Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and prognosis of hypertensive patients hospitalised with COVID-19

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Abstract

Background: Among hypertensive patients, the association between treatment with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) and the clinical severity of COVID-19, remains uncertain.

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Aims: To determine whether hypertensive patients hospitalised with COVID-19 are at risk of worse outcomes if on treatment with ACEI or ARB compared to other anti-hypertensive medications.

Methods: This is a retrospective study conducted at a single academic medical centre (Fondazione Policlinico A. Gemelli IRCCS, Rome, Italy) from 1 to 31 March 2020. We compared patients on treatment with an ACEI/ARB (ACEI/ARB group) to patients receiving other anti-hypertensive medications (No-ACEI/ARB group). The end-points of the study were the all-cause in-hospital death and the combination of in-hospital death or need for intensive care unit (ICU) admission.

Results: The sample included 166 COVID-19 patients; median age was 74 years and 109 (66%) were men. Overall, 111 (67%) patients were taking an ACEI or ARB. Twenty-nine (17%) patients died during the hospital stay, and 51 (31%) met the combined end-point. After adjustment for comorbidities, age and degree of severity at the presentation, ACEI or ARB treatment was an independent predictor neither of in-hospital death nor of the combination of in-hospital death/need for ICU. No differences were documented between treatment with ACEI compared to ARB.

Conclusions: Among hypertensive patients hospitalised for COVID-19, treatment with ACEI or ARB is not associated with an increased risk of in-hospital death.

Introduction

The severe acute respiratory coronavirus-2 (SARS CoV-2) is associated with viral pneumonia named coronavirus disease-2019 (COVID-19), whose ongoing pandemic is posing great challenges to the healthcare systems worldwide. World Health Organization estimates there have been over 25 million confirmed COVID-19 cases worldwide, with a mortality rate of approximately 4%, despite some differences across countries.[1] Older individuals, those with pre-existing respiratory or cardiovascular medical conditions, as well as those with diabetes and hypertension, appear to be at higher risk of severe complications and death.[2–5] Available data suggest that hypertension is the most frequent comorbidity in patients with COVID-19, and it is associated with a more severe course of the disease and a higher mortality.[6–12] However, sparse data are available on hypertensive COVID-19 patients, and the role played by anti-hypertensive medications is unclear. Since the SARS CoV-2 uses the receptor angiotensin-converting enzyme (ACE) 2 to infect target cells,[13] a controversial debate is ongoing about whether angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) should possibly be the reason for the emerging association between hypertension and worse outcomes in patients with COVID-19.[14–19] On one hand, it has been speculated that both these medications could increase SARS CoV-2 infection susceptibility, and worsen the course of the respiratory syndromes. Indeed, in animal models and in humans it has been shown that ACEI and ARB may increase ACE2 levels in the lungs.[20–23] On the other hand, other authors have hypothesised that an increased level of the soluble form of ACE2, secondary to ACEI/ARB treatment, may act as a competitive interceptor of SARS-CoV-2, thus slowing virus entry and protecting the lungs from injury.[24]

Three recently published studies in China reported that hypertensive patients hospitalised with COVID-19 experienced a lower risk of all-cause mortality if on treatment with ACEI/ARB compared to ACEI/ARB non-users.[10–12] Moreover, latest reports showed no evidence that ACE inhibitors or ARB affected the risk of COVID-19[25] and did not confirm a harmful role of ACEI or ARB in admission to hospital or in-hospital death.[26]

All the scientific societies have issued statements against any change in the current indications for the use of these medications in view of well documented beneficial effects.[27,28]

Hence, the aim of the present study is to analyse the association between treatment with ACEI or ARB and in-hospital death and/or the need of intensive care unit (ICU) admission, among hypertensive patients hospitalised with COVID-19.

Methods

This is a retrospective study conducted at the Fondazione Policlinico A.Gemelli IRCCS, Rome, Italy, an academic medical centre identified as one of the referral centre for COVID-19 in central Italy.

Study population

We derived data from the electronic medical records of all the patients consecutively admitted to our emergency

department (ED) for suspected COVID-19, between 1 and 31 March 2020.

We identified all the patients with an established diagnosis of hypertension who have been continuously taking any oral antihypertensive medication for at least 3 months. All of the patients received a definitive diagnosis of COVID-19 as for the World Health Organization (WHO) interim guidance. In this respect, a definitive laboratory confirmation of SARS CoV-2 infection was defined as a positive result on real-time reverse transcription–polymerase chain reaction assay of nasal or oro-pharyngeal swab specimens.[29]

From the study, sample were excluded patients aged <18 years, pregnant women and patients with a definitive diagnosis of COVID19 who were discharged home because of mild symptoms and a normal chest X-ray.

Data elements

Electronic medical records were identified and the following data elements were derived: age, gender, clinical symptoms at presentation, Glasgow Coma Scale score, chest X-ray finding, and prior medical history including information on comorbid conditions and pharmacological treatment. The comorbid conditions considered were: heart disease, including a history of heart failure, coronary artery disease, cardiomyopathy, heart valve disease and arrhythmias; obesity, defined by a body mass index >30; chronic obstructive pulmonary disease (COPD); and diabetes. Furthermore, for each patient, at ED admission six physiological parameters were routinely recorded for the National Early Warning Score (NEWS) calculation: (i) respiratory rate; (ii) peripheral oxygen saturation (SpO_2); (iii) temperature; (iv) systolic blood pressure; (v) heart rate; and (vi) the level of consciousness assessed by the response on the AVPU (Alert, Voice, Pain, Unresponsive) scale.[30] The NEWS scoring system, as described by the Royal College of Physicians, allows division of patients into the following three risk categories: low score (NEWS 0–4); medium score (NEWS 5–6); and high score (NEWS ≥7).[31]

Antihypertensive medications were classified into the following therapeutic classes: ACEI; ARB; mineralcorticoid receptor antagonists; beta-blockers; calcium channel blockers; alpha-1 adrenergic blockers; central alpha-adrenoceptor agonists; nitrates; and diuretics.

For the analysis, we compared patients on treatment with an ACEI/ARB (ACEI/ARB group), and patients on treatment without an ACEI/ARB (No-ACEI/ARB group).

All patients included in the analysis were treated according to the standard of care in the enrolling period, as defined by the Italian Society of Infectious and Tropical Diseases guidelines on the management of COVID-19.[32]

Degree of severity

To adjust for disease severity, we stratified patients based on the NEWS score at ED admission.

ICU admission

Criteria for ICU admission of COVID-19 patients were clearly established, did not change over the study period and they needed to be respected mandatorily. The criteria included the need for invasive respiratory support, the presence of extra-pulmonary organ failure, such as circulatory shock requiring vasopressors, or renal failure.

Definition of outcome variables

The end-points of the study were the all-cause in-hospital death and the combination of in-hospital death and need for ICU admission.

Statistical analysis and sample size

Continuous variables are reported as median (interquartile range) and are compared by univariate analysis using the Mann–Whitney U-test. Categorical variables are reported as absolute number (percentage) and are compared using the Chi-squared test (with Fisher's test if appropriate).

Variables with a statistically significant association at the univariate analysis were entered into logistic regression multivariate models. Age, gender and ACEI/ARB treatment were forced into all the logistic models. As the NEWS score was included, the physiological parameters used for its calculation were excluded from the analysis to avoid estimation redundancy. As two variables were entered into each logistic regression model, a minimum number of 20 events would be needed for a correct parameter estimation. Therefore, our sample size was adequate for a correct estimation of both death and combined outcome of death/ICU admission.

A P-value ≤0.05 was considered as statistically significant. Data were analysed by SPSS v25® (IBM, Armonk, NY, USA).

Statement of ethics

This study was approved by the local Ethics Committee and it was performed in accordance with good clinical

Results

Between 1 and 31 March 2020, a total of 512 patients was admitted to the ED with a definitive diagnosis of COVID-19. One hundred and seventy-six patients were excluded from the analysis for insufficient clinical data on electronic medical record and two patients were excluded as they were already intubated at ED arrival. Among the 334 eligible patients, the final study sample included 166 hypertensive patients aged between 30 and 98 years, with the majority (66%) males (Fig. 1).

Overall, 49 (30%) patients were taking ACEI and 62 (37%) were taking ARB, and none of the patients was receiving both at the same time. Collectively, among the 111 patients in the ACEI/ARB group, 77 (70%) patients

were taking one or more additional anti-hypertensive medications. The most common combinations were with beta-blockers (42 patients), diuretics (32 patients) and calcium antagonists (30 patients). Among patients in the no-ACEI/ARB group, 62% were taking more than one antihypertensive drug; the more common medications were calcium-antagonists (56.4%), beta-blockers (45.4%) and diuretics (16.4%).

Sample characteristics

Patients in the ACEI/ARB group had comparable baseline characteristics, including comorbidities, with those in the no-ACEI/ARB group (Table 1). A NEWS score ≥2 was adjudicated for 53% of patients in the ACEI/ARB group, compared to 36% in the no-ACEI/ARB group, $P < 0.05$ (Table 1).

Outcomes

Overall, 29 (17%) patients died during the hospital stay, 6 patients in the first 24 h of hospital arrival. Age and gender did not differ between those who died and those who survived. Among the relevant comorbidities, COPD showed a higher prevalence among non-survivor patients (14%, $P = 0.028$). Furthermore, the patients who died presented in worse general conditions with 86% of them having a NEWS score ≥2 compared to 44% of the survivors, $P < 0.001$ (Table 2). Twenty out of 29 (69%) patients who died were on ACEI/ARB therapy, compared to the 91 of 137 (66%) survived, $P = 0.792$.

Fifty-one (31%) patients met the combined outcome death and/or ICU admission during hospital stay (Table 1), with an event occurring in the first 48 h for nearly 90% of the patients. Thirty-eight out of 51 (74%) patients that met the combined end-point were on ACEI/ARB therapy, compared to the 73 of 115 (62.4%) non-ICU/survived, $P = 0.164$ (Table 2).

Multivariate analysis

A NEWS score ≥2 was estimated to be an independent predictor of all outcomes, with a sevenfold increased risk of death and a sixfold increased risk of the combined outcome death/ICU admission (Table 3). The association of COPD with death was not significant in the multivariate analysis. When forced into the regression models, only age was an independent predictor of death alone (odds ratio 1.05), but not of the combined outcome death/ICU admission.

Treatment with ACEI/ARB was not associated with both death and the combined outcome death/ICU admission.
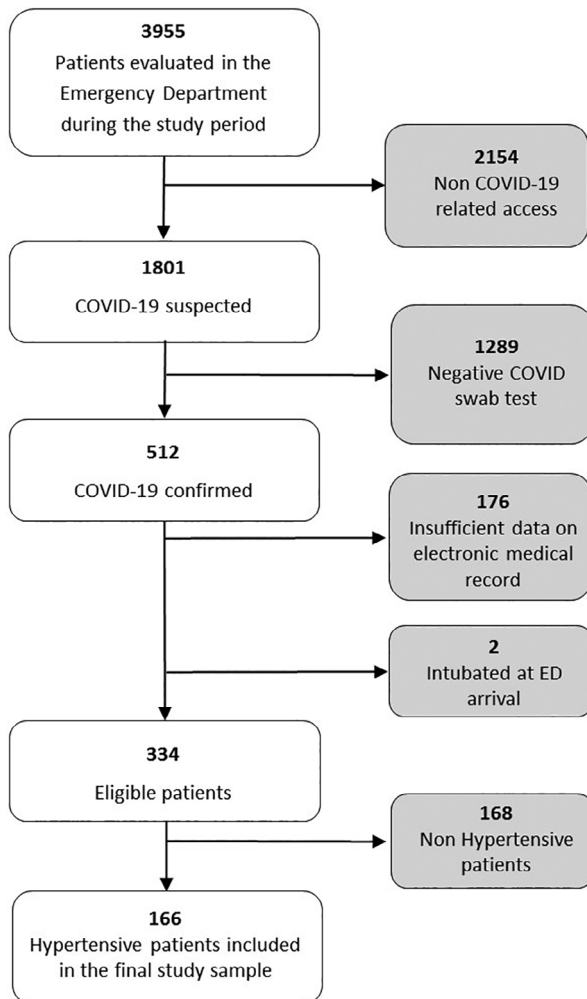
Figure 1 Flow-chart of the cohort selection for the study.

Table 1 Demographic and clinical variables of hypertensive patients in the study cohort at emergency department admission

| Variable | n (%) | | | P-value |
	All patients (n = 166)	ACEI/ARB (n = 111)	No-ACEI/ARB (n = 55)	
Age, median (IQR) (years)	74 (65–82)	72 (66–81)	77 (65–82)	0.480
Male/female	109/57 (65.7/34.3)	78/33 (70.3/29.7)	31/24 (56.4/43.6)	0.076
Heart rate, median (IQR) (b.p.m.)	88 (78–101)	86 (77.3–100)	90 (85–106)	0.211
Respiratory rate, median (IQR) (breaths/min)	16 (14–20)	16 (13–20)	16 (15–20)	0.122
GCS, median (IQR)	15 (15–15)	15 (15–15)	15 (15–15)	0.647
Systolic BP, median (IQR) (mmHg)	130 (120–145)	130 (120–142)	130 (120–145)	0.655
Diastolic BP, median (IQR) (mmHg)	80 (67–84)	80 (64–85)	80 (73–83)	0.693
SpO_2, median (IQR) (%)	94 (89–96)	94 (89–97)	94 (89–96)	0.745
Temperature, median (IQR) (°C)	37.2 (36.2–37.7)	37.2 (36.2–37.7)	37.1 (36.3–37.7)	0.924
NEWS, median (IQR)	2 (1–4)	2 (1–4)	3 (0.5–4)	0.945
NEWS ≥ 2	79 (47.6)	59 (53.2)	20 (36.4)	0.041
Comorbidities				
Diabetes	22 (13.3)	18 (16.2)	4 (7.3)	0.110
COPD	9 (5.4)	5 (4.5)	4 (7.3)	0.458
Heart disease	70 (42.2)	48 (43.2)	22 (40)	0.690
Obesity	7 (4.2)	6 (5.4)	1 (1.8)	0.279
Outcomes				
Death	29 (17.5)	20 (18.0)	9 (16.3)	0.792
Combined of death/admission to ICU	51 (30.7)	38 (34.2)	13 (23.6)	0.164

ACEI, angiotensin converting enzymes inhibitors; ARB, angiotensin receptor blockers; BP, blood pressure; COPD, chronic obstructive pulmonary disease; GCS, Glasgow Coma Scale; ICU, intensive care unit; IQR, interquartile range; NEWS, National Early Warning Score; SpO_2, peripheral oxygen saturation.

Table 2 Univariate analysis for the study end-points

| Variable | Death, n (%) | | | Death/admission to ICU, n (%) | | |
	Yes (n = 29)	No (n = 137)	P-value	Yes (n = 51)	No (n = 115)	P-value
Male	18 (62.1)	91 (66.4)	0.654	34 (66.7)	75 (65.2)	0.856
Age, median (IQR) (years)	78 (73–81)	73 (63–82)	0.122	74 (66–80)	75 (64–80)	0.646
NEWS ≥ 2	25 (86.2)	61 (44.5)	**<0.001**	41 (80.4)	45 (39.1)	**<0.001**
Heart disease	14 (48.3)	56 (40.9)	0.464	26 (51.0)	44 (38.3)	0.126
Diabetes	3 (10.3)	19 (13.9)	0.611	4 (7.8)	18 (15.7)	0.171
COPD	4 (13.8)	5 (3.6)	**0.028**	4 (7.8)	5 (4.3)	0.359
Obesity	1 (3.4)	6 (4.4)	0.821	4 (7.8)	3 (2.6)	0.122
ACEI/ARB	20 (69.0)	91 (66.4)	0.792	38 (74.5)	73 (63.5)	0.164

Values in bold are statistically signficant (P ≤ 0.05). ACEI, angiotensin converting enzymes inhibitors; ARB, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; NEWS, National Early Warning Score.

Table 3 Multivariable logistic regression for the association between clinical characteristics and study end-points

Variable	Death, OR (95% CI)	P-value	Death/admission to ICU, OR (95% CI)	P-value
Males	1.41 (0.52–3.83)	0.493	1.22 (0.54–2.72)	0.624
Age	1.05 (1.01–1.10)	**0.016**	1.01 (0.98–1.04)	0.508
NEWS ≥ 2	7.00 (2.23–21.95)	**0.001**	5.99 (2.70–13.30)	**<0.001**
COPD	2.27 (0.50–10.21)	0.284		
ACEI/ARB	0.78 (0.29–2.09)	0.631	1.30 (0.58–2.92)	0.516

Values in bold are statistically signficant (P ≤ 0.05). ACEI, angiotensin converting enzymes inhibitors; ARB, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; OR, odds ratio; NEWS, National Early Warning Score.

ACEI versus ARB comparison

The 49 patients taking ACEI were comparable for all parameters to the 62 patients taking ARB. Any of the outcomes occurred at a similar rate (Fig. 2).

Discussion

The main finding of the present study was that among patients with hypertension hospitalised for COVID-19, treatment with ACEI or ARB was not associated with an increased risk of in-hospital death. Moreover, no
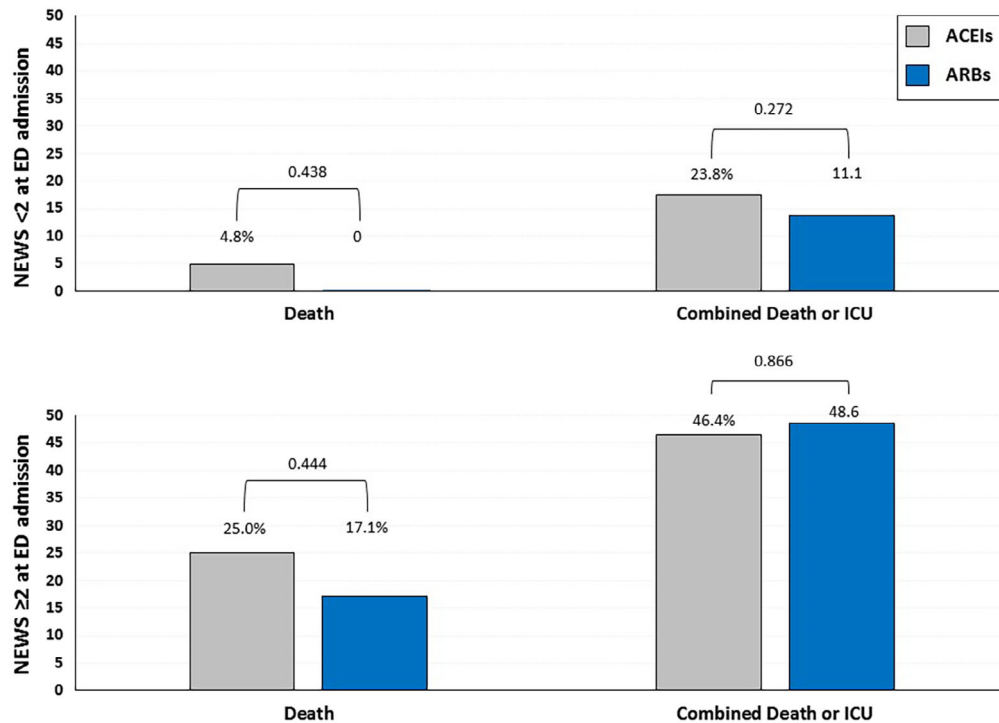
Figure 2 Comparison of patients on angiotensin-converting enzyme inhibitor (ACEI) therapy versus angiotensin receptor blockers (ARB) therapy. Comparison of death and combined death/intensive care unit (ICU) admission between patients on ACEI therapy versus patients on ARB therapy. Data are shown according to National Early Warning Score (NEWS) at emergency department (ED) admission. (▫), ACEI; (▪), ARB.

differences were highlighted between treatment with ACEI compared to ARB.

Initial epidemiological reports from China have shown that hypertension and diabetes, as well as other cardiovascular diseases, are highly prevalent among COVID-19 patients.[6–8] Among patients who experienced worse outcomes, including need for ICU admission, use of mechanical ventilation and death,[6,7,33,34] the prevalence of hypertension was much higher compared to that of less severe COVID-19 patients. Likewise, in a study evaluating the prognosis of SARS CoV-2 patients admitted to ICU, the prevalence of hypertension was higher among patients who died compared to that of patients who could be stabilised and discharged from the ICU.[9] In addition, an analysis of the characteristics of COVID-19 related deaths in Italy documented that 73% of the patients (mean age 79 years) had an established diagnosis of hypertension, and 30 and 17% respectively, reported a treatment with ACEI or ARB.[35]

Collectively, these evidences have suggested a link between hypertension and the severity of COVID-19 infection. Furthermore, a growing concern has developed that the use of antihypertensive medications, mainly ACEI and ARB, may have contributed to the adverse outcomes observed in the initial studies of COVID-19 patients.[2–8]

Indeed, since SARS-CoV2 binds to ACE2 receptor to infect host cells, it has been hypothesised that ACEI and ARB could upregulate ACE2 expression leading to an increased susceptibility to viral entry and propagation.[15,17] Furthermore, it has been postulated that the up-regulation of ACE2 could increase the lung viral load and worsen the respiratory disease severity.[17]

However, recent studies did not confirm these concerns. Yang *et al.*,[12] conducted a retrospective study including 126 COVID-19 patients with hypertension of whom 43 (34%) patients were on ACEI or ARB treatment. Compared to ACEI/ARB non-users, those on ACEI or ARB experienced a lower death rate but failed to reach statistical significance. Another Chinese study on 362 hypertensive patients with COVID-19, of whom 115 (32%) were on ACEI or ARB, suggested that these medications were not associated with COVID-19 severity or mortality.[11] Furthermore, Zhang *et al.*[10] had recently published a retrospective multi-centre study in China including 1128 hypertensive adult patients diagnosed with COVID-19. One hundred and eighty-eight (17%) patients using ACEI/ARB were paired at 1:1 based on a propensity matching with patients using other anti-hypertensive medications. Use of ACEI/ARB was associated with a lower risk of COVID-19 mortality at 28 days,

albeit the authors themselves admit that residual confounding cannot be ruled out. More recently, a large population-based study conducted in Italy did not provide evidences that ACEI or ARB could affect the risk of COVID-19 infection.[25]

In this study, we did not find an association between treatment with ACEI or ARB and the in-hospital death (Fig. 1). Similarly, a case-population study done in Spain showed that there is no evidence of a causal relationship between ACE2 levels and outcomes in COVID-19 patients, nor is it known conclusively if a higher viral load is associated with a worse prognosis in SARS-CoV-2 infection. Moreover, ACEI or ARB did not increase the risk of COVID-19 requiring admission to hospital.[26]

The findings of our study failed to demonstrate that patients on ACEI/ARB could experience a higher risk of the combined end-point of in-hospital death and ICU admission suggesting that ACEI or ARB treatment did not influence only the risk of death, but also the course of disease. Furthermore, we could not document any differential impact on the outcomes between ACEI and ARB (Fig. 2) but, due the relatively small sample size, this finding remains questionable. Indeed, the evidence prior to the COVID-19 era was mixed. A systematic review has indicated that ACEI, but not ARB, have a protective role towards the risk of community-acquired pneumonia and its related mortality.[36] In contrast, among patients with COPD, it has been suggested that ARB might be more effective than ACEI to reduce the severity and mortality due to COPD.[37]

Moreover, in our cohort of COVID-19 patients, among the comorbidities analysed, a history of COPD showed a higher prevalence among non-survivor patients. Likewise, in a recent meta-analysis, COVID-19 infection was associated with substantial severity and mortality rates in patients with COPD.[38] In addition, although in a limited sample, the present data suggest that the risk of death could be age-dependent, confirming what is stated in other surveys.[9,34,39] However, no sufficient data were available to demonstrate the independent role of age. Indeed, in a previous report, mortality appeared not predicted by advanced age.[40]

Typically, COVID-19 patients present with fever, myalgia or fatigue and dry cough.[7] Severe cases progress to severe dyspnoea and hypoxaemia usually within 1 week after the onset of symptoms.[41] In hospitalised COVID-19 patients, the prevalence of hypoxaemic respiratory failure is approximately 20%, and more than 25% may require intensive care treatment.[42] In the present study, we elected to focus on the worse case scenario, for example, death or the composite of death/ICU admission during hospital stay. In order to account for the different clinical severity at presentation, patients were stratified according to NEWS, a widely adopted early warning score. The NEWS score is based on a rapid and quantitative assessment of changes in vital signs,[43] and was developed to identify and track patients at risk of deterioration in non-critical areas of the hospital in order to ensure an early stabilisation and ICU transfer and to prevent avoidable cardiac arrest.[44] In recent years, the NEWS score has been validated in the ED setting to predict ICU admission and mortality.[45] Furthermore, although not yet validated, the NEWS score has recently been proposed for the triage of COVID-19 patients in ED.[41] The findings of our study document that patients with a more severe degree of respiratory illness, defined by a NEWS score ≥2 at presentation, were at high risk of rapid deterioration, with a consistent increased risk of death and death/ICU admission.

These results are consistent with those reported in a recent prospective cohort study in which the NEWS score at hospital admission appeared superior to the quick Sepsis-Related Organ Failure Assessment score and other widely used clinical risk scores in prediction of severe disease and in-hospital mortality from COVID-19.[46] However, larger studies are needed to confirm this finding, and to investigate the optimal cut-off value for clinical use.

As for any retrospective study, several limitations are worth considering. First, despite a fair sample size, the number of events was small thus limiting the power of our study. The study was conducted at a single medical centre and, as such, the findings might be not representative of the general population of COVID-19 patients. The study focussed on the worse case scenarios, that is, in-hospital death or death/ICU admission. For this reason, we cannot extrapolate the findings to different outcomes as length of hospital stay, other complications, permanent need of oxygen support, loss of autonomy or need to transfer to residential nursing facilities. Similarly, the effect of ACEI/ARB might be different among patients managed in the outpatient setting. Finally, some patients might have been excluded from the analytical sample because it was suggested to interrupt ACEI/ARB treatment due to prior concerns.

Conclusions

Among patients with hypertension hospitalised for COVID-19, treatment with ACEI or ARB was not associated with an increased risk of in-hospital death. Moreover, noticeably, no differences were documented between treatment with ACEI compared to ARB.

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