RAAs inhibitors and outcome in patients with SARS-CoV-2 pneumonia. A case series study.

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Running Title: COVID-19 and RAAs inhibitors

Research Letter

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Key words:
SARS-coronavirus-2
ace-inhibitor
angiotensin receptor blocker
COVID-19

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ACE2, an enzyme that physiologically counters the activation of the renin-angiotensin-aldosterone system (RAAs), is the functional receptor for SARS-CoV-2, the virus responsible for the COVID-19 pandemic. Since ACE-inhibitors (ACEi) and angiotensin receptor blockers (ARBs) may affect ACE2 expression[1], concerns regarding their safety in patients with COVID-19 have been raised. Aim of the present study was to describe patients characteristics, ongoing pharmacologic treatment at the time of admission and any association between chronic use of ACEi/ARBs and adverse COVID-19 clinical outcome in the first 191 consecutive patients admitted to our institution.

This is a retrospective, observational study from a single tertiary center (San Raffaele Hospital, Milan) involved in frontline care during COVID-19 outbreak in Italy. We included all adult patients admitted to our hospital from February 27 to March 17, 2020, with a confirmed diagnosis of SARS-CoV-2 pneumonia by chest x-ray- or CT-scan and real-time PCR. Data were obtained from electronic medical records. Heart failure (HF) and chronic kidney disease (CKD) were defined according to ESC and KDIGO guidelines. Multivariate analysis was performed including only covariates that were significantly associated with the risk of death at univariate analysis and the convention of limiting the number of independent variables to one for approximately ten events was followed. The study was approved by the local ethic committee.

During the index period, 212 patients were admitted to the emergency department of our hospital and then hospitalized for SARS-CoV-2 pneumonia. Excluding patients with incomplete data collection and lost to follow-up, the final study population consisted of 191 patients (mean age 63.4±14.9 years, 68.6% males) of whom 22 (11.5%) required intensive care unit (ICU) admission. Baseline clinical characteristics are reported in **Table 1.**

Ninety-six patients (50.2%) were affected by hypertension (76.3% males, mean age 70.6±11.8 years) of whom 68 (70.1%) were on ACEi/ARBs (ACEi n=35; ARBs n=33). Medications were continued in all patients during hospital stay, unless not tolerated, with close monitoring of blood pressure and renal function, while they were withdrawn in case of ICU admission.

At a median follow-up of 28 (21-32) days, 42 patients (22%) died during hospitalization and 121(63.3%) were discharged. As of April 9, 28 patients were still hospitalized, of whom 4 in ICU. ICU stay was longer in survivors compared to non-survivors. Non-survivors were significantly older and were more frequently affected by comorbidities (**Table 1**). Univariate predictors of mortality are shown in **Table 1**. Only age, HF and CKD, but not hypertension, were independently associated with all-cause mortality. Treatment with ACEi/ARBs was not an independent predictor of poor outcome.

At sensitivity analysis no differences were observed in the severity of pulmonary involvement at chest x-ray (bilateral consolidation: 36.5% vs 41.7%, p=0.586) or in laboratory findings on admission (CRP:111±69 vs 112±90 mg/l, p=0.959; creatinine 1.3±1.6 vs 1.5±1.2mg/dl, p=0.430) between patients treated with or without ACEi/ARBs. Although a decline in renal function (difference between eGFR at admission and nadir eGFR during hospital stay) was evident in the overall population, there was no significant difference according to concomitant ACEi/ARBs treatment (-7.8 ±19.0 versus -10.8±24.8 ml/min 1.73m^2, patients with and without ACEi/ARBs respectively, p=0.28). According to AKIN criteria, 38 patients (19.8%) developed acute kidney injury, with no difference between patients treated with or without ACEi/ARBs (p=0.18). At Cox regression analysis age and HF were the only independent predictors of mortality. (**Table 1**).

This is one of the first studies that evaluated COVID-19 outcome with relation to antihypertensive treatment with RAAs blockers. We demonstrated that in patients hospitalized for pneumonia, chronic treatment with ACEi/ARBs was not burdened by excess mortality, worse clinical presentation or deterioration of renal function. Overall mortality was high (22%) and identified predictors of poor prognosis were age and comorbidities such as HF and CKD, all findings consistent with prior reports from Wuhan, China [2].

Since the expression of ACE2 is upregulated by RAAs inhibitors [1], concerns have been raised over a potential facilitation of infection and viral propagation by these drugs as in SARS a higher viral load was associated with a worse prognosis [3]. On the other hand, lung injury is partially mediated by RAAs activation, with evidence of ACE2 downregulation after SARS-CoV infection and reduction of IL-6 levels in ARDS after rhACE2 injection [4], thus providing support for lack of harm by chronic treatment with RAAs blockers in our study.

The prevalence of hypertension in our population was high, but the data are consistent with its expected prevalence in this age group in Italy. Despite the relatively small number of patients, our findings are consistent with treatment of hypertensive patients in Italy, 70% of whom receive RAAs inhibitors.

In recently published studies, hypertension was associated with a 1.8 to 3-fold hazard ratio of in-hospital mortality for COVID-19, but it was not included in the multivariate model [2,5], while in our study only age, HF and CKD were independent predictors of mortality.

The relatively small sample size and the lack of power to detect the effect of withdrawal of therapy during hospital stay are the main limitations of our study. Finally, whether chronic use of RAAs blockers would facilitate infection with SARS-CoV-2 is yet to be determined.

In conclusion, in hospitalized patients for COVID-19 during the early outbreak in Italy, chronic treatment with RAAs blockers was not associated with increased mortality: this represents one of the first clinical evidence supporting the continuation of chronic RAAs blockers in the context of COVID-19.

Sources of Funding: None

Disclosures: None

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Table 1 Baseline clinical characteristics and predictors of all-cause mortality among overall population and hypertensive patients.

Overall population			
	Survivors N=149	**Non-survivors** N=42	**P value**
Age, years	60.4 ±13.7	75.3 ±12.9	**0.001**
Male	100(67.6%)	31(73.8%)	0.440
Symptoms onset to admission, days	6.5±3.8	6.4±3.9	0.827
O2 Sat at admission, %	93.0±8.9	86.7±10.2	**0.001**
EF, % *	58.7±6.1	43.2±17.4	**0.028**
ICU length of stay, days	14.6 ±7.3	5.2 ±3.1	**0.001**
Comorbidities			
Hypertension	62 (42.3%)	34 (81.0%)	**0.003**
Heart Failure	2 (1.3%)	7 (16.7%)	**0.001**
CAD	19 (12.8%)	9 (21.4%)	0.160
Diabetes	17 (11.4%)	11 (26.2%)	**0.017**
COPD	4 (2.7%)	6 (14.3%)	**0.003**
Cancer	16 (10.7%)	11 (26.2%)	**0.011**
CKD	28 (18.8%)	22 (55.0%)	**0.001**
Antihypertensive therapy			
ACEi/ARBs	48 (32.2%)	21 (50.0%)	**0.034**
B-blocker	31 (21.1%)	21 (50.0%)	**0.010**
CCB	16 (10.8%)	9 (21.4%)	0.072
Thiazide	12 (8.1%)	4 (9.5%)	0.771
Number of drugs	0.7±0.6	1.3±0.9	0.001
Other			
Loop diuretic	7 (4.7%)	12 (28.6%)	**0.001**
Statin	21 (14.2%)	9 (21.4%)	0.256
Laboratory findings			
WBC, 10^9/L	7.7±4.6	10.0±5.4	0.371
Creatinine, mg/dl	1.1±1.0	1.4±1.0	**0.043**
eGFR, ml/min 1.73 m^2	80.3 ±20.3	65.9 ±33.6	**0.046**
CRP, mg/L	93.7±71.9	134.0±84.9	0.099
Radiograph findings			
Interstitial texture	52 (44.4%)	10 (30.3%)	0.145
Consolidation	26 (22.2%)	7 (21.2%)	0.902
Bilateral consolidation	35 (29.9%)	16 (48.5%)	**0.047**
Hypertensive patients			
	Survivors N=62	**Non-survivors** N=34	**P value**
Age, years	67.3±10.3	76.9±10.9	**0.001**
Male			

Symptoms onset to admission, days	7.1±4.0	6.8±3.7	0.753
%O2 sat	92.9±4.3	87.0±10.1	**0.001**
Comorbidities			
Heart Failure	2 (3.2%)	6 (17.6%)	**0.013**
CAD	18 (28.6%)	9 (26.5%)	0.826
Diabetes	13 (20.6%)	9 (26.5%)	0.513
COPD	4 (6.3%)	5 (14.7%)	0.176
Cancer	8 (12.7%)	8 (23.5%)	0.170
CKD	20 (31.7%)	20 (62.5%)	**0.004**
Antihypertensive therapy			
ACEi/ARBs	47 (74.6%)	21 (61.8%)	0.188
ACEi	21 (33.3%)	14 (41.2%)	0.443
ARBs	26 (41.3%)	7 (20.6%)	**0.040**
B-blocker	29 (46.8%)	21 (61.8%)	0.160
CCB	16 (25.8%)	9 (26.5%)	0.943
Thiazide	12 (19.4%)	4 (11.8%)	0.256
Number of drugs	1.6±0.7	1.6±0.7	0.837

Overall population

	Univariate		**Multivariate Cox (Model 1)**		**Multivariate Cox (Model 2)**	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Age	1.1 (1.0 – 1.2)	**0.001**	1.1 (1.0 – 1.2)	**0.001**	1.1 (1.0 – 1.1)	**0.001**
Female sex	0.8 (0.4 – 1.5)	0.518				
Hypertension	4.7 (2.2 – 10.3)	**0.001**	ns			
Heart Failure	6.1 (2.7 -14.0)	**0.001**	3.1 (1.3 – 7.5)	**0.008**		
CAD	1.7 (0.8 – 3.6)	0.142				
Diabetes	2.3 (1.1 – 4.5)	**0.017**	ns			
COPD	3.3 (1.4 – 7.9)	**0.007**			ns	
Cancer	2.6 (1.1 - 5.3)	**0.005**			ns	
CKD	4.2 (2.3 – 7.9)	**0.001**			2.1 (1.1 – 4.0)	**0.033**
ACEi/ARBs	1.8 (1.0 – 3.3)	**0.047**	ns			
B-blocker	3.0 (1.6 – 5.6)	**0.001**			ns	

Hypertensive patients

	Univariate		**Multivariate Cox**	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age	1.1 (1.0 – 1.2)	**0.004**	1.1 (1.0 – 1.1)	**0.009**
Female	0.8 (0.2 – 2.0)	0.753		
Heart Failure	3.7 (1.5 – 9.0)	**0.004**	2.8 (1.1 – 6.9)	**0.023**
CAD	0.9 (0.4 – 2.0)	0.919		
Diabetes	1.3 (0.6 – 2.7)	0.494		
CKD	2.9 (1.4 – 5.9)	**0.003**	ns	
COPD	2.5 (0.6 – 10.1)	0.187		
Cancer	2.0 (0.9 – 4.4)	0.083		
ACEi/ARBs	0.5 (0.2 – 1.2)	0.133		

ACEi	1.2 (0.6 – 2.4)	0.591	
ARBs	0.4 (0.2 – 1.1)	0.059	
B-blocker	1.7 (0.8 – 3.3)	0.145	

ICU=intensive care unit; EF= ejection fraction; CAD=coronary artery disease; COPD=chronic obstructive pulmonary disease; CKD=chronic kidney disease; ACEi=angiotensin converting enzyme inhibitors; ARBs=angiotensin receptor blockers; CCB=calcium channel blockers; WBC white blood cell count; CRP= C-reactive protein.
*Data on ejection fraction was available on 31 patients

Overall population:

Multivariate Model 1: Age, Hypertension, Heart failure; Diabetes; ACEi/ARBs. C-statistic 0.83 (95% CI 0.76 – 0.90) Hosmer-Lemeshow test p=0.57.

Multivariate Model 2: Age, CKD; COPD, Cancer, Beta-blocker. C-statistic 0.82 (95% CI 0.74 – 0.89) Hosmer-Lemeshow test p=0.97.

Hypertensive patients:

Multivariate: Age, Heart failure, CKD. C-statistic 0.78 (95% CI 0.69 – 0.89) Hosmer-Lemeshow test p=0.148.