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Association of Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with Coronavirus Disease 2019 Severity and Mortality

Patricia Díaz-Guardiola[1, 4], Virginia Martín-Borge[1, 4], Cristina García-Fernández[2, 4], María Teresa Ramírez-Prieto[3, 4], Marcela Irma Ramírez-Belmar[1], Gema García-Romero[1, 4], Esther de la Calle[1], José Antonio Balsa[1, 4, *]

[1]Department of Endocrinology and Nutrition, Infanta Sofía University Hospital, San Sebastián de los Reyes, Spain

[2]Department of Preventive Medicine, Infanta Sofía University Hospital, San Sebastián de los Reyes, Spain

[3]Department of Pneumology, Infanta Sofía University Hospital, San Sebastián de los Reyes, Spain

[4]Faculty of Medicine, European University of Madrid, Madrid, Spain

Email address:

pdiaz.hnor@salud.madrid.org (P. Díaz-Guardiola), virginia.martinb@salud.madrid.org (V. Martín-Borge),
cristina.garcia@salud.madrid.org (C. García-Fernández), mtramirezp@salud.madrid.org (M. T. Ramírez-Prieto),
marcelairma.ramirez@salud.madrid.org (M. I. Ramírez-Belmar), gemaromerodetejada@gmail.com (G. García-Romero),
esther.delacalle@salud.madrid.org (E. de la Calle), jbalsa@salud.madrid.org (J. A. Balsa)
*Corresponding author

Abstract: Background: A potential association between use of angiotensin-converting–enzyme inhibitors (ACEI) or angiotensin-receptor blockers (ARB) and coronavirus disease 2019 (COVID-19) severity has been suggested. We conducted a retrospective study to investigate the association between ACEI/ARB use and COVID-19 severity and mortality. Methods: The first 1,000 consecutive patients with COVID-19 who were attended in the emergency department at the Infanta Sofía University Hospital were included. Clinical data was manually extracted by reviewing medical records, and the ACEI/ARB prescription was assessed from an electronic pharmacy database. The primary endpoints were critical COVID-19 and mortality. Results: A total of 241 (24.1%) patients had a critical COVID-19 and 171 (17.1%) died. ACEI use was associated with critical COVID-19 (OR 1.90, 95% CI 1.34-2.70), and with mortality (OR 1.98, 95% CI 1.35-2.91) in the unadjusted analysis, but not after adjusting by age, sex and comorbidities (OR 1.15 95% CI 0.69-1.94, and OR 1.00 95% CI 0.56-1.77, respectively). Similarly, ARB use was associated with critical COVID-19 (OR 1.58, 95% CI 1.11-2.58), although not with mortality (OR 1.47, 95% CI 0.98-2.19) in the unadjusted analysis, but not after adjusting by age, sex and comorbidities (OR 0.97, 95% CI 0.57-1.65, and OR 0.74, 95% CI 0.41-1.33, respectively). Conclusion: These results suggest that the use of ACEI/ARB is not independently associated with COVID-19 severity and mortality.

Keywords: ACEI/ARB, COVID-19 Severity, COVID-19 Mortality

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has developed into a pandemic in the last months affecting Europe after February 2020. Extracellular domain of the transmembrane angiotensin-converting enzyme 2 (ACE2) receptor is used by the virus to gain entry into host cells [1], and several studies have shown that angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) upregulate

ACE2 expression in cardiovascular tissues of animal models [2, 3]. In addition, a study has shown that Captopril increases the pulmonary ACE2 expression in rats both in the basal state as well as after lipopolysaccharide-induced lung injury [4]. In addition, a higher fatality is found in patients with COVID-19 who suffer hypertension, diabetes, and cardiovascular diseases [5, 6]. As the use of inhibitors of renin–angiotensin–aldosterone system (RAAS) is frequent in these comorbidities, a big controversy has arisen about the eventual role of these drugs to facilitate the virus access into the lung cells, thus increasing the severity of COVID-19 [7, 8]. However, several retrospective studies using a different approach have suggested a neutral effect of ACEI/ARB in the COVID-19 course [9-13]. On the contrary, as ACE2 is an anti-inflammatory pathway, and both Captopril and Losartan partially restore the decrease in ACE2 expression observed in animal models of acute respiratory distress syndrome (ARDS) [4, 14], a protective role of ACEI/ARB in COVID-19 has been also suggested [15]. In line with this hypothesis, two retrospective studies have found a reduction in the mortality rate from COVID-19 in patients treated with ACEI or with ACEI/ARB [16, 17].

In this study, we sought to clarify the potential association of ACEI or ARB use with the likelihood of having differences in COVID-19 severity and mortality.

2. Methods

2.1. Study Population

First, we obtained an Institutional Review Board approval for the retrospective review of the medical records. The data were manually extracted by the study team in a uniform and systematized way. The charts of the first 1,000 consecutive adult patients with a diagnosis of SARS-CoV-2 who were attended in the emergency department at the Infanta Sofía University Hospital of Madrid, Spain were reviewed. The diagnosis of SARS-CoV-2 was done by nasopharyngeal or oropharyngeal swab RT-PCR in 864 cases and by clinical assessment in 136 cases. The clinical diagnosis was assumed only when the patient was admitted because of interstitial bilateral pneumonia with hypoxia plus lymphopenia and/or high levels of D-Dimer, and no other cause of pneumonia was found. The clinical diagnosis was done only when RT-PCR test was not available due to increasing demand and limitations of testing capabilities. In order to analyze the association of the ACEI/ARB treatment with the illness course, the severity of COVID-19 was established on the basis of the World Health Organization guidance [18]. Patients were classified in three groups: a) the mild COVID-19 group included patients with uncomplicated upper respiratory tract viral infection and those with pneumonia who did not need supplemental oxygen (all these patients were discharged from the emergency room and the clinical follow-up was done by general practitioners through phone calls to patient's home), b) the severe COVID-19 group included patients with severe pneumonia (needing supplemental oxygen), and c) the critical COVID-19 group included patients with ARDS who needed non-invasive mechanical ventilation

(NIMV) or ICU admission for intubation and mechanical ventilation (MV), and those who died during their hospital admission. In all cases, the following comorbid conditions were registered: hypertension, diabetes mellitus, heart disease, chronic kidney disease (CKD) with a stage 3a or higher according to NKF-KDOQI guidelines, body mass index (BMI), chronic obstructive pulmonary disease (COPD), malignancy, and immune compromised state (that was defined as an underlying disease or condition needing immunosuppressive therapy). The ACEI/ARB prescription was confirmed by checking the electronic pharmacy database of Madrid (*Módulo Unico de Prescripción de la Comunidad de Madrid*). Only prescriptions with duration longer than one month were included. The two primary endpoints were critical disease and death in-hospital. As previously stated, critical disease was a composite of the occurrence of any of the following: requirement of respiratory supportive care with NIMV, ICU admission for intubation and MV, or death in-hospital. All endpoints were recorded but only the worst one of each patient was used in the statistical analysis. All patients had completed their hospital course at study end.

2.2. Statistical Analysis

Continuous variables were reported as mean (SD) and categorical variables as counts (percentages). Data are presented as observed with no imputation for missing values and they were available on all patients except for BMI (N=880).

Age and BMI did not fit a normal distribution; therefore, Kruskal–Wallis test was used to test for differences between the three COVID-19 severity groups. As patients with critical COVID-19 were significantly older, we stratified age into quartiles to further analysis. A $\chi2$ or Fisher exact test were performed to compare categorical variables. A logistic-regression was used to analyze the effect of ACEI/ARB treatment, age, sex, and comorbid conditions on illness severity and mortality. Illness severity was entered into this analysis as dichotomous variable in order to compare critical COVID-19 or death in-hospital with non-critical COVID-19 (i.e., the composite of mild and severe groups). Age and BMI were entered as continuous variables. Separate age-adjusted analyses were also performed.

To verify the robustness of our findings, data were also analyzed after excluding those patients who were diagnosed based on clinical assessment. All the analyses were done using SPSS (IBM). A p-value less than 0.05 was considered significant.

3. Results

The mean (SD) patient age was 62.2 (16.9) years. There were 454 (45.4%) females and 546 (54.6%) males. Mild COVID-19 was found in 108 (10.8%) cases, severe COVID was found in 651 (65.1%) cases, and critical COVID was found in 241 (24.1%) cases. From these patients, there were 171 (17.1%) in-hospital deaths. A total of 354 (35.4%) patients were using ACEI/ARB, 176 (17.6%) an ACEI and 178 (17.8%) an ARB. The rates of patients treated with ACEI/ARB progressively increased according to illness

severity. Thus, 12 (11.1%) patients with mild COVID-19, 224 (34.5%) with severe COVID-19, and 118 (48.8%) patients who fulfilled the criteria of critical COVID-19 were using an ACEI or an ARB, (P for trend < 0.001). The hypertension rate increased in parallel with increasing COVID-19 severity: 18 (16.7%) vs 285 (43.8%) vs 160 (66.1%), respectively (P for trend < 0.001). Similar results were observed with respect to the rates of heart disease: 9 (8.3%) vs 87 (13.4%) vs 61 (25.2%), P for trend < 0.001; the rates of diabetes: 7 (6.5%) vs 119 (18.3%) and 65 (26.9%), P for trend < 0.001; and the rates of CKD: 5 (4.6%) vs 35 (5.4%) vs 38 (15.7%), P for trend < 0.001. Other comorbidities such as COPD, cancer, and immunosuppression were also more frequent in critical COVID-19. On the other hand, patients with critical COVID-19 were significantly older 47.8 (14.4) vs 60.9 (16.3) vs 72.3 (13.5), respectively (P for trend < 0.001). The male sex rate also gradually increased with the disease severity: 34 (31.5%) vs 367 (56.5%) vs 145 (59.9%); P for trend < 0.001. Table 1 summarizes these data stratified by COVID-19 severity.

The rate of patients treated with ACEI/ARB progressively increased when patients were stratified by age quartiles: 21 (8.6%), 71 (28.2%), 125 (51.2%), and 137 (52.9%), respectively (P for trend <0.001). Similarly, there was a significant association between age quartile and the rate of critical COVID-19: 16 (6.5%), 42 (16.7%), 71 (29.1%), and 112 (43.2%), respectively (P for trend < 0.001), as well as between age quartile and mortality 5 (2.0%), 14 (5.6%), 46 (18.9%), and 106 (40.9%), respectively (P for trend <0.001). All comorbidities but obesity and immunosuppression also significantly increased according to age (Table 2).

Table 3 shows unadjusted estimates of the risk of critical COVID-19 according to the use of ACEI or ARB, as well as according to age (per year increase) and comorbid conditions. Both ACEI and ARB use were associated with a worse course of COVID-19 in the unadjusted analysis (OR 1.90, 95% CI,

1.34-2.70; and OR 1.58, 95% CI, 1.11-2.58; respectively). Hypertension, BMI, diabetes, heart disease, CKD, COPD and cancer were also associated which this endpoint. However, after adjusting for age, the association between use of ACEI or ARB and critical COVID-19 was no longer observed (OR 1.40, 95% CI, 0.95-2.08; and OR 1.17, 95% CI, 0.79-1.74; respectively). Similarly, after multivariable adjustment for age and comorbid conditions, only age (OR 1.05, 95% CI 1.04-1.07, per year increase), BMI (OR 1.05, 95% CI 1.01-1.08, per point of BMI increase), male sex (OR 1.46, 95% CI 1.04-2.05), and CKD (OR 1.72, 95% CI 1.01-2.94) were independently associated with critical COVID-19, but not use of ACEI (OR 1.15, 95% CI 0.69-1.94) or use of ARB (OR 0.97, 95% CI 0.57-1.65).

Table 4 shows unadjusted estimates of COVID-19 mortality according to treatment with ACEI or ARB, as well as according to age, and comorbid conditions. Again, ACEI use was associated with COVID-19 mortality in the unadjusted analysis (OR 1.98, 95% CI, 1.35-2.91), but not use of ARB (OR 1.47, 95% CI, 0.98-2.19). After adjusting for age, both ACEI and ARB use were not associated with mortality (OR 1.29, 95% CI 0.82-2.02; and OR 0.98, 95% CI 0.62-1.55; respectively). Similarly, after multivariable adjustment for age and comorbid conditions, only age (OR 1.08, 95% CI 1.06-1.10, per year increase), CKD (OR 2.11, 95% CI 1.19-3.73), cancer (OR 2.50, 95% CI 1.16-5.41), and immunosuppression (OR 2.49, 95% CI 1.09-5.66) were independently associated with COVID-19 mortality but not ACEI use (OR 1.00, 95% CI 0.56-1.77) nor ARB use (OR 0.74, 95% CI 0.41-1.33).

The results shown in Tables 3 and 4 did not substantially change when patients who were diagnosed based on clinical criteria were excluded. Thus, both ACEI and ARB use was neither associated with critical COVID (OR 1.10, 95% CI 0.64-1.94; and OR 1.09, 95% CI 0.62-1.92; respectively) nor with mortality (OR 0.93, 95% CI 0.50-1.73; and OR 0.81, 95% CI 0.43-1.52; respectively).

Table 1. *Clinical characteristics of the patients stratified by severity of COVID-19. Values are numbers (percentages) except for age and BMI [mean (SD)].*

	Total (N=1000)	Mild (N=108)	Severe (N=651)	Critical (N=241)	P
Age (y)	62.2 (16.9)	47.8 (14.4)	60.9 (16.3)	72.3 (13.5)	<0.001
Female sex	454 (45.4)	454 (45.4)	74 (68.5)	283 (43.5)	<0.001
Male sex	546 (54.6)	546 (54.6)	34 (31.5)	367 (56.5)	
ACEI	176 (17.6)	6 (5.6)	108 (16.6)	62 (25.6)	<0.001
ARB	178 (17.8)	6 (5.6)	116 (17.8)	56 (23.1)	<0.001
ACEI/ARB	354 (35.4)	12 (11.1)	224 (34.5)	118 (48,8)	<0.001
Hypertension	463 (46.3)	18 (16.7)	285 (43.8)	160 (66.1)	<0.001
BMI (kg/m^2)	28.8 (5.2)	28.0 (5.3)	28.7 (5.0)	29.5 (5.5)	0.058
Diabetes	191 (19.1)	7 (6.5)	119 (18.3)	65 (26.9)	<0.001
Heart disease*	157 (15.7)	9 (8.3)	87 (13.4)	61 (25.2)	<0.001
CKD	78 (7.8)	5 (4.6)	35 (5.4)	38 (15.7)	<0.001
COPD	69 (6.9)	0 (0.0)	36 (5.5)	33 (13.6)	<0.001
Cancer	37 (3.7)	0 (0.0)	19 (2.9)	18 (7.4)	0.001
Immunosuppression	41 (4.1)	3 (2.8)	23 (3.5)	15 (6.2)	0.186

Severity of COVID-19 was defined according to WHO guideline: Mild COVID-19 included patients with uncomplicated upper respiratory tract viral infection and those with pneumonia not needing supplemental oxygen. Severe COVID-19 included patients with severe pneumonia (needing supplemental oxygen). Critical COVID-19 included patients with ARDS who needed noninvasive mechanical ventilation, ICU admission for invasive mechanical ventilation, and those who died during their hospital admission. ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; BMI: body mass index; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease.
*Heart disease is the composite of ischemic heart disease, heart failure and arrhythmia.

Table 2. Clinical characteristics and outcomes of the patients stratified by age quartiles. Values are numbers (percentages) except for age and BMI [mean (SD)].

	Age (quartiles)				P
	Q1 (18-49)	Q2 (50-62)	Q3 (63-74)	Q4 (75-102)	
Age (y)	39.6 (7.6)	56.3 (3.7)	69.0 (3.6)	83.0 (5.8)	
Female sex	119 (48.6)	97 (38.5)	105 (43.0)	133 (51.4)	0.018
Male sex	126 (51.4)	155 (61.5)	139 (57.0)	126 (48.6)	
Critical COVID-19	16 (6.5)	42 (16.7)	71 (29.1)	112 (43.2)	<0.001
Death in-hospital	5 (2.0)	14 (5.6)	46 (18.9)	106 (40.9)	<0.001
ACEI	10 (4.1)	43 (17.1)	54 (22.1)	69 (26.6)	<0.001
ARB	11 (4.5)	28 (11.1)	71 (29.1)	68 (26.3)	<0.001
ACEI/ARB	21 (8.6)	71 (28.2)	125 (51.2)	137 (52.9)	<0.001
Hypertension	27 (11.0)	86 (34.1)	146 (59.8)	204 (78.8)	<0.001
BMI (kg/m2)	28.5 (5.7)	29.3 (4.9)	29.0 (5.1)	28.5 (5.0)	0.183
Diabetes	9 (3.7)	36 (14.3)	60 (24.6)	86 (33.2)	<0.001
Heart disease	3 (1.2)	19 (7.5)	40 (16.4)	95 (36.7)	<0.001
CKD	4 (1.6)	7 (2.8)	17 (7.0)	50 (19.3)	<0.001
COPD	0 (0.0)	8 (3.2)	19 (7.8)	42 (16.2)	<0.001
Cancer	1 (0.4)	8 (3.2)	13 (5.3)	15 (5.8)	0.001
Immunosuppression	6 (2.4)	14 (5.6)	13 (5.3)	8 (3.1)	0.196

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; BMI: body mass index; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease.

Table 3. Odds Ratios for the associations of critical COVID-19 with use of ACEI or ARB, age, sex, and comorbid conditions.

	Odds Ratio for critical COVID-19 (95% CI)		
	Unadjusted	Adjusted by age	Adjusted by all covariates
ACEI	1.90 (1.34-2.70)	1.40 (0.95-2.08)	1.15 (0.69-1.94)
ARB	1.58 (1.11-2.58)	1.17 (0.79-1.74)	0.97 (0.57-1.65)
Age (yr)	1.06 (1.05-1.07)	1.05 (1.04-1.07)	1.05 (1,04-1.07)
Sex (male)	1.32 (0.98-1.77)		1.46 (1.04-2.05)
Hypertension	2.90 (2.14-3.93)		1.04 (0.62-1.73)
BMI (kg/m^2)	1.03 (1.00-1.06)		1.05 (1.01-1.08)
Diabetes	1.80 (1.28-2.54)		0.93 (0.63-1.37)
Heart disease	2.34 (1.63-3.36)		0.90 (0.59-1.38)
CKD	3.37 (2.10-5.39)		1.72 (1.01-2.94)
COPD	2.98 (1.82-4.91)		1.39 (0.80-2.43)
Cancer	3.14 (1.62-6.09)		1.94 (0.94-3.99)
Immunosuppression	1.87 (0.97-3.59)		1.89 (0.90-3.95)

CI denotes confidence interval. Both unadjusted and adjusted estimates by age (per year increase) and by all covariates are shown. Fully adjusted estimates were obtained from a unique multivariate analysis. ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; BMI: body mass index; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease.

Table 4. Odds Ratios for the associations of mortality with the use of ACEI or ARB, age, sex, and comorbid conditions.

	Odds Ratio for mortality (95% CI)		
	Unadjusted	Adjusted by age	Adjusted by all covariates
ACEI	1.98 (1.35-2.91)	1.29 (0.82-2.02)	1.00 (0.56-1.77)
ARB	1.47 (0.98-2.19)	0.98 (0.62-1.55)	0.74 (0.41-1.33)
Age (yr)	1.09 (1.07-1.10)	1.09 (1.07-1.10)	1.08 (1.06-1.10)
Sex (male)	0.96 (0.69-1.34)		1.11 (0.74-1.66)
Hypertension	4.24 (2.93-6.13)		1.32 (0.74-2.37)
BMI (kg/m^2)	1.01 (0.98-1.04)		1.03 (0.99-1.07)
Diabetes	2.25 (1.55-3.26)		1.10 (0.71-1.71)
Heart disease	3.25 (2.22-4.77)		0.99 (0.62-1.58)
CKD	5.00 (3.09-8.09)		2.11 (1.19-3.73)
COPD	4.03 (2.42-6.71)		1.65 (0.91-2.98)
Cancer	3.97 (2.03-7.78)		2.50 (1.16-5.41)
Immunosuppression	2.35 (1.19-4.64)		2.49 (1.09-5.66)

CI denotes confidence interval. Both unadjusted and adjusted estimates by age (per year increase) and by all covariates are shown. Fully adjusted estimates were obtained from a unique multivariate analysis. ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; BMI: body mass index; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease.

4. Discussion

Our study suggests that use of RAAS inhibitors is not associated with COVID-19 severity and mortality, and shows that older age is the main predictor of these outcomes.

Animal or cell line studies have shown that the virus accesses cells through ACE2, and both ACEI and ARB induce ACE2 overexpression in cardiovascular tissues [2, 3], as does Captopril in the lung of normal rats [4]. Since ACE2 overexpression in cell lines increases viral load [19], it has been speculated that ACEI/ARB treatment could increase the severity of COVID-19. On the other hand, RAAS inhibitors are one of the most widely prescribed class of drugs for the management of hypertension, and initial studies described hypertension as the most frequent comorbidity associated with severe COVID-19 [5, 6] thus supporting a possible deleterious role of these drugs in the COVID-19 course. However, this observation was adjusted neither by age nor by other clinical characteristics. Our data suggests that this association is mostly due to the well-known relationship between age and prevalence of hypertension [20, 21]. In fact, the association of hypertension with COVID -19 severity and mortality was no longer observed after adjusting the model for age, and for age, sex, and comorbidities.

The opposite hypothesis (i.e., a protective role of these drugs) was also suggested on the basis that Losartan treatment mitigated the decrease in ACE2 observed in animal models of ARDS [4, 14] and partially attenuated different histological parameters of lung injury caused by acid instillation and simultaneous intraperitoneal injection of SARS-CoV-1 Spike protein into mice [22]. Different retrospective studies aimed to analyze the role of RAAS inhibitors in COVID-19, both in the possibility of becoming infected with SARS-Cov-2 and in the risk of mortality, have been previously published [9-13, 23]. Collectively, the results of these studies support the concept of a neutral effect of ACEI/ARB on susceptibility to infection by SARS-CoV-2 and severity of COVID-19 [24]. However, some discrepancies have emerged. Thus, it has been suggested that in-hospital use of ACEI/ARB could reduce mortality from COVID-19 in hypertensive patients [16], mainly in those patients treated with an ARB [17]. Conversely, another study found that these drugs could increase the chance of hospitalization and ICU admission [23]. A recent meta-analysis including 9 retrospective studies suggests that the use of ACEI/ARB could decrease the mortality of COVID-19 but not the disease severity [25]. It is plausible that biases associated with the retrospective nature of these studies or the way in which the adjustment of the covariates is carried out can explain the divergent results of these studies as it has been suggested [26]. Thus, only one previous study has included adjustment by obesity although this comorbidity is associated with COVID-19 mortality [27], and it is well known the association of obesity and comorbidities in which the use of RAAS inhibitors is frequent such as hypertension, diabetes, heart disease or CKD [28-31].

Our study shows that aging is the most powerful predictor of COVID-19 severity and mortality. In fact, an exponential trend was observed after stratification by age quartiles, a finding that is in line with previous studies [32, 33]. A higher frequency of comorbidities such as hypertension, diabetes, CKD, COPD or heart disease in elderly patients, together with the frailty associated with aging could explain this trend. On the other hand, the importance of advanced age in mortality has also been shown in other viral infections such as respiratory syncytial virus and influenza [34]. Therefore, the strong association of aging with COVID-19 severity and mortality as well as with use of RAAS inhibitors could be an important confounding factor to analyze the relationship between these drugs and both outcomes in retrospective studies, mainly to confirm an eventual protective role.

Our study has several limitations. Firstly, a possible overrepresentation of elderly patients could be possible due to patient inclusion was restricted to a single hospital that provides healthcare to an area with many nursing homes. Secondly, compliance with the ACEI/ARB treatment could not be tested. Thirdly, the sample size could not have enough statistical power to delimit the relative influence of other comorbidities such as heart disease, CKD, cancer, COPD, or immunosuppression given the limited representation of these patients in this case series. However, it has several strengths such as the detailed data extraction that was performed with the manual review of each chart, and confirmation of ACEI/ARB use in an official electronic prescription database.

5. Conclusion

In conclusion, our study did not find that the use of ACEI/ARB influences the severity and mortality of COVID-19. These results are in line with most of the studies published so far. However, they clearly show the limitation of retrospective studies to answer this question. Therefore, randomized trials are necessary to evaluate an eventual protective role of these drugs on the COVID-19 course.

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