Relationship between angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and COVID-19 incidence or severe disease

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Abstract

Background: Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) may be associated with higher susceptibility of COVID-19 infection and adverse outcomes. We compared ACEI/ARB use and COVID-19 positivity in a case-control design, and severity in COVID-19 positive patients.

Methods: Consecutive patients who attended Hong Kong's public hospitals or outpatient clinics between 1st January and 28th July 2020 for COVID-19 real time- polymerase chain reaction (RT-PCR) tests were included. Baseline demographics, past comorbidities, laboratory tests and use of different medications were compared between COVID-19 positive and negative patients. Severe endpoints for COVID-19 positive patients were 28-day mortality, need for intensive care admission or intubation.

Results: This study included 213,788 patients (COVID-19 positive: n=2774 patients; negative: n=211014). In total 162 COVID-19 positive patients (5.83%) met the severity outcome. The use of ACEI/ARB was significantly higher amongst cases than controls (n=156/2774, 5.62% vs. n=6708/211014, 3.17%; P<0.0001). Significant univariate predictors of COVID-19 positivity and severe COVID-19 disease were older age, higher Charlson score, comorbidities, use of ACEI/ARB, antidiabetic, lipid-lowering, anticoagulant and antiplatelet drugs and laboratory tests (odds ratio>1, P<0.05). The relationship between the use of ACEI/ARB and COVID-19 positivity or severe disease remained significant after multivariable adjustment. No significant differences in COVID-19 positivity or disease severity between ACEI and ARB use were observed (P>0.05).

Conclusions: There was a significant relationship between ACEI/ARB use and COVID-19 positivity and severe disease after adjusting for significant confounders.

Introduction

The coronavirus disease 2019 (COVID-19) has become a pandemic, affecting more than 200 countries globally, placing significant burdens on healthcare systems. Recent studies have demonstrated that patients with pre-existing cardiovascular comorbidities are at a higher risk of more severe disease course and mortality (1, 2). Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) are common drugs that are used to treat these conditions, but different investigators have raised concerns about the potential adverse effects of these drugs in COVID-19. The SARS-COV-2 virus utilizes angiotensin-converting enzyme-2 (ACE2) to gain entry into different cell types (3). It has subsequently been hypothesized that the ACEIs or ARBs could increase the expression of ACE2, thereby increasing the susceptibility of COVID-19 infection. In this study, using territory-wide electronic health records, we examined whether the use of ACEIs/ARBs is associated with COVID-19 positivity or severe COVID-19 disease using logistic regression.

Methods

Study design and population

This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. This was a retrospective, territory-wide cohort

study of patients undergoing COVID-19 real time-polymerase chain reaction (RT-PCR) testing between 1st January and 28th July 2020. The patients were identified from the Clinical Data Analysis and Reporting System (CDARS), a territory-wide database that centralizes patient information from individual local hospitals to establish comprehensive medical data, including clinical characteristics, disease diagnosis, laboratory results, and drug treatment details. Charlson score was calculated, past comorbidities of diabetes mellitus, hypertension, heart failure, liver diseases, heart block, dementia, acute myocardial infarction (AMI), chronic obstructive pulmonary disease (COPD), ischemic heart disease (IHD), peripheral vascular disease (PVD), stroke/ transient ischemic attack (TIA), gastrointestinal bleeding, cancer and obesity were extracted by the International Classification of Diseases, Ninth Edition (ICD-9) codes (**Supplementary Table 1**). This system has previously been used by our and other local teams for conducting population-based studies (4, 5), including COVID-19-related research (6-8).

Statistical analysis and outcomes

Continuous variables were presented as median (95% confidence interval [CI] or interquartile range [IQR]) and categorical variables were presented as count (%). The Mann- Whitney U test was used to compare continuous variables. The χ^2 test with Yates' correction was used for 2×2 contingency data. The primary outcome was COVID-19 positivity. The secondary outcome was the severe composite outcome of mortality and need for intensive care or intubation. COVID-19 patients who

passed away 28 days later or longer after discharge were excluded. The last follow-up date was 8th August 2020.

Logistic regression was used to identify potential predictors of COVID-19 positivity or severe COVID-19 disease, including patient demographics, past comorbidities, and medication of ACEI/ARB, steroid, lopinavir/ritonavir, ribavirin, interferon beta-1B, hydroxychloroquine, calcium channel blockers, beta-blockers, diuretics for hypertension, nitrates, antihypertensive drugs, antidiabetic drugs, statins and fibrates, lipid-lowering drugs, anticoagulants, and antiplatelet agents. The odds ratio (OR) and the P-value of the regression was presented. All statistical analyses were performed using RStudio software (Version: 1.1.456) and Python (Version: 3.6).

Results

A total of 213788 patients admitted to public hospitals of the Hong Kong Hospital Authority between 1st January 2020 and 28th July 2020 were included in this study. A total of 2774 patients were tested positive and 211014 patients were tested negative for COVID-19. In total 162 COVID-19 positive patients (5.83%) developed the severe composite outcome of mortality or needing intensive care or intubation. Positive patients who died after 28 days or longer after discharge were excluded. Characteristics of patients undergoing tests for COVID-19 were shown in **Table 1**. There was no significant difference in sex between COVID-19 positive and negative groups (P>0.05) but there was a significant difference in age and Charlson score (P>0.05). There was a higher frequency of diabetes mellitus, hypertension, stroke/TIA, gastrointestinal bleeding, and obesity. There were higher

prescription rates for ACEI/ARB, steroid, lopinavir/ritonavir, ribavirin, interferon beta-1B, hydroxychloroquine, calcium channel blockers, beta-blockers, diuretics for hypertension, antihypertensive drugs, antidiabetic drugs, statins and fibrates, lipid-lowering drugs, anticoagulants and antiplatelets classes among the COVID-19 cases in comparison to the controls ($P<0.05$).

The baseline characteristics for the patients undergoing tests for COVID-19 with/without ACEI/ARB use are shown in **Table 2**. Univariable logistic regression identified the predictors of positive COVID-19 status (**Table 3**) and severe COVID-19 disease (**Table 4**). Multivariable logistic regression showed that ACEI/ARB use remained a significant predictor of both positive COVID-19 status and severe COVID-19 disease after adjustment for significant confounders ($OR>1$, $P<0.0001$)

Further, we excluded those with concomitant use of ACEI and ARB (N=457) and constructed a subset of patients with only ACEI or ARB use (N=12329) to allow a direct comparison between these two drug classes (**Supplementary Table 2**). In total, 295 patients (2.39%) were tested positive while 12034 were negative.Amongst those who were tested positive, 63 patients (0.51%) developed severe composite outcome. The characteristics of these patients were compared between ACEI and ARB users (**Supplementary Table 3**). Univariate logistic regression analysis was used to identify the predictors of COVID-19 positivity (**Supplementary Table 4**). Moreover, univariate logistic regression found no significant difference in the odds of severe disease between ACEI and ARB users (**Supplementary Table 5**). No significant differences in COVID-19 positivity or disease severity between ACEI and ARB use were observed (P value>0.05).

Discussion

The main findings of this territory-wide cohort study from Hong Kong are that the use of ACEI/ARB was higher among COVID-19 cases in comparison to controls, and ACEI/ARB use was a significant predictor of COVID-19 positivity and severe disease after adjusting for confounders.

Previous studies have examined the risk of developing an infection in patients who have been prescribed ACEIs or ARBs, as summarized by a recent systematic review and meta-analysis of 25 observational studies (9). This study did not reveal any significant association between ACEI/ ARB use and COVID-19 positivity. A recent prospective study of 8.28 million participants from the United Kingdom General Practice records found that ACEIsand ARBs are associated with reduced risks of COVID-19 disease after adjusting for a wide range of variables (10). By contrast, ACEI/ARB use compared with other antihypertensive drugs was not significantly associated with higher incidence of COVID-19 (11). A population-based case-control study in the Lombardy region of Italy found that Use of ACEI/ARB use did not show any association with COVID-19 among patients overall (12). Another cohort study of individuals from Ohio and Florida in the United States found no association between ACEI or ARB use and COVID-19 test positivity (13). A study from New York did not identify a significant association between any single medication class (including ACEIs and ARBs) and an increased likelihood of a positive COVID-19 test. (14). In our study, we included data from a population-wide administrative database, which included all patients undergoing testing at clinics or hospitals managed by the public sector in Hong Kong. Interestingly, we found that after adjusting for patients' demographic, comorbidities and drug prescription, ACEI/ARB use remained a significant predictor of COVID-19 positivity. It may be explained by the hypothesis of SARS-CoV-2 enters

human cells by attaching to the membrane-bound aminopeptidase ACE2, the expression of which might be altered by ACEI/ARB chronic exposure (15-17). Other possible explanations include residual confounding factors, difference in drug indication between COVID-19 cases and controls, and immortal time or collider bias (18-23). Nevertheless, a multi-national study of 1.3 million patients from the United States and Spain found no clear association between increased risk of COVID-19 positivity or disease outcomes (19).

Moreover, some studies have reported better, no difference, or worse outcomes with ACEI/ARB use in COVID-19 patients (9). Another meta-analysis of 28,872 patients showed a trend of lowering risk of death or critical disease under ACEI/ARB use (24). In our study, the use of ACEI/ARB remained a significant predictor of worse outcomes after adjusting for comorbidities, use of different medications and significant laboratory tests. Moreover, it has been suggested that ACEI and ARB may impact on the prognosis of COVID-19 positive patients differently (25-27). However, in the present study, we found no significant effects of ACEI use over ARB on COVID-19 positivity and severe disease. Our results nevertheless confirm previous reports that a greater burden of comorbidities is associated with a worse prognosis in COVID-19 patients (7, 28-33). It must be stressed that even with multivariable adjustment, residual bias cannot be removed completely. Therefore, to better ascertain the associations between ACEI/ARB use and positivity and severe disease outcomes, future randomized controlled trials should be conducted. In addition to the limitations described above owing to study design, our strengths include the territory-wide nature of this study, with complete capture of COVID-19 testing in the public sector, and the application of multivariable regression to adjust for potential confounding variables.

Conclusion

There was a significant relationship between ACEI/ARB use and COVID-19 positivity and severe disease after adjusting for significant confounders.

Conflicts of Interest

None.

Funding

None.

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Table 1. Characteristics of patients undergoing tests for COVID-19 in Hong Kong up to and including 28th July 2020.
COVID-19 = coronavirus disease 2019; ACEI=Angiotensin-Converting Enzyme Inhibitors; ARB=Angiotensin Receptor Blockers; IQR = Interquartile range; AMI= acute myocardial infarction; COPD= chronic obstructive pulmonary disease; IHD= ischemic heart disease; PVD= peripheral vascular disease; TIA= transient ischemic attack; APTT= applied partial thromboplastin time; * for p≤ 0.05, ** for p ≤ 0.01, *** for p ≤ 0.001; # indicates the difference between COVID-19 positive and COVID-19 negative patients.

Characteristics	**Overall (N=213788) Median (IQR);Max;N or Count(%)**	**COVID-19 positive (N=2774) Median (IQR);Max;N or Count(%)**	**COVID-19 negative (N=211014) Median (IQR);Max;N or Count(%)**	**P value#**
Male gender	102117(47.76%)	1369(49.35%)	100748(47.74%)	0.3278
Age, years	50.36(31.84-68.56);120.6;n=213788	43.52(28.59-60.0);97.5;n=2774	50.48(31.87-68.7);120.6;n=211014	<0.0001***
Charlson score	1.0(0.0-3.0);16.0;n=213788	2.0(1.0-3.0);12.0;n=2774	1.0(0.0-3.0);16.0;n=211014	<0.0001***
Diabetes mellitus	3218(1.50%)	58(2.09%)	3160(1.49%)	0.0153*
Hypertension	18292(8.55%)	406(14.63%)	17886(8.47%)	<0.0001***
Heart failure	708(0.33%)	5(0.18%)	703(0.33%)	0.2215
Liver diseases	748(0.34%)	4(0.14%)	744(0.35%)	0.0929
Heart block	1497(0.70%)	8(0.28%)	1489(0.70%)	0.0128*
Dementia	1241(0.58%)	6(0.21%)	1235(0.58%)	0.0162*
AMI	2445(1.14%)	21(0.75%)	2424(1.14%)	0.0689
COPD	2077(0.97%)	25(0.90%)	2052(0.97%)	0.7803
IHD	5959(2.78%)	78(2.81%)	5881(2.78%)	0.9851
PVD	774(0.36%)	7(0.25%)	767(0.36%)	0.4202
Stroke/TIA	2577(1.20%)	52(1.87%)	2525(1.19%)	0.0018**
Gastrointestinal bleeding	2376(1.11%)	46(1.65%)	2330(1.10%)	0.0084**
Cancer	9572(4.47%)	65(2.34%)	9507(4.50%)	<0.0001***

Obesity	123(0.05%)	5(0.18%)	118(0.05%)	0.0208*
ACEI/ARB	12786(5.98%)	156(5.62%)	6708(3.17%)	<0.0001***
Steroid	440(0.20%)	405(14.59%)	35(0.01%)	<0.0001***
Lopinavir/ritonavir	1116(0.52%)	1105(39.83%)	11(0.00%)	<0.0001***
Ribavirin	885(0.41%)	859(30.96%)	26(0.01%)	<0.0001***
Interferon beta-1B	1393(0.65%)	1345(48.48%)	48(0.02%)	<0.0001***
Hydroxychloroquine	89(0.04%)	89(3.20%)	0(0.00%)	<0.0001***
Calcium channel blockers	17471(8.17%)	477(17.19%)	16994(8.05%)	<0.0001***
Beta blockers	9465(4.42%)	208(7.49%)	9257(4.38%)	<0.0001***
Diuretics for hypertension	837(0.39%)	117(4.21%)	720(0.34%)	<0.0001***
Nitrates	4344(2.03%)	64(2.30%)	4280(2.02%)	0.345
Antihypertensive drugs	115(0.05%)	105(3.78%)	10(0.00%)	<0.0001***
Antidiabetic drugs	338(0.15%)	325(11.71%)	13(0.00%)	<0.0001***
Statins and fibrates	403(0.18%)	390(14.05%)	13(0.00%)	<0.0001***
Lipid-lowering drugs	391(0.18%)	378(13.62%)	13(0.00%)	<0.0001***
Anticoagulants	217(0.10%)	207(7.46%)	10(0.00%)	<0.0001***
Antiplatelets	271(0.12%)	192(6.92%)	79(0.03%)	<0.0001***
Mean corpuscular volume, fL	86.9(82.87-90.3);110.8;n=1786	86.8(82.8-90.25);110.8;n=1690	88.04(84.75-90.35);105.9;n=96	0.3863
Basophil, x10^9/L	0.01(0.0-0.02);0.2;n=2580	0.01(0.0-0.02);0.2;n=2486	0.01(0.0-0.03);0.2;n=94	0.2372
Eosinophil, x10^9/L	0.03(0.0-0.1);4.5;n=2694	0.03(0.0-0.1);4.5;n=2598	0.04(0.0-0.1);1.91;n=96	0.8237
Lymphocyte, x10^9/L	1.38(1.0-1.84);58.38;n=2701	1.39(1.0-1.84);58.38;n=2605	1.16(0.9-1.74);3.8;n=96	0.0239*
Metamyelocyte, x10^9/L	0.09(0.06-0.21);0.81;n=12	0.09(0.06-0.21);0.81;n=11	0.02(0.02-0.02);0.02;n=1	0.1461
Monocyte, x10^9/L	0.5(0.36-0.61);4.17;n=2701	0.5(0.36-0.61);4.17;n=2605	0.5(0.4-0.66);2.01;n=96	0.0747
Neutrophil, x10^9/L	3.3(2.4-4.49);30.3;n=2701	3.3(2.4-4.46);30.3;n=2605	3.7(2.33-4.8);16.29;n=96	0.1891
White cell count, x10^9/L	5.5(4.36-6.9);67.1;n=2765	5.5(4.36-6.9);67.1;n=2669	5.49(4.33-6.95);19.52;n=96	0.5233

Mean cell haemoglobin, pg	30.1(28.5-31.7);37.0;n=2765	30.1(28.5-31.7);37.0;n=2669	29.9(28.75-30.84);36.5;n=96	0.172
Myelocyte, x10^9/L	0.18(0.07-0.35);1.29;n=32	0.19(0.08-0.35);1.29;n=31	0.03(0.03-0.03);0.03;n=1	0.1289
Platelet, x10^9/L	215.0(175.5-267.5);631.0;n=2764	215.0(175.0-268.0);631.0;n=2668	216.0(182.05-260.5);441.0;n=96	0.8599
Reticulocyte, x10^9/L	47.4(31.04-78.44);318.0;n=27	46.55(31.04-78.44);318.0;n=26	57.0(57.0-57.0);57.0;n=1	0.6531
Red cell count, x10^12/L	4.69(4.33-5.08);7.18;n=2766	4.69(4.34-5.08);7.18;n=2670	4.7(4.2-5.07);6.54;n=96	0.4999
Hematocrit, L/L	0.4(0.37-0.43);0.516;n=558	0.4(0.37-0.43);0.516;n=545	0.41(0.38-0.42);0.487;n=13	0.7693
Potassium, mmol/L	3.84(3.6-4.1);6.3;n=2702	3.85(3.6-4.1);6.3;n=2633	3.8(3.38-4.18);5.47;n=69	0.1091
Urate, mmol/L	0.3(0.25-0.4);0.635;n=115	0.3(0.25-0.39);0.635;n=114	0.44(0.44-0.44);0.436;n=1	0.2848
Albumin, g/L	41.0(37.35-44.0);378.0;n=2706	41.0(37.4-44.0);378.0;n=2635	40.0(36.0-43.0);50.0;n=71	0.1038
Sodium, mmol/L	139.0(137.4-141.0);152.0;n=2707	139.0(137.4-141.0);152.0;n=2637	139.0(136.4-140.0);144.0;n=70	0.0516
Urea, mmol/L	3.96(3.12-4.9);42.7;n=2706	3.95(3.1-4.9);42.7;n=2636	4.45(3.4-6.06);35.9;n=70	0.0044**
Protein, g/L	74.0(70.8-78.0);92.7;n=2424	74.0(70.8-78.0);92.7;n=2367	74.1(70.1-77.2);84.0;n=57	0.4594
Creatinine, umol/L	69.0(58.0-84.0);1346.0;n=2707	69.0(58.0-84.0);1346.0;n=2637	74.75(61.0-87.0);1216.2;n=70	0.0187*
Alkaline phosphatase, U/L	65.0(54.0-81.0);550.0;n=2706	65.0(54.0-81.0);550.0;n=2636	65.0(56.0-89.35);287.0;n=70	0.3622
Aspartate transaminase, U/L	26.0(21.0-39.3);1807.4;n=921	26.0(21.0-40.0);1807.4;n=901	27.5(16.6-35.55);166.0;n=20	0.4002
Alanine transaminase, U/L	22.0(16.0-34.0);275.0;n=2199	22.0(16.0-34.0);275.0;n=2142	21.0(15.0-29.2);152.0;n=57	0.5961
Bilirubin, umol/L	7.3(5.1-10.3);109.0;n=2706	7.3(5.2-10.3);109.0;n=2636	7.25(4.55-10.6);18.2;n=70	0.6396
Triglyceride, mmol/L	1.3(0.96-1.9);10.58;n=497	1.3(0.96-1.9);10.58;n=484	1.19(0.92-1.48);2.95;n=13	0.3597
Low-density lipoprotein, mmol/L	2.33(1.81-3.1);6.9;n=470	2.33(1.81-3.09);6.9;n=458	2.44(1.82-3.33);3.7;n=12	0.9751
High-density lipoprotein, mmol/L	1.18(0.96-1.44);2.97;n=479	1.18(0.96-1.46);2.97;n=467	1.18(0.96-1.38);1.7;n=12	0.8617
Cholesterol, mmol/L	4.23(3.56-5.03);9.4;n=484	4.23(3.56-5.03);9.4;n=472	4.55(3.35-5.16);5.7;n=12	0.9317
HbA1c, g/dL	13.7(12.7-14.8);89.0;n=2776	13.7(12.7-14.8);89.0;n=2680	13.62(12.4-14.8);49.6;n=96	0.3201
Glucose, mmol/L	5.58(5.0-6.75);29.29;n=2153	5.58(5.0-6.74);29.29;n=2107	5.55(5.2-6.85);11.3;n=46	0.5282

D-dimer, ng/mL	319.0(190.0-595.9);11200.0;n=512	320.0(190.0-599.9);11200.0;n=485	241.0(0.6-467.74);2347.0;n=27	0.0461*
High sensitive troponin-I, ng/L	3.1(1.51-6.9);3876.3;n=1155	3.05(1.5-6.68);3876.3;n=1087	3.78(1.62-10.2);428.0;n=68	0.1057
Lactate dehydrogenase, U/L	198.0(167.0-242.0);1116.0;n=2057	198.0(166.7-242.0);1116.0;n=1997	193.0(171.0-236.8);423.7;n=60	0.7178
APTT, second	30.9(27.75-34.4);120.0;n=1466	31.0(27.75-34.4);120.0;n=1402	30.3(27.55-35.05);51.3;n=64	0.7643
Prothrombin time, second	12.0(11.4-12.6);110.0;n=1033	12.0(11.4-12.6);110.0;n=991	12.0(11.65-12.35);17.2;n=42	0.7217
C- reactive protein, mg/dL	0.37(0.13-1.35);34.0;n=2691	0.36(0.13-1.34);34.0;n=2627	0.62(0.23-1.88);28.9;n=64	0.0294*

Table 2. Characteristic comparisons of patients undergoing tests for COVID-19 with/without ACEI/ARB use. COVID-19 = coronavirus disease 2019; ACEI=Angiotensin-Converting Enzyme Inhibitors; ARB=Angiotensin Receptor Blockers; IQR = Interquartile range; AMI= acute myocardial infarction; COPD= chronic obstructive pulmonary disease; IHD= ischemic heart disease; PVD= peripheral vascular disease; TIA= transient ischemic attack; APTT= applied partial thromboplastin time; * for p≤ 0.05, ** for p ≤ 0.01, *** for p ≤ 0.001

Characteristics	**ACEI/ARB (N=12786)** **Median (IQR);Max;N or Count(%)**	**No ACEI/ARB (N=201002)** **Median (IQR);Max;N or Count(%)**	**P value**
Male gender	6896(53.93%)	95221(47.37%)	<0.0001***
Age, years	73.46(62.11-84.57);108.8;n=12786	48.3(31.0-66.58);120.6;n=201002	<0.0001***
Charlson score	3.0(2.0-4.0);15.0;n=12786	0.0(0.0-2.0);16.0;n=201002	<0.0001***
Diabetes mellitus	844(6.60%)	2374(1.18%)	<0.0001***
Hypertension	3823(29.89%)	14469(7.19%)	<0.0001***
Heart failure	219(1.71%)	489(0.24%)	<0.0001***
Liver diseases	73(0.57%)	675(0.33%)	<0.0001***
Heart block	216(1.68%)	1281(0.63%)	<0.0001***
Dementia	136(1.06%)	1105(0.54%)	<0.0001***
AMI	623(4.87%)	1822(0.90%)	<0.0001***
COPD	206(1.61%)	1871(0.93%)	<0.0001***
IHD	1507(11.78%)	4452(2.21%)	<0.0001***
PVD	154(1.20%)	620(0.30%)	<0.0001***
Stroke/TIA	442(3.45%)	2135(1.06%)	<0.0001***
Gastrointestinal bleeding	278(2.17%)	2098(1.04%)	<0.0001***
Cancer	899(7.03%)	8673(4.31%)	<0.0001***
Obesity	34(0.26%)	89(0.04%)	<0.0001***
Steroid	53(0.41%)	387(0.19%)	<0.0001***
Lopinavir/ritonavir	168(1.31%)	948(0.47%)	<0.0001***

Ribavirin	95(0.74%)	790(0.39%)	<0.0001***
Interferon beta-1B	226(1.76%)	1167(0.58%)	<0.0001***
Hydroxychloroquine	13(0.10%)	76(0.03%)	0.0013**
Calcium channel blockers	7864(61.50%)	9607(4.77%)	<0.0001***
Beta blockers	4818(37.68%)	4647(2.31%)	<0.0001***
Diuretics for hypertension	495(3.87%)	342(0.17%)	<0.0001***
Nitrates	2477(19.37%)	1867(0.92%)	<0.0001***
Antihypertensive drugs	51(0.39%)	64(0.03%)	<0.0001***
Antidiabetic drugs	153(1.19%)	185(0.09%)	<0.0001***
Statins and fibrates	198(1.54%)	205(0.10%)	<0.0001***
Lipid-lowering drugs	196(1.53%)	195(0.09%)	<0.0001***
Anticoagulants	81(0.63%)	136(0.06%)	<0.0001***
Antiplatelets	132(1.03%)	139(0.06%)	<0.0001***
Mean corpuscular volume, fL	88.6(85.05-91.2);105.9;n=248	86.7(82.5-90.1);110.8;n=1538	<0.0001***
Basophil, x10^9/L	0.01(0.0-0.03);0.1;n=298	0.01(0.0-0.02);0.2;n=2282	0.0945
Eosinophil, x10^9/L	0.03(0.0-0.12);4.5;n=308	0.03(0.0-0.1);1.91;n=2386	0.4997
Lymphocyte, x10^9/L	1.3(0.93-1.7);58.38;n=308	1.4(1.0-1.86);27.0;n=2393	0.0131*
Metamyelocyte, x10^9/L	0.19(0.12-0.21);0.23;n=3	0.09(0.06-0.13);0.81;n=9	0.6427
Monocyte, x10^9/L	0.53(0.4-0.67);1.5;n=308	0.48(0.36-0.6);4.17;n=2393	0.0002***
Neutrophil, x10^9/L	3.88(2.94-5.2);16.1;n=308	3.23(2.39-4.37);30.3;n=2393	<0.0001***
White cell bount, x10^9/L	6.0(4.72-7.61);67.1;n=310	5.4(4.3-6.8);42.5;n=2455	<0.0001***
Mean corpuscular haemoglobin, pg	31.3(29.55-33.2);36.3;n=310	30.0(28.4-31.5);37.0;n=2455	<0.0001***
Myelocyte, x10^9/L	0.28(0.13-0.38);1.29;n=12	0.16(0.06-0.27);0.54;n=20	0.0699
Platelet, x10^9/L	205.5(167.0-261.0);567.0;n=310	215.0(176.5-268.0);631.0;n=2454	0.0318*

Reticulocyte, x10^9/L	55.05(35.64-71.14);123.487;n=10	45.7(30.7-77.81);318.0;n=17	0.6155
Red cell count, x10^12/L	4.5(4.11-4.93);6.74;n=310	4.71(4.37-5.1);7.18;n=2456	<0.0001***
Hematocrit, L/L	0.39(0.35-0.42);0.504;n=85	0.4(0.37-0.43);0.516;n=473	0.0501
Potassium, mmol/L	4.0(3.68-4.36);6.3;n=306	3.81(3.6-4.1);6.13;n=2396	<0.0001***
Urate, mmol/L	0.35(0.27-0.44);0.62;n=27	0.3(0.24-0.39);0.635;n=88	0.0637
Albumin, g/L	38.76(34.0-42.0);378.0;n=305	41.0(38.0-44.11);177.0;n=2401	<0.0001***
Sodium, mmol/L	140.0(137.0-141.13);152.0;n=307	139.0(137.44-141.0);147.1;n=2400	0.0668
Urea, mmol/L	5.3(4.1-6.82);42.7;n=307	3.81(3.05-4.7);31.92;n=2399	<0.0001***
Protein, g/L	73.5(69.95-77.0);91.6;n=268	74.2(71.0-78.0);92.7;n=2156	0.0069**
Creatinine, umol/L	79.0(65.0-99.0);1216.2;n=307	68.0(57.0-82.0);1346.0;n=2400	<0.0001***
Alkaline phosphatase, U/L	69.0(57.0-83.0);354.3;n=306	65.0(53.0-80.0);550.0;n=2400	0.0041**
Aspartate transaminase, U/L	29.0(22.65-45.5);1713.0;n=138	26.0(21.0-38.5);1807.4;n=783	0.0132*
Alanine transaminase, U/L	25.0(19.0-40.0);166.0;n=248	22.0(15.25-33.0);275.0;n=1951	<0.0001***
Bilirubin, umol/L	8.0(6.0-11.35);33.0;n=306	7.2(5.0-10.1);109.0;n=2400	0.0002***
Triglyceride, mmol/L	1.36(1.02-1.9);10.58;n=171	1.3(0.9-1.88);8.6;n=326	0.1416
Low-density lipoprotein, mmol/L	2.01(1.52-2.71);5.17;n=163	2.58(1.93-3.27);6.8719;n=307	<0.0001***
High-density lipoprotein, mmol/L	1.18(0.96-1.42);2.437;n=167	1.18(0.95-1.49);2.97;n=312	0.5688
Cholesterol, mmol/L	3.84(3.31-4.6);7.12;n=168	4.5(3.72-5.17);9.43;n=316	<0.0001***
HbA1c, g/dL	13.5(12.2-15.0);89.0;n=310	13.7(12.7-14.8);78.2;n=2466	0.2622
Glucose, mmol/L	6.52(5.6-8.25);29.29;n=276	5.5(4.98-6.5);26.8;n=1877	<0.0001***
D-dimer, ng/mL	519.0(320.0-896.0);5166.88;n=65	290.0(190.0-560.05);11200.0;n=447	<0.0001***
High sensitive troponin-I, ng/L	9.28(3.62-20.25);3876.3;n=154	3.0(1.4-5.46);327.1;n=1001	<0.0001***
Lactate dehydrogenase, U/L	242.0(189.0-308.0);1096.0;n=233	194.65(164.0-235.0);1116.0;n=1824	<0.0001***

APTT, second	30.3(27.0-34.5);66.4;n=215	31.0(27.9-34.4);120.0;n=1251	0.2503
Prothrombin time, second	11.9(11.4-12.5);18.0;n=141	12.0(11.4-12.6);110.0;n=892	0.5058
C-reactive protein, mg/dL	1.1(0.34-4.1);34.0;n=305	0.32(0.12-1.18);32.529;n=2386	<0.0001***

Table 3. Univariate logistic regression to identify significant predictors of COVID-19 positivity. COVID-19 = coronavirus disease 2019; ACEI=Angiotensin-Converting Enzyme Inhibitors; ARB=Angiotensin Receptor Blockers; IQR = Interquartile range; AMI= acute myocardial infarction; COPD= chronic obstructive pulmonary disease; IHD= ischemic heart disease; PVD= peripheral vascular disease; TIA= transient ischemic attack; APTT= applied partial thromboplastin time. * for p≤ 0.05, ** for p ≤ 0.01, *** for p ≤ 0.001

Characteristics	**Odds Ratio (95% CI)**	**P-value**
Male gender	1.1[1.0,1.1]	0.0925
Age, years	1.0[1.0,1.0]	<0.0001***
Charlson score	1.1[1.0,1.2]	<0.0001***
Diabetes mellitus	1.4[1.1,1.8]	0.0112*
Hypertension	1.9[1.7,2.1]	<0.0001***
Heart failure	0.5[0.2,1.3]	0.1704
Liver diseases	0.4[0.2,1.1]	0.0740
Heart block	0.4[0.2,0.8]	0.0113*
Dementia	0.4[0.2,0.8]	0.0147*
AMI	0.7[0.4,1.0]	0.0557
COPD	0.9[0.6,1.4]	0.7041
IHD	1.0[0.8,1.3]	0.9372
PVD	0.7[0.3,1.5]	0.3356
Stroke/TIA	1.6[1.2,2.1]	0.0013**
Gastrointestinal bleeding	1.5[1.1,2.0]	0.0060**
Cancer	0.5[0.4,0.7]	<0.0001***
Obesity	3.2[1.3,7.9]	0.0104*
ACEI/ARB	1.9[1.7,2.2]	<0.0001***
Steroid	1030.5[727.9,1459.0]	<0.0001***
Lopinavir/ritonavir	12699.9[6999.0,23044.6]	<0.0001***
Ribavirin	3640.1[2457.8,5391.1]	<0.0001***
Interferon beta-1B	4136.8[3087.5,5542.7]	<0.0001***
Hydroxychloroquine	-	-
Calcium channel blockers	2.4[2.1,2.6]	<0.0001***
Beta blockers	1.8[1.5,2.0]	<0.0001***
Diuretics for hypertension	12.9[10.5,15.7]	<0.0001***
Nitrates	1.1[0.9,1.5]	0.3014
Antihypertensive drugs	830.1[433.5,1589.7]	<0.0001***
Antidiabetic drugs	2154.0[1235.5,3755.0]	<0.0001***
Statins and fibrates	2655.2[1525.7,4620.9]	<0.0001***
Lipid-lowering drugs	2560.6[1471.0,4457.5]	<0.0001***
Anticoagulants	1701.5[901.0,3213.3]	<0.0001***
Antiplatelets	198.5[152.4,258.8]	<0.0001***
Mean corpuscular volume, fL	0.931[0.928,0.933]	<0.0001***
Basophil, x10^9/L	0.774[0.767,0.782]	<0.0001***

Eosinophil, x10^9/L	0.903[0.9,0.907]	<0.0001***
Lymphocyte, x10^9/L	0.943[0.941,0.944]	<0.0001***
Metamyelocyte, x10^9/L	0.338[0.221,0.517]	<0.0001***
Monocyte, x10^9/L	0.909[0.906,0.912]	<0.0001***
Neutrophil, x10^9/L	0.963[0.962,0.964]	<0.0001***
White cell count, x10^9/L	0.959[0.958,0.961]	<0.0001***
Mean corpuscular haemoglobin, pg	0.831[0.826,0.836]	<0.0001***
Myelocyte, x10^9/L	0.468[0.371,0.592]	<0.0001***
Platelet, x10^9/L	0.947[0.945,0.949]	<0.0001***
Reticulocyte, x10^9/L	0.26[0.135,0.499]	<0.0001***
Red cell count, x10^12/L	0.934[0.932,0.936]	<0.0001***
Hematocrit, L/L	0.866[0.855,0.877]	<0.0001***
Potassium, mmol/L	0.886[0.882,0.89]	<0.0001***
Urate, mmol/L	0.483[0.373,0.624]	<0.0001***
Albumin, g/L	0.929[0.926,0.931]	<0.0001***
Sodium, mmol/L	0.911[0.908,0.914]	<0.0001***
Urea, mmol/L	0.948[0.946,0.95]	<0.0001***
Protein, g/L	0.925[0.922,0.928]	<0.0001***
Creatinine, umol/L	0.915[0.912,0.919]	<0.0001***
Alkaline phosphatase, U/L	0.889[0.884,0.893]	<0.0001***
Aspartate transaminase, U/L	0.9[0.893,0.907]	<0.0001***
Alanine transaminase, U/L	0.941[0.939,0.944]	<0.0001***
Bilirubin, umol/L	0.774[0.768,0.781]	<0.0001***
Triglyceride, mmol/L	0.918[0.911,0.925]	<0.0001***
Low-density lipoprotein, mmol/L	0.933[0.926,0.939]	<0.0001***
High-density lipoprotein, mmol/L	0.891[0.88,0.901]	<0.0001***
Cholesterol, mmol/L	0.914[0.906,0.923]	<0.0001***
HbA1c, g/dL	0.926[0.924,0.928]	<0.0001***
Glucose, mmol/L	0.949[0.947,0.951]	<0.0001***
D-dimer, ng/mL	0.958[0.955,0.961]	<0.0001***
High sensitive troponin-I, ng/L	0.975[0.973,0.976]	<0.0001***
Lactate dehydrogenase, U/L	0.959[0.957,0.96]	<0.0001***
APTT, second	0.92[0.917,0.924]	<0.0001***
Prothrombin time/INR, second	0.817[0.809,0.825]	<0.0001***
C-reactive protein, mg/dL	0.975[0.973,0.976]	<0.0001***

Table 4. Univariate logistic regression to predict composite outcomes in COVID-19 positive patients. COVID-19 = coronavirus disease 2019; ACEI=Angiotensin-Converting Enzyme Inhibitors; ARB=Angiotensin Receptor Blockers; IQR = Interquartile range; AMI= acute myocardial infarction; COPD= chronic obstructive pulmonary disease; IHD= ischemic heart disease; PVD= peripheral vascular disease; TIA= transient ischemic attack; APTT= applied partial thromboplastin time. * for p≤ 0.05, ** for p ≤ 0.01, *** for p ≤ 0.001

Characteristics	**Odds Ratio (95% CI)**	**P-value**
Male gender	1.8[1.3,2.5]	0.0004***
Age, years	1.0[1.0,1.0]	<0.0001***
Charlson score	1.6[1.5,1.7]	<0.0001***
Diabetes mellitus	6.1[3.3,11.2]	<0.0001***
Hypertension	7.4[5.4,10.3]	<0.0001***
Heart failure	4.0[0.5,36.4]	0.2121
Liver diseases	5.4[0.6,52.2]	0.1451
Heart block	50.2[10.0,250.7]	<0.0001***
Dementia	33.0[6.0,181.7]	0.0001***
AMI	8.4[3.3,21.1]	<0.0001***
COPD	3.1[1.1,9.2]	0.0390*
IHD	5.7[3.3,9.9]	<0.0001***
PVD	22.0[4.9,99.2]	0.0001***
Stroke/TIA	9.5[5.2,17.2]	<0.0001***
Gastrointestinal bleeding	5.4[2.7,10.8]	<0.0001***
Cancer	6.8[3.9,12.0]	<0.0001***
Obesity	4.0[0.5,36.4]	0.2121
ACEI/ARB	6.7[4.8,9.5]	<0.0001***
Steroid	1.4[0.9,2.0]	0.1469
Lopinavir/ritonavir	4.0[2.8,5.7]	<0.0001***
Ribavirin	1.2[0.9,1.7]	0.3074
Interferon beta-1B	5.1[3.4,7.6]	<0.0001***
Hydroxychloroquine	2.4[1.2,4.5]	0.0096**
Calcium channel blockers	7.2[5.2,10.0]	<0.0001***
Beta blockers	6.5[4.4,9.4]	<0.0001***
Diuretics for hypertension	3.2[1.9,5.4]	<0.0001***
Nitrates	5.3[2.9,9.7]	<0.0001***
Antihypertensive drugs	4.8[2.9,7.9]	<0.0001***
Antidiabetic drugs	14.7[10.4,20.6]	<0.0001***
Statins and fibrates	8.1[5.8,11.3]	<0.0001***
Lipid-lowering drugs	8.3[5.9,11.5]	<0.0001***
Anticoagulants	54.8[37.2,80.8]	<0.0001***
Antiplatelets	8.7[6.0,12.5]	<0.0001***
Mean corpuscular volume, fL	0.999[0.997,1.0]	0.1014

Basophil, x10^9/L	0.996[0.988,1.004]	0.3696
Eosinophil, x10^9/L	0.993[0.988,0.997]	0.0004***
Lymphocyte, x10^9/L	0.991[0.989,0.994]	<0.0001***
Metamyelocyte, x10^9/L	0.665[0.539,0.822]	0.0002***
Monocyte, x10^9/L	1.0[0.997,1.002]	0.8440
Neutrophil, x10^9/L	1.002[1.002,1.003]	<0.0001***
White cell count, x10^9/L	1.0[0.999,1.001]	0.4300
Mean corpuscular haemoglobin, pg	1.014[1.009,1.018]	<0.0001***
Myelocyte, x10^9/L	0.862[0.82,0.907]	<0.0001***
Platelet, x10^9/L	0.996[0.994,0.999]	0.0010*
Reticulocyte, x10^9/L	0.953[0.883,1.029]	0.2222
Red cell count, x10^12/L	0.992[0.989,0.994]	<0.0001***
Hematocrit, L/L	1.0[0.996,1.004]	0.8632
Potassium, mmol/L	1.002[0.999,1.005]	0.2496
Urate, mmol/L	0.984[0.974,0.995]	0.0041**
Albumin, g/L	0.991[0.99,0.993]	<0.0001***
Sodium, mmol/L	0.997[0.995,0.998]	0.0001***
Urea, mmol/L	1.004[1.003,1.005]	<0.0001***
Protein, g/L	0.997[0.996,0.999]	0.0027**
Creatinine, umol/L	0.997[0.996,0.998]	<0.0001***
Alkaline phosphatase, U/L	0.998[0.997,1.0]	0.0261*
Aspartate transaminase, U/L	0.999[0.997,1.002]	0.5193
Alanine transaminase, U/L	1.001[1.0,1.003]	0.0494*
Bilirubin, umol/L	0.996[0.994,0.998]	0.0005***
Triglyceride, mmol/L	0.992[0.99,0.993]	<0.0001***
Low-density lipoprotein, mmol/L	0.994[0.993,0.995]	<0.0001***
High-density lipoprotein, mmol/L	0.987[0.985,0.99]	<0.0001***
Cholesterol, mmol/L	0.991[0.989,0.992]	<0.0001***
HbA1c, g/dL	0.997[0.993,1.002]	0.2469
Glucose, mmol/L	0.999[0.999,1.0]	0.3068
D-dimer, ng/mL	0.997[0.996,0.999]	0.0002***
High sensitive troponin-I, ng/L	0.999[0.998,1.0]	0.0130*
Lactate dehydrogenase, U/L	1.003[1.002,1.004]	<0.0001***
APTT, second	0.992[0.989,0.994]	<0.0001***
Prothrombin time, second	0.98[0.973,0.986]	<0.0001***
C-reactive protein, mg/dL	1.003[1.002,1.003]	<0.0001***

Table 5. Multivariate logistic regression to identify significance of ACEI/ARB on COVID-19 positivity and composite outcome presentation.

COVID-19 = coronavirus disease 2019; ACEI=Angiotensin-Converting Enzyme Inhibitors; ARB=Angiotensin Receptor Blockers; CI = Confidence Interval.

* for p≤ 0.05, ** for p ≤ 0.01, *** for p ≤ 0.001

	COVID-19 positivity in tested patients	
	Odds Ratio (95% CI)	**P-value**
Model 1	1.94[1.71,2.18]	<0.0001***
Model 2	2.86[2.51, 3.25]	<0.0001***
Model 3	2.51[2.19, 2.87]	<0.0001***
Model 4	2.22[1.71, 2.89]	<0.0001***
	Composite outcome in COVID-19 positive patients	
	Odds Ratio (95% CI)	**P-value**
Model 1	6.74[4.79, 9.49]	<0.0001***
Model 2	2.00[1.37, 2.93]	<0.0001***
Model 3	1.81[1.19, 2.75]	<0.0001***
Model 4	1.78[1.16, 2.73]	<0.0001***

Model 1: adjusted for none.

Model 2: adjusted for significant demographics.

Model 3: adjusted for significant demographics and past comorbidities.

Model 4: adjusted for significant demographics, past comorbidities and other medications.