

Severity of COVID-19 Infection in ACEI/ARB Users in Two Saudi Public Specialty Hospitals; Retrospective Cohort Study

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Abstract

The uncertainty about COVID-19 outcomes in angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB) users continues with contradictory findings. The aim of this study was to determine the effect of ACEI/ARB use in patients with severe COVID-19. This retrospective cohort study done in two Saudi public specialty hospitals designated as COVID-19 referral facilities. We included 354 patients with confirmed diagnosis of COVID-19 between April and June 2020, of which 146 were ACEI/ARB users and 208 were non-ACEI/ARB users. Controlling for confounders, we conducted a multivariate logistic regression and a sensitivity analysis using propensity score matched (PSM) patients. Compared to non-ACEI/ARB users, ACEI/ARB users had an eight-fold higher risk of developing critical or severe COVID-19 (OR=8.25, 95%CI=3.32-20.53); a nearly 7-fold higher risk of intensive care unit (ICU) admission (OR=6.76, 95%CI=2.88-15.89) and a nearly 5-fold higher risk of requiring noninvasive ventilation (OR=4.77,95%CI=2.15-10.55). Patients with diabetes, hypertension, and/or renal disease had a five-fold higher risk of severe COVID-19 disease (OR=5.40,95%CI=2.0-14.54]. These results were confirmed in the PSM analysis. In general, but especially among patients with hypertension, diabetes, and/or renal disease, ACEI/ARB use is associated with a significantly higher risk of severe or critical COVID-19 disease, and ICU care.

Introduction

Coronavirus disease 2019 (COVID-19) is pandemic disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. It emerged in Wuhan, the largest city in Hubei Province, China and rapidly spread to become a worldwide pandemic [2]. The World Health Organization (WHO) reported as of 31 August 2020 more than 25 million confirmed cases of COVID-19 and more than 800,000 death cases globally [3,4]. The virus is transmitted through respiratory droplets or aerosols and direct contact, is characterized by a wide range of symptoms, and patients may experience mild, severe, or critical illness [5]. The overall mortality rate in various countries ranges from 2% to 13% [6,7].

Risk factors associated with the clinical severity of COVID-19 include age (especially >75 years old), obesity, selected medications, and comorbidities such as hypertension, diabetes, and cardiovascular disease[8-14]. Noteworthy is the frequent presence of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II type-I receptor blockers (ARB) frequently in these patients' pharmacological treatment. It has been hypothesized that exposing patients to ACEI/ARB may increase the expression of ACE2 by a negative feedback mechanism, thus facilitating the binding process of coronavirus to epithelial cells of the kidney, intestine, lung, and blood vessels [15] and increasing the risk of developing severe and fatal COVID-19 disease [16-18]. Clinical research evidence to date has been equivocal, especially in terms of identifying differentiating factors that may mediate the ACEI/ARB and COVID-19 severity relationship [19-23].

In the case of Saudi Arabia, we have a young developing country with a median age of 30.8 years burdened with comorbid diseases [24]. The Saudi Arabia's healthcare system is mainly funded by the public sector through the Ministry of Health (MOH) which serves 23 million people. Thought at different levels, critical care services are provided in primary, secondary, and tertiary/specialty hospitals; with complex cases being referred to tertiary/specialty hospitals that are well equipped with specialized intensive care units (ICU) and highly trained intensivists [25]. Regarding comorbid disease in the Saudi general population and in spite of extensive healthcare resources, the WHO ranks Saudi Arabia 7th in the world in terms rates of diabetes with an estimated 7 million people affected, followed by hypertension (26.1%), and, rapidly emerging because of its association with both conditions, chronic kidney disease (6%) [26-28]. Studies link the development of these diseases to ACE insertion/deletion (I/D) polymorphism in certain populations including Saudis [29-32].

The uncertainty about COVID-19 outcomes in ACE/ARB users may be a function of how patients with diabetes, hypertension, and/or chronic renal disease are clinically compromised and therefore more susceptible to severe COVID-19 disease. A systematic review concluded that patients with diabetes, hypertension, and chronic renal disease had an increased mortality risk in the setting of Middle Eastern respiratory syndrome (MERS) coronavirus infection (a corona virus closely related to SARS-CoV-2 that originated in Saudi Arabia in 2012) [33]. We report here on a retrospective real-world clinical study in two public tertiary/specialty hospitals to which severe COVID-19 cases were referred to assess the association of ACEI/ARB and clinical severity of COVID-19.

Severity of COVID–19 disease in ACEI/ARB users was based on the following variables: ICU admission, non-invasive and invasive mechanical ventilation, in-hospital mortality, and hospital length of stay. In addition to outcomes observed in the overall population of referred patients, we also evaluated severity outcomes for high risk patients with diabetes, hypertension and/or renal disease.

Methodology

Study Design and Study Setting:

This retrospective was conducted in the tertiary specialty referral hospitals known as King Fahad Medical City (KFMC; 1200 beds) and Prince Mohammed Bin Abdulaziz hospital (PMAH; 500 beds), both in Riyadh, Saudi Arabia. The Institutional Review Boards at KFMC and PMAH (IRB 20–200) approved the study. All methods were performed in accordance with the relevant guidelines and regulations. Informed consent was waived since it was an exempt study conducting a retrospective analysis.

Participant selection:

Lists of discharged or dead COVID–19 patients were obtained from the health informatics officer and categorized into ACEI/ARB users and ACEI/ARB non-users based on their medication history. Inclusion criteria were age >18 years admitted at KFMC or PMAH from April to June 2020; being treated with ACE/ ARB inhibitors 6 months before and continued during hospital admission and after discharge for any indications such as hypertension, stroke, heart failure, myocardial infarction, diabetes mellitus, chronic kidney disease or nephrotic syndrome (criteria only for ACEI/ARB users); and SARS-CoV–2 infection confirmed by real-time polymerase chain reaction (RT-PCR) from nasopharyngeal swab for inclusion. Patients were excluded if pregnant, incomplete medical records due to patients being transferred recently from other hospitals, or unknown medications history.

Data Collection:

Data were extracted manually from electronic health records (Cortex system and HIM system in KFMC, and Cerner Systems in PMAH) by a trained team and included demographic and anthropometric variables such as age, height, weight, body mass index (BMI), class of obesity; medical history of hypertension, diabetes, asthma, cardiovascular disease (including coronary artery disease, heart failure), renal disease (chronic kidney disease or nephrotic syndrome); COVID–19 treatment regimen; use of ACE/ARB; spectrum of illness severity; need for ICU admission; need for non-invasive ventilation (NIV) (e.g., face mask, nasal cannula, nasal mask, or helmet); need for invasive mechanical ventilation (MV); in hospital-death; and length of hospitalization.

COVID–19 Spectrum of Severity definitions:

We defined the spectrum of disease severity according to the WHO [34]. Mild illness was defined as uncomplicated upper respiratory tract viral infection and may have non-specific symptoms such as fever, fatigue, cough, anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, or headache. Moderate illness was the development of non-severe pneumonia that does not require supplemental oxygen. Severe pneumonia was defined as fever plus symptoms ≥ 1 of the following: respiratory rate ≥ 30 /min, dyspnea, respiratory distress, $SpO_2 \leq 93\%$ on room air, PaO_2/FiO_2 ratio < 300 , lung infiltrate $> 50\%$ of lung field within 24–48hr. Critical illness manifested by symptoms ≥ 1 of the following: acute respiratory distress syndrome (ARDS), septic shock, altered consciousness, or multi-organ Failure.

Study Outcomes:

The primary outcome was COVID–19 severity classified as mild, moderate, severe, or critical according to the above WHO classification in ACEI/ARB users as compared to non-ACEI/ARB users. Secondly, we evaluated need of ICU admission, NIV and MV, in-hospital death, and length of hospital stay in patients on ACEI/ARB as compared to non-ACEI/ARB users. We also assessed COVID–19 severity (severe or critical) in patients with (1) one of the three comorbidities of interest (diabetes, hypertension or renal disease); (2) both diabetes and hypertension; (3) diabetes only; and (4) hypertension only.

Statistical Analysis:

Using R Core Team (2020) software (R Foundation for Statistical Computing, Version 4.0.1, Vienna, Austria), continuous data were expressed as mean with standard deviation (\pm SD) or median with interquartile range (IQR). If the normality assumption was met using normal Q-Q plot and the Shapiro–Wilk test, we used the Student’s t-test for group comparisons; if not met, we used the Mann-Whitney. Categorical data were reported as frequencies and percentages and analyzed either using the Chi-square test for $m \times m$ tables or Fisher’s exact test for 2x2 tables group comparisons. To obtain odds ratios, we performed a multivariable logistic regression model adjusting for the confounders (either $P < 0.3$ in a univariable logistic regression model or clinically important confounders) of age, sex, BMI, diabetes, hypertension, renal disease, number of comorbidities (diabetes, hypertension, cardiovascular disease [heart failure/coronary artery disease], stroke, renal disease, asthma and obesity) and COVID–19 treatment regimen. All statistical inferences were drawn with 95% confidence intervals with $P < 0.05$. Bonferroni adjustments were applied to control for multiplicity [35].

Propensity score-matched analysis

A sensitivity analysis to confirm the multivariable logistic regression was performed using nearest neighbor 1:3 propensity score matching (PSM) with replacement with a caliper of 0.1 and with the following confounding covariates: age, BMI, diabetes, hypertension, renal disease and number of comorbidities as defined above and using the same rationale as above. Additionally, significant interaction terms were considered. The balance of the matched data was evaluated using standardized mean difference (SMD) before and after matching. Values of SMD < 0.1 indicated adequate balance and fruitful matching. The propensity score distribution was also evaluated using mirror diagram and the love plot for SMD distribution (see Supplementary Fig. S1 and Fig. S2). We performed the analysis using the MatchIt package [36] in the R Core Team (2020) software interface.

Results

From April to June 2020, a total of 532 confirmed cases of COVID–19 disease were admitted to the KFMC and PMAH hospitals. Of these, 178 patients were excluded from analysis as they did not meet eligibility criteria. A total of 146 patients on ACEI/ARB and 208 were non-ACEI/ARB users included in multivariable logistic regression analysis. Propensity score matching yielded 145 ACEI/ARB users and 63 patients’ non-ACEI/ARB users (Fig. 1).

The mean (\pm SD) age of the ACEI/ARB group was 56.3 (11.9), BMI was 28.8 kg/m² (6.3) and 78.1% were men, compared with 40.2 years (11.5), BMI of 27.4 kg/m² (7.4) and 81.7% were men in non-ACEI/ARB group (Table 1). Rates of diabetes of 41.6%, hypertension of 34.5%, and renal disease of 7.3% were observed in the total sample. The propensity score matching controlling for the selected covariates was balanced [Table 2; see also Supplementary Fig. S1 and Fig. S2 (love plot) for propensity scores distribution and balance of covariates, respectively].

Sample

From crude counts and percentages (Table 3), the two multivariable logistic regression models estimated the adjusted odds ratios for the unmatched and matched data for the entire sample. Compared to non-ACEI/ARB users, patients treated with ACEI/ARB were at significantly higher risk of developing severe/critical COVID–19 compared to non-users (OR = 8.25, 95%CI = 3.32–20.53, $P < 0.001$); being admitted to the ICU (OR = 6.76, 95%CI = 2.88–15.89, $P < 0.001$); and requiring noninvasive ventilation (OR = 4.77, 95%CI = 2.15–10.55, $P < 0.001$); but at statistically equal risk of requiring mechanical ventilation or in-hospital death. The results remained significant after adjusting for multiplicity and were confirmed in the PSM sensitivity analysis. Cases classified as mild-moderate category were higher among non-ACEI/ARB users ($P < 0.001$; Supplementary Table S1). All other comparisons between ACEI/ARB users and non-users on the outcomes of interest were statistically non-significant. Of note, age was independently associated with an increased need of non-invasive ventilation in the multivariable logistic regression (OR = 1.03, 95%CI = 1.002–1.059, $P = 0.036$).

Diabetes, Hypertension or Renal disease

Patients with diabetes, hypertension, or renal diseases on ACEI/ARB therapy were found to have significantly higher COVID-19 severity as compared to non-ACEI/ARB users (72.2% vs 27.8%) with OR 5.34[95% CI = 1.87- 15.30] (Table 4). Patients with diabetes and hypertension, diabetes alone or hypertension on ACEI/ARB had a higher severity when compared to non-ACEI/ARB users (Table 4). After adjusting for multiplicity, results remained significant except for the presence of diabetes alone. The PSM sensitivity analyses confirmed these results except for the presence of hypertension and diabetes.

Discussion

Our findings suggested that ACEI/ARB use can adversely affect the severity of COVID-19 illness by increasing the need of ICU admission, and non-invasive ventilation (suggesting more oxygen demand) in ACEI/ARB users. However, similar to the majority of reported studies, there was no association found in increase need of mechanical ventilation and in-hospital death [19][37–38].

The prevalence of hypertension, diabetes, and renal disease were high in ACEI/ARB group as expected, since these medications are typically used to manage these comorbidities in clinical practice. To overcome the influence of confounding factors, we performed two models for the whole sample: a multivariable logistic regression model and a propensity score matching as a sensitivity analysis. In both of these analyses, outcomes remained significant confirming these findings. The presence of diabetes was found to be marginally non-significant after Bonferroni adjustment. Due to subjects' loss in the PSM sensitivity analyses, the presence of diabetes and hypertension was not significant.

The renin angiotensin aldosterone system (RAAS) is reported to play a major role in the pathogenesis of type 2 diabetes and hypertension [39]. To date, there are over 30 different variants of the ACE2 gene reported in the Lieden open variation database (LOVD) [40]. Several studies showed a potential link between certain ACE2 variants and the development of cardiovascular diseases such as hypertension, while other reports find the evidence is inconclusive [41–43]. The high rates of comorbidities in our population may be linked to the existence of ACE2 polymorphism. In particular, the association between ACE insertion/deletion (I/D) polymorphism and the development of type 2 diabetes and hypertension was reported by Alsaikhan et al in 2017 in Saudi Arabian population [29]. Moreover, studies in Malaysian, Taiwanese, Iranian and Turkish populations reported similar findings [30–32][44]. The use of ACEI/ARB in COVID-19 patients is still controversial in the pharmacological and clinical communities. It is argued that since SARS-CoV-2 uses ACE2 receptors for cellular entry, ACEI/ARB use can block the receptor preventing viral attachment, entry and multiplication which ultimately, improve patients' outcomes. It could also be argued that continuous use of these medications may lead to over-expression of ACE2 receptors by a negative feedback mechanism and then increasing coronaviruses binding to target cells [15][45]. Whether the existence of genetic susceptibility to ACE2 polymorphism and ACEI/ARB use has an effect on COVID-19 severity or not is yet to be determined [46].

Certainly, the contradictory findings reported in different populations with regards to the severity of COVID-19 may suggest population differences at play [20–23][47–49]. For example, in a study by Mehta et al. in the United States, showed no significant association between ACEI/ARB use and mortality, while it reported potential harmful effects with ACEI/ARB use including higher hospital and ICU admissions [20]. Another study in France by Liabeuf et al and two studies in the United States by Rentsch et al and Richardson et al reported similar findings with regards to increase severity [49][23]. On the contrary, a large multi-center retrospective study in the United Kingdom (UK) by Bean et al and a single center retrospective study in Italy by Felice et al reported significantly lower severity of COVID-19 illness among ACEI/ARB users. Most of the above-mentioned studies defined severity of COVID-19 illness as ICU admission rates [48][21]. Interestingly, in another large cohort study from the UK, Black Africans on ACEI/ARB were found to have higher risk of COVID-19 disease [50]. Our population may be considered similar to a study conducted in Turkey [51]. They reported that ACEI/ARB use in hypertensive patients was independently associated with ICU admission, mechanical ventilation and in-hospital mortality. Despite the fact that outcome definitions need to be harmonized across studies, based on our findings, we believe that there could be a potential signal for ethnic differences that make certain populations susceptible to severe COVID-19 disease. Further, an important key driving factor may be related to how vulnerable these patients are into developing comorbidities; namely diabetes, hypertension and/or renal diseases.

Our study provides an additional insight to the topic in question. First, to our knowledge, this is the first retrospective study conducted in two public specialty hospitals in the Gulf Cooperation Council (GCC) region. The setting adds some external validity to the study as we see patients from all backgrounds that presents with greater complexity compared to other hospitals. The general population in Saudi uniquely suffers from high prevalence rates of comorbidities that include hypertension, diabetes, chronic kidney disease that is among other factors, potentially linked to ACE insertion/deletion (I/D) polymorphism[29]. In our analysis with these comorbidities, we found a strong association of COVID–19 severity and ACEI/ARB use. Secondly, we used multiple definitions to capture the severity of the disease, all of which were significant except for the need for MV, length of stay and in-hospital death. Thirdly, unlike other studies, we conducted two models to adjust for potential confounders with adjustment for multiplicity problem. [52–55][47]. We recognize that the retrospective nature of this study is a major limitation. Moreover, we could not stratify patients according to their chronicity of ACEI/ARB use. In despite of performing multiple models to adjust for confounding variables, we could have missed other variables that can explain the severity of COVID–19 illness. The wide confidence intervals may limit the interpretability of the results. Additionally, we could not assess the duration of non-invasive ventilation in patients on ACEI/ARB as compared to non-ACEI/ARB users. Lastly, our study was not designed to spot outcome differences between the two classes (ACEI or ARB).

For future direction, a temporary ACEI/ARB withdrawal in hospitalized patients with frequent blood pressure monitoring and management with other appropriate therapies maybe a prudent action especially for ICU patients where the risk is higher than benefit in the short term, until control trials reveals the impact of interim ACEI/ARB cessation in COVID–19 patients in the hospital setting. Indeed, this is a strong statement that goes against the mainstream recommendations with regards to continuation of these medications [56]. Still, we argue from an indirect evidence that a short-term ACEI/ARBs withdrawal (≤ 2 weeks) strategy does not seem increase risk of cardiovascular disease deterioration in low risk patients. In a control randomized trial (RCT) comparing ACEI (quinapril) continuation or withdrawal (by giving placebo) for 16 weeks in heart failure patients, it showed an increase of heart failure symptoms worsening occurred only after 4–6 weeks of the ACEI withdrawal [57]. The two weeks strategy we propose might be useful in reducing the severity of COVID–19 disease, need of ICU admission, and need of oxygen through non-invasive ventilation. This is not to say we should take the results of this study as a definite answer to the problem. Admittedly, this debated question can be answered by well-designed RCTs. There are RCTs currently undergoing, REPLACECOVID trial in the US, the BRACE-CORONA trial in Brazil and ACEI-COVID trial in Austria, comparing the effecting of ACEI/ARB continuation or withdrawal in hospitalized COVID19 patients[58–60]. Our findings suggest the urgent need for RCT trial with a similar design in our own population to answer this heavily debated question with firm conclusions

Conclusion

This study illustrates how ACEI/ARB use adversely affected the severity of COVID–19 disease in Saudi Arabian population. As compared to non-ACE/ARB users, ACEI/ARB users had higher severity, need of ICU admission and noninvasive ventilation. Notably, patients on ACEI/ARB with diabetes, hypertension and renal disease were at higher risk of developing severe COVID–19 disease compared to non-ACEI/ARB. The results of this study suggest the need for a well-designed RCT to confirm these findings.

Declarations

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Disclosure statement:

The authors have no potential conflicts of interest to disclose.

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Authors contributions:

A. A.A conceived the idea of this research, drafted research proposal, obtained IRB, secured funds and drafted an initial manuscript. N. M.A, Y.M, M. M.A, W.A, M. A.A, A. S.A, A. I.B and M. M.A jointly collected and ensured the quality of the data. A.A (in consultation with I.A) analyzed the data using the statistical software, produced all tables and jointly drafted the final manuscript with A. A. A.M.E, N. K.A, B.A, T. M.K and I.A contributed with their edits to the final manuscript. S. M. B.A contributed to data interpretation and critically revised the manuscript.

Competing interests

The author(s) declare no competing interests.

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Tables

Table1. Patients' baseline characteristics

Baseline	ACEI/ARB (intervention) n= 146	Non-ACEI/ARB (control) n= 208	Total n= 354	P value
Age, mean (\pm SD)	56.36 (11.9)	40.29 (11.6)	46.9(14.11)	< 0.001
Male, n (%)	114 (78.1)	170 (81.7)	284 (80.2)	0.396
BMI, mean (\pm SD)	28.8 (6.3)	27.4 (7.4)	28(6.9)	0.059
Obesity, n (%)	41 (28.1)	40 (19.2)	81 (22.9)	0.051
Hypertension, n (%)	123 (84.2)	22 (10.6)	145 (41.0)	< 0.001
Diabetes, n (%)	98 (67.1)	42 (20.2)	140 (39.5)	< 0.001
Cardiovascular disease (HF,CAD), n (%)	42 (28.8)	5 (2.4)	47 (13.3)	< 0.001
Stroke, n (%)	3 (2.1%)	1 (0.5)	4 (1.1)	0.168
Renal disease, n (%)	17 (11.6)	9 (4.3)	26 (7.3)	0.009
Asthma, n (%)	24 (11.5)	15 (10.3)		0.708
Current use of NSAIDs, n (%)	24 (16.4)	27 (13.0)	51 (14.4)	0.362
Number of comorbidities*, Median (IQR)	3.322 (1.050) 1.000 - 6.000	1.688 (0.990) 0 (0-1)	2.362 (1.295) 1.000 - 6.000	< 0.001
COVID-19 regimen				
Supportive Care	105 (71.4)	159 (76.4)	264 (74.6)	
Lopinavir/ritonavir	2 (1.4)	0(0)	2 (0.6)	
Favipravir	2 (1.4)	0(0)	2 (0.6)	
Hydroxychloroquine+Azithromycin	29 (19.9)	39(18.8)	68 (19.2)	
Hydroxychloroquine	8 (5.5)	10(4.8)	18 (5.1)	

*Comorbidities include: diabetes, hypertension, cardiovascular disease (heart failure/coronary artery disease), stroke, renal disease, asthma and obesity.

IQR: Interquartile range. SD: Standard deviations. ACEI: Angiotensin-converting-enzyme inhibitors. ARBs: Angiotensin II receptor blockers. COVID-19: Coronavirus disease 2019. HF: heart failure. CAD: coronary artery disease

Table 2. Propensity Score-Matching (PSM) model results

Confounders	ACEI/ARBs (unmatched) n=146	Non-ACEI/ARB (unmatched) n=208	SMD* before matching	ACEI/ARB (matched) n=145	Non-ACEI/ARB (matched) n=63	SMD* after matching
Age (years), mean (\pm SD)	56.36 (11.87)	40.29 (11.57)	1.353	56.46 (11.84)	49.21 (12.54)	-0.083
BMI (kg/m ²), mean (\pm SD)	28.81(6.32)	27.39 (7.35)	0.224	28.68 (6.13)	29.22 (6.58)	-0.229
Diabetes, n (%)	98 (67.1)	42 (20.2)	0.995	97 (66.9)	29 (46.0)	0.124
Hypertension, N (%)	123 (84.2)	22 (10.6)	2.015	122 (84.1)	22 (34.9)	0.066
Renal disease, n (%)	17 (11.6)	9 (4.3)	0.737	17 (11.7)	9 (14.3)	0.092
Number of Comorbidities [¶] , median (IQR)	2 (2-3)	0 (0-1)	1.217	2 (2-3)	1 (1-3)	-0.061

Propensity score matching with age, BMI, diabetes, hypertension, renal disease and number of comorbidities

[¶]Comorbidities include: diabetes, hypertension, cardiovascular disease (heart failure/coronary artery disease), stroke, renal disease, asthma and obesity

*Standardized mean difference

IQR: Interquartile range. SD: Standard deviation. SMD: Standardized mean difference: Angiotensin-converting enzyme inhibitors (ACE). ARB: Angiotensin II receptor blockers. BMI: body mass index

Table 3. Adjusted odds ratio for clinical outcomes among users and non-users of ACEI/ARB

Variable	ACEI/ARB (unmatched) n=146	Non-ACEI/ARBs (unmatched) n=208	Adjusted odds ratio [†] (95% CI)	P value	Bonferroni adjustment ^a	ACEI/ARB (matched) n=145	Non-ACEI/ARB (matched) n=63	Adjusted odds ratio [‡] (95% CI)	P value	Bonferroni adjustment ^a
Severe or critical [¶] , n (%)	126 (86.3)	67 (32.2)	8.25 (3.32 - 20.53)	<0.001	<0.001	125 (86.2)	30 (47.6)	5.55 (2.41 - 12.80)	<0.001	<0.001
ICU admission, n (%)	74 (50.7)	23 (11.1)	6.76 (2.88 - 15.89)	<0.001	<0.001	73 (50.3)	11 (17.5)	4.98 (2.02 - 12.21)	<0.001	0.002
Noninvasive Ventilation, n (%)	103 (70.5)	54 (26.0)	4.77 (2.15 - 10.55)	<0.001	<0.001	103 (71.0)	25 (39.7)	3.57 (1.68 - 8.80)	0.001	0.005
Mechanical ventilation, n (%)	32 (21.9)	13 (6.2)	1.68 (0.58 - 4.83)	0.337	1.000	31 (21.4)	6 (9.5)	1.63 (0.53 - 4.96)	0.358	1.000
In-hospital death, n (%)	3 (2.1)	2 (1.0)	0.35 (0.03 - 4.63)	0.427	1.000	3 (2.1)	2 (3.2)	0.48 (0.05 - 4.49)	0.521	1.000

[¶]Severe or critical defined according to WHO severity definition. ICU: Intensive care unit.

[†]Odds ratio adjusted using logistic regression model with the following variables: age, sex, BMI, diabetes, hypertension, renal disease, number of comorbidities (that includes diabetes, hypertension, cardiovascular disease (heart failure/coronary artery disease), stroke, renal disease, asthma and obesity) and inpatient COVID-19 regimen.

[‡]Odds ratios adjusted using propensity score matching model

^a For multiplicity correction, Bonferroni method was used to adjust the P values

Table 4. Clinical severity by comorbidity.

Variable	ACEI/ARB (unmatched) n, (%)	Non-ACEI/ARB (unmatched) n, (%)	Adjusted odds ratio [†] (95% CI)	P value	Adjustment ^a	ACEI/ARB (matched) n, (%)	Non-ACEI/ARB (matched) n, (%)	Adjusted odds ratio [†] (95% CI)	P value	Adjustment ^a
DM or HTN or Renal disease unmatched (n= 187) matched (n=173)	135(72.2)	52(27.8)	-	-	-	134(77.5)	39(22.5)	-	-	-
Severe or critical [¶] , n (%)	117(86.7)	28(53.8)	5.34(1.87-15.30)	0.002	0.004	116(86.6)	19(48.7)	5.40(2.01-14.54)	<0.001	0.003
DM + HTN unmatched (n=100) matched (n=99)	87(87)	13(13.0)	-	-	-	86(86.9)	13(13.1)	-	-	-
Severe or critical [¶] , n (%)	81(93.1)	10(76.9)	5.54(2.00-15.34)	0.001	0.004	80(93)	10(76.9)	5.01(0.80-31.43)	0.085	0.339
DM alone unmatched (n=140) matched (n=126)	98(70)	42(30.0)	-	-	-	97(77)	29(23)	-	-	-
Severe or critical [¶] , n (%)	89(90.8)	24(57.1)	5.19(1.29-20.87)	0.020	0.081	88(51.7)	15(90.7)	5.32(1.45-19.56)	0.012	0.047
HTN alone unmatched (n=145) matched (n=144)	123(84.8)	22(15.2)	-	-	-	122(84.7)	22(15.3)	-	-	-
Severe or critical [¶] , n (%)	108(87.8)	13(59.1)	5.72(1.69-19.32)	0.005	0.020	107(87.7)	13(59.1)	5.279(1.60-17.47)	0.006	0.025

[¶]Severe or critical defined according to WHO severity definition. ICU: Intensive care unit.

[†]Odds ratio adjusted using logistic regression model with the following variables: age, sex, BMI, diabetes, hypertension, renal disease, number of comorbidities (that includes diabetes, hypertension, cardiovascular disease (heart failure/coronary artery disease), stroke, renal disease, asthma and obesity) and inpatient COVID-19 regimen.

^a For multiplicity correction, Bonferroni method was used to adjust the P values.

DM: Diabetes; HTN: hypertension; CI: Confidence interval;

Figures

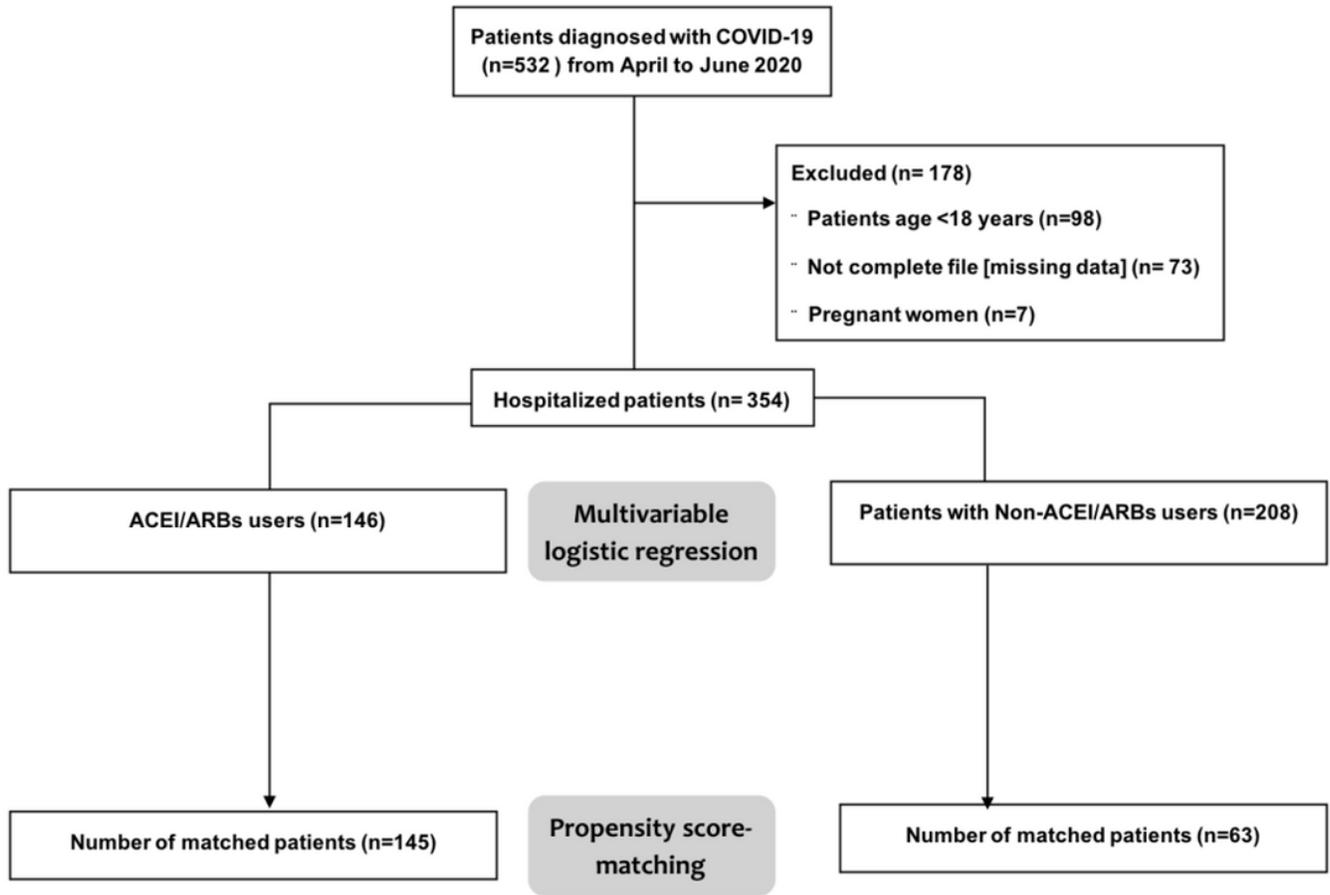


Figure 1

Study flow diagram. Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; COVID-19, coronavirus disease 2019