1016/j.dsx.2020.06.003.
19. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020;323(20):2052-9. doi: 10.1001/jama.2020.6775.
20. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, et al. 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.
21. Furuhashi M, Moniwa N, Mita T, Fuseya T, Ishimura S, Ohno K, Shibata S, Tanaka M, Watanabe Y, Akasaka H, Ohnishi H, Yoshida H, Takizawa H, Saitoh S, Ura N, Shimamoto K, Miura T. Urinary angiotensin-converting enzyme 2 in hypertensive patients may be increased by olmesartan, an angiotensin II receptor blocker. Am J Hypertens. 2015;28(1):15-21. doi: 10.1093/ajh/hpu086.
22. Emilsson V, Gudmundsson EF, Aspelund T, Jonsson BG, Gudjonsson A, Launer LJ, Jennings LL, Gudmundsdottir V, Gudnason V. Antihypertensive medication uses and serum ACE2 levels: ACEIs/ARBs treatment does not raise serum levels of ACE2. medRxiv [Preprint]. 2020 May 25:2020.05.21.20108738. doi: 10.1101/2020.05.21.20108738.
23. Campbell DJ, Zeitz CJ, Esler MD, Horowitz JD. Evidence against a major role for angiotensin converting enzyme-related carboxypeptidase (ACE2) in angiotensin peptide metabolism in the human coronary circulation. J Hypertens. 2004;22(10):1971-6. doi: 10.1097/00004872-200410000-00020.
24. Burchill LJ, Velkoska E, Dean RG, Griggs K, Patel SK, Burrell LM. Combination renin-angiotensin system blockade and angiotensin-converting enzyme 2 in experimental myocardial infarction: implications for future therapeutic directions. Clin Sci (Lond). 2012;123(11):649-58. doi: 10.1042/cs20120162.

25. Ren L, Yu S, Xu W, Overton JL, Chiamvimonvat N, Thai PN. Lack of association of antihypertensive drugs with the risk and severity of COVID-19: A meta-analysis. J Cardiol. 2021;77(5):482-91. doi: 10.1016/j.jjcc.2020.10.015.
26. Jeon S, Ko M, Lee J, Choi I, Byun SY, Park S, et al. Identification of antiviral drug candidates against SARS-CoV-2 from FDA-approved drugs. Antimicrob Agents Chemother. 2020;64(7):e00819-20. doi: 10.1128/aac.00819-20.
27. Aveyard P, Gao M, Lindson N, Hartmann-Boyce J, Watkinson P, Young D, et al. Association between pre-existing respiratory disease and its treatment, and severe COVID-19: a population cohort study. Lancet Respir Med. 2021;9(8):909-23. doi: 10.1016/s2213-2600(21)00095-3.
28. Yamaya M, Nishimura H, Deng X, Sugawara M, Watanabe O, Nomura K, et al. Inhibitory effects of glycopyrronium, formoterol, and budesonide on coronavirus HCoV-229E replication and cytokine production by primary cultures of human nasal and tracheal epithelial cells. Respir Investig. 2020;58(3):155-68. doi: 10.1016/j.resinv.2019.12.005.
29. Yang M, Zhang Y, Chen H, Lin J, Zeng J, Xu Z. Inhaled corticosteroids and risk of upper respiratory tract infection in patients with asthma: a meta-analysis. Infection. 2019;47(3):377-85. doi: 10.1007/s15010-018-1229-y.
30. Cheng W, Li Y, Cui L, Chen Y, Shan S, Xiao D, et al. Efficacy and safety of corticosteroid treatment in patients with COVID-19: a systematic review and meta-analysis. Front Pharmacol. 2020;11:571156. doi: 10.3389/fphar.2020.571156.
31. Chen Y, Lv X, Lin S, Arshad M, Dai M. The association between antidiabetic agents and clinical outcomes of COVID-19 patients with diabetes: a Bayesian network meta-analysis. Front Endocrinol (Lausanne). 2022;13:895458. doi: 10.3389/fendo.2022.895458.
32. Pranata R, Henrina J, Raffaello WM, Lawrensia S, Huang I. Diabetes and COVID-19: the past, the present, and the future. Metabolism. 2021;121:154814. doi: 10.1016/j.metabol.2021.154814.
33. Yang Y, Cai Z, Zhang J. Insulin treatment may increase adverse outcomes in patients with COVID-19 and diabetes: a systematic review and meta-analysis. Front Endocrinol (Lausanne). 2021;12:696087. doi: 10.3389/fendo.2021.696087.
34. Han T, Ma S, Sun C, Zhang H, Qu G, Chen Y, et al. Association between anti-diabetic agents and clinical outcomes of COVID-19 in patients with diabetes: a systematic review and meta-analysis. Arch Med Res. 2022;53(2):186-95. doi: 10.1016/j.arcmed.2021.08.002.
35. Filgueiras LR, Capelozzi VL, Martins JO, Jancar S. Sepsis-induced lung inflammation is modulated by insulin. BMC Pulm Med. 2014;14:177. doi: 10.1186/1471-2466-14-177.
36. Luk AOY, Yip TCF, Zhang X, Kong APS, Wong VW, Ma RCW, et al. Glucose-lowering drugs and outcome from COVID-19 among patients with type 2 diabetes mellitus: a population-wide analysis in Hong Kong. BMJ Open. 2021;11(10):e052310. doi: 10.1136/bmjopen-2021-052310.