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Role of Drugs Used for Chronic Disease Management on Susceptibility and Severity of COVID-19: A Large Case-Control Study

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This study aimed to investigate whether specific medications used in the treatment chronic diseases affected either the development and/ or severity of coronavirus disease 2019 (COVID-19) in a cohort of 610 COVID-19 cases and 48,667 population-based controls from Zhejiang, China. Using a cohort of 578 COVID-19 cases and 48,667 population-based controls from Zhejiang, China, we tested the role of usage of cardiovascular, antidiabetic, and other medications on risk and severity of COVID-19. Analyses were adjusted for age, sex, and body mass index and for presence of relevant comorbidities. Individuals with hypertension taking calcium channel blockers had significantly increased risk (odds ratio (OR) = 1.73, 95% confidence interval (CI) 1.2–2.3) of manifesting symptoms of COVID-19, whereas those taking angiotensin receptor blockers and diuretics had significantly lower disease risk (OR = 0.22, 95% CI 0.15–0.30 and OR = 0.30, 95% CI 0.19–0.58, respectively). Among those with type 2 diabetes, dipeptidyl peptidase-4 inhibitors (OR = 6.02, 95% CI 2.3–15.5) and insulin (OR = 2.71, 95% CI 1.6–5.5) were more and glucosidase inhibitors were less prevalent (OR = 0.11, 95% CI 0.1–0.3) among with patients with COVID-19. Drugs used in the treatment of hypertension and diabetes influence the risk of development of COVID-19, but, not its severity.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Cardiovascular disease and diabetes have been highlighted as comorbidities contributing to a more severe form of coronavirus disease 2019 (COVID-19) and medication to treat them may also influence the risk of COVID-19 and its clinical outcomes.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Does specific medications used in the treatment of chronic diseases influence the risk for the susceptibility to severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection of severity of COVID-19?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The study confirms that higher body mass index, diabetes, and cardiovascular,and cerebrovascular disease as independent risk factors for the development of COVID-19. Angiotensin receptor blockers (ARBs) and diuretics were associated with reduced risk and calcium channel blockers with increased risk of developing COVID-19. Among those with type 2 diabetes (T2D), dipeptidyl peptidase-4 and insulin were associated with increased and glucosidase inhibitors with reduced risk development of COVID-19. None of the antihypertensive or antidiabetic drugs were associated with increased risk of severe or critical form of the infection. Drugs used in the treatment of hypertension and diabetes influence the risk of development of COVID-19, but are not associated with severity of the disease.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Findings from the current large case-control study confirmed no evidence to alter ARB or angiotensin-converting enzyme inhibitor therapy in the context of COVID-19 severity in clinical practice. Hypertension significantly increases the risk of severe or critical SARS-CoV-2 infection indicating that carefully controlled blood pressure should be a priority to reduce the healthcare burden of COVID-19.

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The pandemic of coronavirus disease 2019 (COVID-19) caused by a new zoonotic coronary virus, severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), has affected over 8.5 million people and caused over 450,000 deaths across the world as of June 21, 2020[1] having a profound impact on health services and public health. The clinical spectrum of SARS-CoV-2 infection appears to be wide, encompassing asymptomatic infection in a minimum of 5%, mild upper respiratory tract illness with fever, fatigue, cough with or without sputum production in 81%, to more severe viral pneumonia in 14% with ground-glass opacity computed tomography (CT) of the chest leading to critical illness in 5% associated with respiratory failure, septic shock, and/ or multi-organ failure.[2] Case-fatality rate ranges from 0.4% to 2.9% on average between different regions.[2]

Large descriptive studies have reported T2D in 7.4–9.6% of patients with COVID-19 and hypertension in 15% as 2 of the most prevalent comorbid conditions.[3–5] Moreover, diabetes (16.2%) and hypertension (23.7%) are highly prevalent among those with severe manifestations.[3] Of the patients admitted to the intensive care unit, 22% of those who died had diabetes.[6]

SARS-CoV-2 virus binds ACE2[7,8] in humans, ACE2 is expressed broadly including epithelial cells of the lungs, intestines, kidneys, heart, and blood vessels.[9] The virus downregulates the ACE2 protein expression in a replication-dependent manner[10] resulting in loss of ACE2 function. Whether variation in ACE2 expression contributes to the virulence in the current pandemic of COVID-19 is still unclear. There is an ongoing debate as to whether and how the interaction among the virus, hypertension, and ACE2 may influence the manifestations of COVID-19.[11–13] Concerns have been raised that angiotensin converting enzyme inhibitors (ACEIs), angiotensin II type 1 receptor blockers (ARBs), and thiazolidinediones often prescribed in patients with diabetes, hypertension, and cardiac disease may increase the risk of COVID-19 and its clinical outcomes.[11,12,14] In contrast, ACE2 is a counter regulatory enzyme that degrades angiotensin II, hence, reducing its effect on vasoconstriction, sodium retention, and fibrosis. Therefore, trials of losartan as a treatment for COVID-19 are underway enrolling patients who have not previously received treatment with ACEIs or ARBs.[15] In addition, dipeptidyl peptidase-4 (DPP4), the receptor for Middle East respiratory syndrome-related coronavirus, has been shown to have similar expression profile to ACE2 in the lungs.[16] DPP4 inhibitors are commonly used in the treatment of T2D.

We have investigated whether any of the medications for chronic conditions, in particular antihypertensive and antidiabetic medications, affected either the development and/ or severity of COVID-19 using a multicenter cohort of 578 patients with common, severe, or critical forms of COVID-19 and 48,667 population-based control subjects from Zhejiang Province, China.

PATIENTS AND METHODS

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The local ethics committees of all hospitals approved the retrospective study of cohorts with COVID-19. The requirement for written consent was waived due to the retrospective and anonymous nature of this study.

Cohort of cases

Consecutive patients presenting to 14 hospitals in Zhejiang Province, China (see collaborators), between January 10, 2020, and February 28, 2020, and confirmed diagnosis of COVID-19 infection were included (**Figure 1**). The diagnosis of COVID-19 was made in accordance with the Guidelines for the Diagnosis and Treatment of New Coronavirus Pneumonia (fifth edition) formulated by the National Health Commission of the People's Republic of China.[17] A confirmed case of COVID-19 was defined as a positive result on real-time reverse-transcriptase polymerase chain reaction assay of nasal and pharyngeal swab specimens. Only laboratory-confirmed cases were included in the study. The

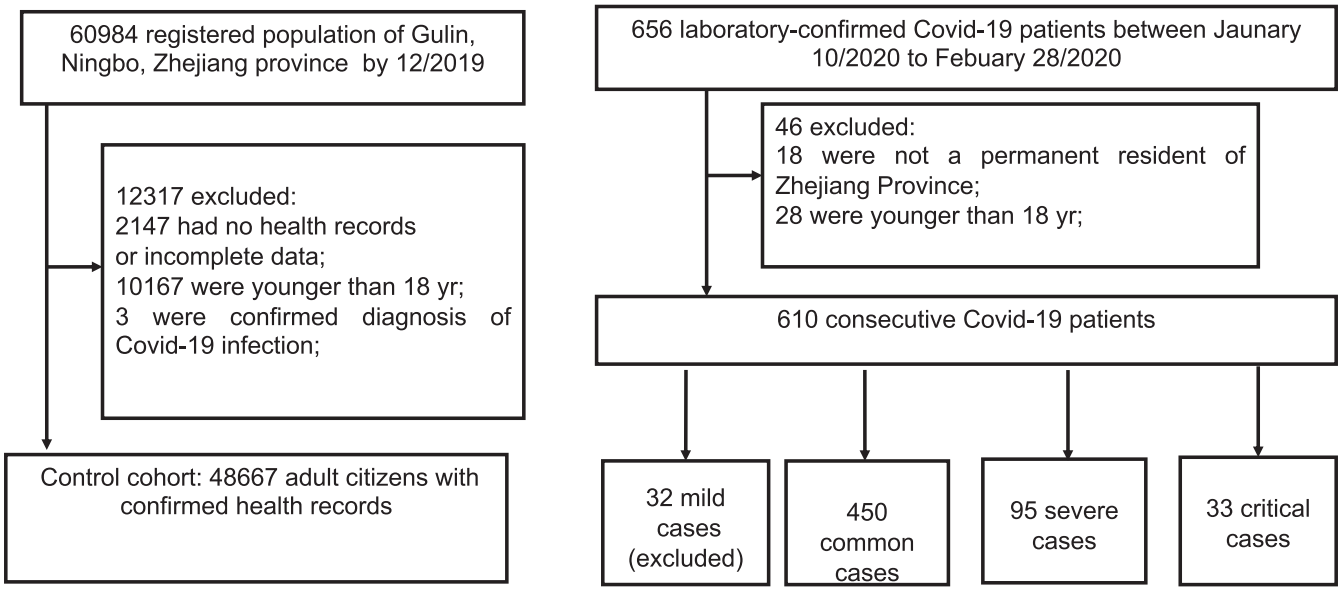

Figure 1 Flow chart of recruitment paths for research study participants. COVID-19, coronavirus disease 2019.

clinical data of all patients were collected from the electronic health records (EHRs). All patients were administered with antiviral and supportive treatment, and prevention of complications based on their clinical condition.

Clinical categories

The severity of the disease was classified into four categories according to the Guidelines for the Diagnosis and Treatment of New Coronavirus Pneumonia (fifth edition)[17]: (i) mild type: patients with mild clinical symptoms and no pulmonary changes on CT imaging, (ii) common type: patients with symptoms of fever and signs of respiratory infection, and having pneumonia changes on CT imaging, (iii) severe type: patients presenting with any one item of the following: (a) respiratory distress, respiratory rate ≥ 30/min, (b) oxygen saturation of finger ≤ 93% in resting condition, and (c) arterial partial pressure of oxygen/oxygen concentration ≤ 300 mmHg (1 mmHg = 0.133 kPa), or (iv) critical type: patients meeting any one of the following criteria: (a) respiratory failure requiring mechanical ventilation, (b) shock, and (c) requiring intensive care unit admission requirement due to multiple organ failure. Because only 32 patients with mild cases were available and they would normally not be hospitalized, these were removed from the analysis (**Figure 1**).

Population-based control group

Detailed methods and data sources used to establish an EHR-based general population-based cohort study in an eastern coastal area of China has been described previously.[18] The control group used in the current study is from the general population from Gulin town, an area of Ningbo City, Zhejiang Province, China, which covers the catchment area of one of the hospitals from which one-quarter of the patients with COVID-19 for this study were recruited. Since 2004, all citizens are offered regular health screening in Gulin Health Center. Detailed medical history is recorded in the Electronic Medical Record System. Gulin town was selected as a center of the "Mega-Project for National Science and Technology Development" under the "13th Five-Year Plan of China" for liver diseases between 2017 and January 2021. We included all adult citizens who had detailed medical records established by 2019. A total of 48,667 adults from 60,984 registered populations who had EHRs were included in this study (**Figure 1**). The following data were collected: (i) age, (ii) sex, (iii) detailed medical history, including diabetes, hypertension, malignancy, other severe diseases (congestive heart failure, severe neurological diseases, and previous organ transplantation), (iv) details of prescription drugs used to treat these medical conditions, and (v) personal health parameters, including history of alcohol consumption and smoking, as well as anthropometric measurements, including body weight, height, waist circumference, and arterial pressure, as well as (vi) laboratory parameters, including serology for hepatitis B and C (HBsAg and anti-HCV). Individuals in the control cohort whose health records showed a diagnosis of COVID-19 ($n = 3$) were removed from the analysis (**Figure 1**).

Health information systems in Gulin include different administrative databases of general demographic characteristics, health check information, health insurance database, inpatient and outpatient EHRs, chronic disease management (diabetes, hypertension, malignancy, and myocardial infarction), and death certificates, and so on. These databases are inherently linked to each other by a unique and encoded identifier for each individual. The system was originally designed in 2006 to facilitate routine primary care services for local general practitioners. Since 2009, this regional system has covered nearly all health-related activities of residents within this region, from birth to death, including children, adolescents, pregnant women, adults, and elderly people. Now, 98% of permanent residents are covered by the national health insurance and have registered in the health information system with a valid healthcare identifier.

All the chronic diseases diagnosed by doctors in Gulin or outside Gulin will be reported to Ningbo Centers for Disease Control and Prevention (CDC) and rechecked by the Department of Chronic Disease Management of Gulin hospital. All the prescription medicines of chronic diseases listed above are recorded and regularly verified.

Use of medication. It is the role of the Department of Chronic Diseases within each community hospital in Zhejiang Province to update the prescriptions of chronic diseases, such as diabetes, hypertension, cardiovascular, cerebrovascular disease, and tumors regularly. From these data, we were able to run a database search, including for this study, individuals who were classified as taking a given medication if they had been given a prescription for a drug at least three times. For patients with COVID-19, the medication was included only if 3 or more 1-month prescriptions were filled before diagnosis of COVID-19, according to the patient's records.

Statistical methods

Categorical variables were expressed as frequency and percentages. Continuous variables were expressed as mean and SDs. Logistic regressions were carried out either unadjusted or adjusting for age, sex, and body mass index (BMI). $P < 0.05$ was considered statistically significant.

RESULTS

The selection of the study population is illustrated in **Figure 1**. A total of 610 patients with COVID-19 were enrolled after admission from various centers in the Zhejiang Province (**Figure 1**). A population-based cohort from the Zhejiang Province consisting of 48,667 adults with health records was used as controls. The descriptive characteristics, comorbidities, and use of medication prior to admission available in both cases and controls were compared (**Table 1**). We found that prevalence of T2D, higher BMI, presence of cardiovascular, or cerebrovascular disease were associated with (all increased in) the patients with COVID-19 (**Table 1**). We then adjusted all factors for age, sex, and BMI. In the case of antihypertensives, we further adjusted for hypertension, in the case of medication used to treat diabetes, we adjusted for the presence of T2D.

All the disease conditions associated with COVID-19 remain statistically significantly associated after adjustment for age, sex, and BMI. There was no significant difference in the use of glucocorticoids between COVID-19 and the population-based controls

Table 1 Comparison between COVID-19 cases and controls, showing univariate ORs from logistic regression, and ORs adjusted for age, sex, and BMI

			Unadjusted			Adjusted for age, sex, BMI			
	Controls	COVID-19	OR	95% CI	*P* value	OR	95% CI		*P* value
n	48,667	578							
sex M, *n*	23,506 (48.3%)	293 (50.7%)	1.10	0.93	1.29	0.25			
Age, years, mean (SD)	49.96 (16.69)	49.18 (14.16)	1.00	0.99	1.00	0.273			
BMI, kg/m^2 mean (SD)	22.79 (2.86)	24.01 (3.43)	1.13	1.10	1.16	< 0.0001			
Smoke, *n*	4,725 (9.7%)	53 (9.2%)	0.90	0.66	1.19	0.477	0.71	0.51	0.98	0.071
HBV, *n*	2,287 (4.7%)	32 (5.5%)	1.22	0.84	1.71	0.275	1.27	0.86	1.81	0.201
Diabetes, *n*	2,920 (6.1%)	57 (9.8%)	1.70	1.28	2.22	0.0001	1.53	1.15	2.11	0.004
Hypertension, *n*	9,855 (20.2%)	130 (22.4%)	1.18	0.97	1.43	0.084	1.01	0.76	1.31	0.851
Cardiovascular or cerebrovascular disease *n*	622 (1.3%)	15 (2.6%)	2.16	1.25	3.45	0.002	2.26	1.22	3.76	0.006
Tumor, *n*	973 (2.0%)	10 (1.8%)	0.86	0.43	1.53	0.648	0.92	0.51	1.73	0.991
Glucocorticoids, *n*	326 (0.6%)	5 (0.8%)	1.29	0.46	2.82	0.568	1.17	0.41	2.73	0.717
ACEI, *n*	555 (1.1%)	5 (0.8%)	0.75	0.27	1.64	0.538	0.61[a]	0.23	1.51	0.362
ARB, *n*	7,485 (15.4%)	50 (8.7%)	0.56	0.41	0.73	< 0.0001	0.22[a]	0.15	0.30	< 0.0001
CCB, *n*	4,740 (9.7%)	84 (14.6%)	1.61	1.27	2.01	< 0.0001	1.73[a]	1.21	2.31	0.001
Diuretic, *n*	2,467 (5.1%)	12.31 (2.1%)	0.43	0.24	0.72	0.003	0.30[a]	0.19	0.58	< 0.0001
Beta-blockers, *n*	1,221.54 (2.5%)	15 (2.3%)	0.96	0.53	1.57	0.892	0.80[a]	0.42	1.47	0.468
Glycosidase inhibitors, *n*	2,019 (4.1%)	15 (2.6%)	0.66	0.38	1.05	0.104	0.11[b]	0.10	0.41	< 0.0001
Biguanides, *n*	1,445 (2.9%)	28 (4.9%)	1.64	1.09	2.37	0.010	1.00[b]	0.58	1.62	0.975
Insulin secretagogues, *n*	700 (1.4%)	16 (2.8%)	1.92	1.12	3.06	0.010	1.23[b]	0.72	2.29	0.395
Thiazolidinediones, *n*	394 (0.8%)	3 (0.5%)	0.64	0.16	1.68	0.446	0.36[b]	0.11	1.21	0.121
DPP4 inhibitors, *n*	486 (0.1%)	6 (0.9%)	9.22	3.54	19.82	< 0.0001	6.02[b]	2.30	15.51	< 0.0001
Insulin, *n*	701 (1.4%)	16 (2.8%)	3.29	1.86	5.34	< 0.0001	2.71[b]	1.57	5.51	0.0002
Statins, *n*	443 (0.9%)	15 (2.6%)	2.82	1.60	4.57	< 0.0001	2.50	1.48	4.21	0.001
Fibrates, *n*	63 (0.1%)	0 (0.0%)	0.05	0.00	30.12	0.417	0.03	0.00	29.26	0.339
Aspirin, *n*	673 (1.3%)	10 (1.8%)	1.45	0.75	2.53	0.220	1.28	0.57	2.63	0.512

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CI, confidence interval; COVID-19, coronavirus disease 2019; DPP4, dipeptidyl peptidase-4; HBV, hepatitis B virus; OR, odds ratio.
[a]There were 134 patients with COVID-19 and with hypertension. [b]There were 58 patients with COVID-19 and with type 2 diabetes.

and a significantly higher use of statins among patients with COVID-19.

We found that among individuals with a diagnosis of hypertension there was no difference in the use of ACEIs or beta-blockers, but individuals with COVID-19 were significantly more likely to be on calcium channel blockers (CCBs) and less likely to be on diuretics and on ARBs.

We also found that after adjustment for demographics and presence of T2D the use of antidiabetic medications was significantly different in patients with T2D with COVID-19 than in those without and this is particularly striking for use of glycosidase inhibitors, which are significantly less prevalent among individuals with T2D infected with COVID-19, and insulin and DPP4 inhibitors, which are much more likely to be used by patients with T2D and COVID-19 (**Table 1**).

We compared these figures graphically between controls and different severity categories in **Figure 2**. We see that, although hypertension in itself is not more prevalent in COVID-19 diagnosed individuals than controls, it is much more prevalent in severe and critical cases (**Table 2**, **Figure 2a**). T2D, male sex, and age over 65 years all show a similar pattern in terms of increased prevalence with severity (**Table 2**, **Figure 2a**).

With regard to antidiabetic medications after adjusting for age, sex, BMI, and diabetes, glucosidase inhibitors are less prevalent among T2D affected individuals symptomatic for COVID-19 and DPP-inhibitors and insulin are much more prevalent among patients with COVID-19. We compared these values to those in COVID-19 severity categories (**Figure 2b** and **Table 3**) and we find that there is no significant association between use of DPP-inhibitors and COVID-19 severity after adjustment for age, sex, and BMI, resulting in odds ratio (OR) = 0.32 (95% confidence interval (CI) 0.02–2.18, $P = 0.31$). For insulin, we observed a trend for higher use among the severe cases with OR = 2.63 (95% CI 0.80–9.07, $P = 0.11$), which, however, did not achieve statistical significance (**Table 3**).

We carried out a similar analysis with antihypertensive medications. We found that comparing population-based controls

Figure 2 Distribution of population demographics and medication use in the control cohort and COVID-19 positive cohort. (**a**) Comparison of demographic and comorbidity distribution between coronavirus disease 2019 (COVID-19) positive individuals grouped according to severity compared with the control cohort. (**b**) Comparison of use of type 2 diabetes (T2D) prescribed medications across the COVID-19 severity range compared with the control cohort. Error bars represent 95% confidence interval (CI). (**c**) Comparison of use of antihypertensive (HTN) prescribed medications across the COVID-19 severity range compared with the control cohort. Error bars represent 95% CI. BMI, body mass index.

to COVID-19 diagnosed individuals, use of ARBs and diuretics was significantly less prevalent in COVID-19 cases with hypertension than among hypertensive controls, whereas use of CCBs was significantly more prevalent among COVID-19 cases than controls after adjustment for age, sex, and BMI (**Table 1**). No significant difference in susceptibility or severity was seen with use of

Table 2 Association among demographics, clinical presentation at admission, comorbidities, and use of medication and COVID-19 severity

Severity category	2 (common)	3 + 4 (severe + critical)	Adj OR severe vs. not	95% CI		*P* value
n	450	128				
Sex, male *n*	207 (46%)	86 (67%)	2.40	1.59	3.65	< 0.0001
Age years mean (SD)	47.26 (13.53)	56 (14.29)	1.04	1.03	1.06	< 0.0001
BMI kg/m^2 mean (SD)	23.63 (3.29)	25.38 (3.59)	1.15	1.09	1.23	< 0.0001
Clinical presentation						
Fever, *n*	365.5 (81.3%)	109.9 (85.9%)	1.61	0.42	2.50	0.111
Cough, *n*	296.64 (65.9%)	102.98 (80.4%)	2.13	1.33	3.49	0.002
Digestive symptoms, *n*	52.02 (11.5%)	20 (15.6%)	1.42	0.80	2.44	0.220
Systolic BP mmHg, mean (SD)	131.65 (19.29)	133 (18.17)	0.97	0.95	1.30	0.011
Diastolic BP mmHg, mean (SD)	81.07 (10.85)	78.75 (10.08)	0.96	0.93	0.99	0.009
Respiratory rate, mean (SD)	19.42 (1.80)	20.86 (4.58)	1.22	1.08	1.33	0.002
Peak temperature C, mean (SD)	37.88 (0.77)	38.08 (0.85)	1.38	1.06	1.80	0.018
Days since disease onset, mean (SD)	6.15 (5.15)	6.57 (3.99)	1.01	0.97	1.01	0.637
Hospital length of stay, mean (SD)	19.31 (18.63)	21.18 (9.87)	1.00	1.00	1.01	0.363
Death, *n*	0 (0.00%)	4* (3.1%)	1,054.07	0.00	inf	0.350
Comorbidities						
Smoke, *n*	31 (6.9%)	20 (15.6%)	0.88	0.45	1.74	0.728
Chronic liver disease, *n*	27 (6.0%)	6 (4.6%)	0.77	0.28	1.80	0.573
Diabetes, *n*	37 (8.2%)	21 (15.6%)	1.13	0.64	1.41	0.570
Hypertension, *n*	77 (17.1%)	57 (44.5%)	2.88	1.54	4.96	0.0007
CVD cerebrovascular, *n*	10 (2.2%)	6 (4.6%)	1.12	0.37	3.39	0.841
Cancer, *n*	6 (1.3%)	4 (3.1%)	1.38	0.42	7.18	0.284

Adj, adjusted; BMI, body mass index; BP, blood pressure; CI, confidence interval; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; OR, odds ratio. ORs were derived by logistic regression severe (severe + critical) vs. not severe (common). *P* values adjusted for age, sex, and BMI, except those for age, sex, and BMI. *, 3 deaths and 1 lung transplant.

[Correction added on 22 October 2020, after first online publication: The values under '3 + 4 (severe + critical)' column pertaining to number of death was corrected to '4* (3.1%)' and the * footnote was added.]

ACEIs (**Figure 2c**, **Table 3**). In terms of severity, there was a trend for use of beta-blockers to be more prevalent in severe and critical cases than in mild and common cases. However, after adjustment for age, sex, and BMI, none of the antihypertensive medications was significantly associated with COVID-19 severity (**Figure 2c**, **Table 3**).

The only type of medications that remained associated with COVID-19 severity after adjustment for age, sex, and BMI were immunosuppressive drugs (glucocorticoids) with an OR = 5.37 (95% CI 0.88–41.15; **Table 3**).

DISCUSSION

Recent descriptive cohort studies have reported T2D in 7.4–9.6% of patients with COVID-19 and hypertension in 15% as 2 of the most prevalent chronic health conditions.[3–5,19] Using a case-control design involving 610 patients with COVID-19 and well-characterized 48,667 population-based controls from the South-east region of China, we have identified higher BMI, diabetes, and cardiovascular, andcerebrovascular disease as independent risk factors for the development of COVID-19. We found the prevalence of hypertension to be slightly higher among patients (22.4%), but this was not statistically significant compared with its prevalence of 20.2% in the population-based control group. Furthermore, age (> 65 years), sex (male), and BMI were associated with the development of severe disease in 128 of 610 of those with COVID-19. In addition, when adjusted for age, sex, and BMI, those with a history of hypertension have over 2-fold risk of developing the severe form of COVID-19.

The analysis of medications acting on the renin-angiotensin-aldosterone system demonstrates that patients with COVID-19 were significantly less likely compared with population-based controls to be taking ARBs (8.7% vs. 15.4%) and diuretics (2.1% vs. 5.1%) prior to their presentation, after adjusting for covariates, such as age, sex, and BMI, as well as presence of hypertension. In contrast, CCBs were associated with increased risk of COVID-19. Although hypertension is clearly a risk factor for severity, we found that none of the antihypertensive medications were positively associated with severity of the disease. In the case-control analysis, patients with T2D, treatment with DPP4 inhibitors, and insulin were associated with increased risk of COVID-19, whereas glucosidase inhibitor therapy was associated with reduced risk. It has been suggested that DPP4 residues might interact with SARS-CoV-2 S1 domain of the Spike protein, also targeted by other coronaviruses that enter the host cells through the functional receptor DPP4.[20]

Table 3 Association between the use of medication and COVID-19 severity

Severity category use of medication	2 (common)	3 + 4 (severe + critical)	Adj OR severe vs. not	95% CI		*P* value
Glucocorticoids	2/450 0.4%	30/128 2.3%	5.37	0.88	41.15	0.034
ACEI[a]	2/77 2.6%	3/57 5.2%	2.08	0.33	16.22	0.855
ARB[a]	33/77 42.8%	20/57 35.1%	0.72	0.35	1.45	0.381
CCB[a]	53/77 68.8%	33/57 57.8%	0.62	0.30	1.27	0.139
Diuretic[a]	8/77 10.3%	5/57 8.7%	0.82	0.24	2.63	0.644
Beta-blockers[a]	5/77 6.4%	9/57 15.7%	2.70	0.87	9.24	0.539
Glycosidase inhibitors[b]	9/37 24.3%	7/21 33.3%	1.65	0.52	5.43	0.498
Biguanides[b]	18/37 48.6%	8/21 38.0%	0.98	0.35	2.60	0.536
Insulin secretagogues[b]	10/37 27.0%	5/21 23.8%	0.84	0.23	2.83	0.788
Thiazolidinediones[b]	1/37 2.7%	2/21 9.5%	3.79	0.34	84.60	0.290
DPP4 inhibitor[b]	5/37 13.5%	1/21 4.7%	0.32	0.02	2.18	0.314
Insulin[b]	7/37 18.9%	8/21 38.0%	2.63	0.80	9.07	0.114
Statins	10/450 2.2%	5/128 3.9%	1.78	0.54	5.13	0.296
Fibrates	0.00%	NA	NA			
Aspirin	8/450 1.7%	3/128 2.3%	1.32	0.28	4.66	0.680

Adj., adjusted; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CI, confidence interval; COVID-19, coronavirus disease 2019; DPP4, dipeptidyl peptidase-4; HBV, hepatitis B virus; OR, odds ratio.
ORs were derived by logistic regression severe (severe + critical) vs. not severe (common). *P* values adjusted for age, sex, and BMI.
[a] There were 134 patients with COVID-19 and hypertension. [b] There were 58 patients with COVID-19 with type 2 diabetes.

In addition to its catalytic functions, DPP4 also has a role in immune mechanisms and the inflammatory process,[20] which may be influenced by DPP4 inhibitors. Treatment with insulin may also reflect the degree of insulin resistance, a well-established risk factor for COVID-19. Alpha glucosidase inhibitors improve glycemic control by acting on intestinal membrane-bound enzymes; their effect on the cellular entry of SARS CoV-2[21] is unclear. In contrast to their association with the development of COVID-19, none of the antidiabetic drugs were associated with the severe or critical form of the disease. To our knowledge, these associations of antidiabetic medications with COVID-19 infection have not been demonstrated so far. The higher intake of antidiabetic medications might be linked to a longer duration or lower glycemic control and points to the role of metabolic inflammation in predisposing individuals to developing the more severe form of the disease.[22]

Among medications, corticosteroid intake at baseline were the only group that increased the risk of severity of COVID-19, but this affected only 2.1% of patients. In the study from OpenSAFELY collaborative, patients with asthma with recent oral steroid treatment had 25% additional risk of in-hospital mortality.[23] Although, in the latter study, oral steroid treatment was used as a marker of severity, the effect on the disease outcome could be related to recent exposure to corticosteroids.

The concerns raised regarding the safety of ACEIs and ARBs in relation to COVID-19 are based on the hypothesis that medications acting on the renin-angiotensin-aldosterone system may raise the expression of ACE2, the postulated receptor for SARS-CoV-2.[14,24–26] The virus uses human ACE2[27] expressed in lung alveolar epithelial cells to trigger the key manifestations and complications of the infection. ACE2 is involved in the hydrolysis of angiotensin I and II into inactive forms 1–9 and 1–7, respectively.[15] Angiotensin 1–7 act on the Mas receptor to play a protective role through vasodilatory and anti-inflammatory properties, hence, balancing the actions of angiotensin II on the type 1 receptor.[14,15] Concerns regarding both ACEIs and ARBs have led to calls for discontinuation of these drugs both prophylactically and in those with suspected COVID-19.[15] In contrast, using a large longitudinal population-based control group and a multi-center cohort of COVID-19 cases, we have demonstrated that those on ARBs are significantly less likely (OR 0.22, 95% CI 0.15–0.30) to develop COVID-19. Potential benefit

from ARBs in this context may be related to the effect of SARS-CoV-2, which once gaining entry through ACE2 into type II pneumocyte downregulates ACE2 leading to unabated angiotensin II induced organ injury. In a mouse model, SARS-CoV-1 induced lung injury could be limited by renin-angiotensin-aldosterone system blockade.[28] Our analysis has not shown ACEIs to have an effect similar to ARBs, consistent with the observations that ACEIs currently in clinical use do not directly affect ACE2 activity.[29] We are not aware of any population-based case-control studies thus far investigating risk factors increasing susceptibility to COVID-19, however, a systematic review[30] found that ACEIs reduced the risk of pneumonia. In the latter study, the benefits of ACEI were substantially greater among Asian patients and these were attributed to a higher prevalence of ACE polymorphisms increasing the ACEI levels and kinin catabolism in this ethnic group.

Of 578 patients with COVID-19, 128 developed severe or critical forms of the disease, higher proportion of patients (42.8%) with common forms of the disease were on ARBs compared with severe/critical (35.1%) forms of the disease. However, neither ARBs nor ACEIs were significantly associated with the severity of COVID-19. A cohort study from Wuhan Province, demonstrated lower (3.7%) 28-day all-cause mortality among 188 patients with COVID-19 receiving ARBs or ACEIs in-hospital compared with 9.8% among those who were not receiving these drugs.[31] That study was not powered to evaluate the effect of ACEIs vs. ARBs. In addition, a lower proportion of patients with COVID-19 overall were on ARBs or ACEIs than expected[32,33] raising the possibility that concerns regarding these drugs at the beginning of the epidemic may have resulted in change in medication in patients on admission. In-hospital use of ACEIs has previously been shown to be associated with lower rate of ventilation and in-hospital mortality with viral pneumonias.[34]

Our case-control analysis showed that those taking CCBs had significantly increased risk (OR 1.73, 95% CI 1.2–2.3) of manifesting symptoms of COVID-19. Two recent studies have shown consistent findings regarding the association between CCBs and increased risk of COVID-19 associated symptoms.[35,36] The mechanisms underlying these findings are unclear as there is no evidence that CCBs alter ACE2 expression. One study including 4,792 patients hospitalized with pneumonia (bacterial and viral) showed an increased incidence of major cardiovascular events among those who were on CCBs, beta-blockers, or corticosteroids.[37] Impaired induction of anti-viral type 1 interferon response to a range of respiratory viruses has been well-described in association with corticosteroids and may also apply in the context of COVID-19, explaining the association of these drugs with the severity of infection in our cohort.[38,39]

Hypertension was a strong risk factor for the development of the severe and critical forms of COVID-19 independently of antihypertensive therapy. This may be related to higher levels of endothelin in patients with hypertension and its effect on innate immune response. There is strong evidence that the innate immune response is key in the development of severe COVID-19.[40] Recent data suggest that macrophages contribute to, and protect from, hypertension and that macrophage depletion augments the chronic hypertensive response to endothelin-1 (ET-1).[41] High levels of ET-1 are linked to lung damage in HIV infection.[42] It is thus possible that arterial hypertension, which is linked to higher levels of ET-1, more vasoconstriction, and lower blood flow, may be contributing to lower levels of macrophages (i.e., lower innate immune response) and potentially to build-up of fluid in the lungs (pulmonary edema).

Our study has a number of strengths. The case-control design with cases from multiple hospitals and a large, prospective, population-based control group with 98% coverage of the local population has provided the power needed to identify independent risk factors, including medication use, to assess the risk factors for COVID-19 in this population. We have included consecutive cases from each of the secondary care hospitals to reflect the full range of case-mix seen in routine clinical practice. Case definition and assessment of severity of COVID-19 were adherent to national guidelines consistently across all the centers involved in this study.[16]

The limitations of our study include the retrospective nature of the COVID-19 cohort, which could lead to possible under-recording of some less common comorbidities and drug history, in particular, related to use of glucocorticoids. Even though we included 578 cases, we may have modest power to evaluate potential risk factors with low frequency. In the large case series (n = 1,099) of patients with COVID-19,[3] a number of comorbidities, such as cardiovascular (2.5%), cerebrovascular (1.4%), and chronic obstructive pulmonary diseases (1.1%) were infrequent, and cancers, immunodeficiency, and chronic kidney disease altogether formed 1.8% of the COVID-19 cases. Most patients with cardiovascular comorbidities qualify for ACEI or ARB therapy. However, prescribing patterns of these drugs vary widely from China to the United Kingdom where ACEIs are much more commonly prescribed.[43] Although with a much larger sample size this may prove to be significant if the effect is real, this compared poorly with other factors contributing to severity, such as hypertension (OR 2.8) or the use of immunosuppressants (OR 5.37). In addition, the low case-fatality rate of 0.6% means that we were not able to assess risk factors associated with mortality. Another limitation is the lack of pre-pandemic data on glycemic control, since DPP4 inhibitors and insulin are usually prescribed to patients with poorer glycemic control than those receiving glucosidase inhibitors. Therefore, differences in severity seen among these medication categories could be reflecting differences in glycemic control and not necessarily an effect of the medication on disease progression. Moreover, although all the medications included corresponded to prescriptions filled 3 or more times before diagnosis of COVID-19, we were unable to adjust for length of use of the medications and the current analysis did not adjust for multiple testing so some of the more modest associations are viewed with caution. Finally, some of the associations show strong statistical significance but, as is the case for CCBs, the ORs are < 2.0 and, therefore, they may not be of high clinical impact.

CONCLUSION/CLINICAL RELEVANCE

We have identified higher BMI, diabetes, and cardiovascular, and cerebrovascular disease as independent risk factors for the development of COVID-19. Prior treatment with ARBs and diuretics was associated with reduced risk and CCBs with increased risk of developing COVID-19. Other antihypertensive drugs were not associated with increased risk of severe or critical forms of the

infection. Therefore, we found no evidence to alter ARB or ACEI therapy in the context of the pandemic. We have also found for the first time, an increased risk of COVID-19 in association with DPP4 inhibitors and insulin as reduced risk with glucosidase inhibitors. If replicated, these findings have clinical and potentially public health implications.

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CONFLICT OF INTEREST

G.P.A. is an advisory board member for Amryt Pharmaceuticals, Astra Zeneca, GSK, and Pfizer. A.M.V. is a consultant for Zoe Global Ltd. and member of the scientific advisory board of CPKelco. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

A.M.V., A.V., and G.P.A. wrote the manuscript. H.Y., T.C., and G.P.A. designed the research. H.Y., S.W., L.L., S.Y., H.W., X.T., J.D., S.J., K.H., F.J., S.Z., N.Z., Y.H., and T.C. performed the research. A.V. and A.M.V. analyzed the data.

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