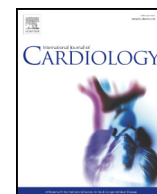




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## The role of anti-hypertensive treatment, comorbidities and early introduction of LMWH in the setting of COVID-19: A retrospective, observational study in Northern Italy☆

Antonio Desai<sup>a,b,\*</sup>, Giuseppe Voza<sup>a</sup>, Silvia Paiardi<sup>a</sup>, Francesca Ilaria Teofilo<sup>a</sup>, Giuseppe Caltagirone<sup>a,b</sup>, Marta Ripoll Pons<sup>a</sup>, Monia Aloise<sup>a</sup>, Maria Kogan<sup>a</sup>, Tobia Tommasini<sup>c</sup>, Victor Savevski<sup>c</sup>, Giulio Stefanini<sup>d</sup>, Claudio Angelini<sup>e</sup>, Michele Ciccarelli<sup>f</sup>, Salvatore Badalamenti<sup>e</sup>, Ana Lleo De Nalda<sup>b,g</sup>, Alessio Aghemo<sup>b,g</sup>, Maurizio Cecconi<sup>b,h</sup>, Filippo Martinelli Boneschi<sup>i,j,1</sup>, Antonio Voza<sup>a,1</sup>,  
on behalf of Humanitas COVID-19 task force

<sup>a</sup> Emergency Department, Humanitas Clinical and Research Center, IRCCS, Milan, Italy

<sup>b</sup> Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy

<sup>c</sup> Artificial Intelligence Center, Humanitas Clinical and Research Center, IRCCS, Milan, Italy

<sup>d</sup> Cardiology Department, Humanitas Clinical and Research Center, IRCCS, Milan, Italy

<sup>e</sup> Humanitas Clinical and Research Center-Nephrology Unit, Rozzano, Milan, Italy

<sup>f</sup> Pneumology Department, Humanitas Clinical and Research Center, Rozzano, Milan, Italy

<sup>g</sup> Department of Internal Medicine and Hepatology, Humanitas University, Humanitas Clinical and Research Center, IRCCS, Rozzano, Milan, Italy

<sup>h</sup> Humanitas Clinical and Research Center, Department and Anaesthesia and Intensive Care, Rozzano, Milan, Italy

<sup>i</sup> Dino Ferrari Centre, Neuroscience Section, Department of Pathophysiology and Transplantation (DEPT), University of Milan, Milan, Italy

<sup>j</sup> Neurology Unit and MS Centre, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

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### ABSTRACT

**Background:** There is a great deal of debate about the role of cardiovascular comorbidities and the chronic use of antihypertensive agents (such as ACE-I and ARBs) on mortality on COVID-19 patients. Of note, ACE2 is responsible for the host cell entry of the virus.

**Methods:** We extracted data on 575 consecutive patients with laboratory-confirmed SARS-CoV-2 infection admitted to the Emergency Department (ED) of Humanitas Center, between February 21 and April 14, 2020.

The aim of the study was to evaluate the role of chronic treatment with ACE-I or ARBs and other clinical predictors on in-hospital mortality in a cohort of COVID-19 patients.

**Results:** Multivariate analysis showed that a chronic intake of ACE-I was associated with a trend in reduction of mortality (OR: 0.53; 95% CI: 0.27–1.03;  $p = 0.06$ ), differently from a chronic intake of ARB (OR: 1.1; 95% CI: 0.5–2.8;  $p = 0.8$ ). Increased age (ORs ranging from 3.4 to 25.2 and to 39.5 for 60–70, 70–80 and >80 years vs <60) and cardiovascular comorbidities (OR: 1.90; 95% CI: 1.1–3.3;  $p = 0.02$ ) were confirmed as important risk factors for COVID-19 mortality. Timely treatment with low-molecular-weight heparin (LMWH) in ED was found to be protective (OR: 0.36; 95% CI: 0.21–0.62;  $p < 0.0001$ ).

**Conclusions:** This study can contribute to understand the reasons behind the high mortality rate of patients in Lombardy, a region which accounts for >50% of total Italian deaths.

Based on our findings, we support that daily intake of antihypertensive medications in the setting of COVID-19 should not be discontinued and that a timely LMWH administration in ED has shown to decrease in-hospital mortality.

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☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

\* Corresponding author at: Department of Emergency Medicine, Humanitas Clinical and Research Center, IRCCS, via Manzoni 56, 20089 Rozzano (Mi), Italy.

E-mail address: [desaiantonio@gmail.com](mailto:desaiantonio@gmail.com) (A. Desai).

<sup>1</sup> These 2 senior authors contributed equally to the work.

### 1. Introduction

In late December 2019, a novel coronavirus emerged in Wuhan, the capital city of Hubei. The enveloped RNA betacoronavirus has been soon named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to its phylogenetic similarity to SARS-CoV [1].

On February 20, 2020, the first case of novel coronavirus disease 2019 (COVID-19) was detected in Italy [2], and 20 days later WHO declared COVID-19 outbreak a global pandemic [3].

Italy has one of the highest rates of SARS-CoV-2 infection worldwide, with 397.1 cases per 100,000 people, as well as the fourth highest mortality rate, 14.5% vs. a global average value of 5.1% (as of June 26th, 2020; <https://coronavirus.jhu.edu/map.html>).

The Lombardy region, with 10.6 Million people living in highly populated areas, has been the epicenter of the infection in Italy, with 39.1% of total cases and almost half of total deaths (<http://www.salute.gov.it/portale/home.html>).

The reason behind the high mortality rate in Italy, and mostly in Lombardy, can have several explanations: 1) the characteristics of the population (Italy has the second oldest population in Europe; <https://ec.europa.eu/eurostat/data/database>); 2) the organization of the health system in Lombardy where most of the medical care is provided at hospital level rather than locally with general practitioners. In addition, a low number of intensive care units is present compared to those needed for Lombardy's population; 3) the possible existence of different virus strains; 4) differences in genetic and environmental factors (e.g. air pollution); 5) overuse of antibiotics and antihypertensive agents, in Italy as compared to other countries.

A recent paper tried to assess the role of genetic variation at ACE2 gene in Italian subjects as compared to other European and East Asian cohorts in candidate genes for viral infection, namely ACE2 and TMPRSS2, as a possible explanation of the high mortality rate in Italy, with some suggestive findings that need to be further validated [4].

As for today, there are discordant results regarding the use of either angiotensin converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARBs) as for their possible impact on COVID-19 mortality. Both ACE-I and ARBs act on the renin-angiotensin-aldosterone system (RAAS) and are widely prescribed for primary hypertension [5], heart failure, diabetic nephropathy and secondary prevention of myocardial infarction (MI) [6]. ACE-I exerts its effect by inhibiting the angiotensin converting enzyme (ACE), a specific protease found primarily in the vascular endothelium of the lungs and kidneys which catalyzes the conversion of angiotensin I to angiotensin II, which in turn causes vasoconstriction [7]. ARBs act by antagonizing the effects of angiotensin II on its AT<sub>1</sub> and AT<sub>2</sub> receptors [8], expressed in kidney [9,10], adrenal cortex [11], arterioles [12], and brain [13,14].

The carboxypeptidase angiotensin-converting enzyme 2 (ACE2), which is highly expressed in the lower airways, degrades angiotensin II into its active form angiotensin 1–7, which in turn dilates blood vessels, reduces inflammation, and inactivates angiotensin II before it could interact with its receptors [15].

SARS-CoV-2 binds to ACE2 with its spike glycoprotein which allows it to gain entry into the host cell and by that to potentially cause an acute respiratory distress syndrome (ARDS) and respiratory failure [16].

In addition, hypertension has been found to be an important risk factor for mortality with a hazard ratio (HR) of 3.05 for in-hospital mortality in 191 COVID-19 patients and of 1.70–1.82 for death and acute respiratory distress syndrome (ARDS) in 201 COVID-19 patients [17]. Similarly, cardiovascular comorbidities are associated with greater mortality [18].

Considering the wide use of antihypertensive drugs, we conducted a single-center retrospective observational study on 575 COVID-19 patients consecutively admitted to the Humanitas Clinical and Research Center Emergency Department (ED) in order to evaluate its possible impact on in-hospital mortality in COVID-19 patients.

The secondary endpoint of our study was to investigate the role of other clinical predictors on in-hospital mortality.

## 2. Methods

### 2.1. Study design and participants

This single-center, retrospective, observational study was conducted at the Emergency Department (ED) of Humanitas Clinical and Research Center. The study was approved by the ethical committee and performed in accordance with the principles of the Helsinki declaration [19].

We analyzed 575 consecutive patients who were admitted to the ED with fever and cough complaints from February 21, 2020, to April 14, 2020, and had been diagnosed with COVID-19, according to WHO interim guidance [20]. Laboratory confirmation of SARS-CoV-2 infection was done by RT-PCR performed on a nasopharyngeal swab in all subjects.

Patients were discharged from the hospital or transferred to a health care facility if they had stable oxygen levels (in room air >95%) for more than 48 h as measured by a pulse oximeter.

### 2.2. Data collection

Clinical electronic medical records were reviewed for all patients tested positive for SARS-CoV-2 infection. Data were collected and stored in a dedicated database built solely for this purpose. Any missing or uncertain records were clarified through direct communication with the relevant health-care providers and family members.

We collected data on age, gender, comorbidities, chronic treatment, time interval between symptoms onset and ED admission, treatment provided during ED stay (antiviral agents, antibacterial agents, hydroxychloroquine and low molecular weight heparin (LWMH) therapy), days of hospitalization, and on outcome in terms of survival.

The data were available only to authorized personnel, stored on a local server and retrieved for this analysis.

### 2.3. Endpoints

The primary endpoint of the study was the occurrence of in-hospital mortality. The secondary outcome was the survival time, which was defined as the time between ED admission and either death, patient's transfer to another health care facility or hospital discharge. Analyses tested the role of ACE-I and ARBs and were adjusted for confounders with potential impact on survival, these including age, gender, comorbidities, time interval between onset of symptoms and ED admission, and treatments provided in the ED.

### 2.4. Statistical analysis

Categorical variables were represented in terms of frequency distributions, while quantitative variables were described as means and standard deviations (SD) or median and interquartile range (IQR). We performed univariate analyses using chi-square test for independence for categorical variables and unpaired *t*-test (or, if assumptions were not met, Mann-Whitney's test) for quantitative variables. Multivariate analysis was performed with in-hospital mortality as dependent variable and as predictors a priori selected variables (age, gender and chronic use of ACE-I and ARBs) and other variables which were significant with *p* < 0.1 at univariate testing with a backward selection based on likelihood ratio to find the most parsimonious model.

Proportionality of hazards was tested by means of Schoenfeld's test. Cox regression model for proportional hazard was used to estimate hazard ratios for those taking ACE-I, ARBs or none of those medications, while controlling for other relevant clinical factors. In inferential testing, *p* < 0.05 was considered statistically significant. Forrest plots have been performed using a logarithmic scale for Odds Ratios (OR) and 95% upper and lower confidence intervals (CI).

Analyses were performed with IBM SPSS software version 26.0 and StataCorp STATA software version 13.1.

### 3. Results

As of April 14, 2020, 1247 consecutive patients presented to our ED were isolated as suspected COVID-19 cases, of whom 672 tested negatives for SARS-CoV-2 on RT-PCR performed on a nasopharyngeal swab the later not included in this study. The remaining 575 adult patients who were found positive for COVID-19 (46.1% of total) represented the study cohort. Among those found positive for SARS-CoV-2 infection, the male to female ratio was 1.94 with a mean age of 64.8 years (SD 14.6, range 27–93 years), 361 subjects (62.7%) were older than 60 years (Table 1).

While a limited number of patients (7.1%) had mild symptoms and were discharged within few hours, the majority required hospitalization and 10.9% were transferred to an Intensive Care Unit (ICU). Chronic diseases were reported in 329 patients (57.1%), these most commonly included: hypertension in 43.1%, cardiovascular diseases in 27.1%, diabetes in 20%, neoplastic diseases in 11.9% and respiratory diseases in 10.1% of patients. The median time from onset of symptoms to hospitalization was 7 days (range: 0–35). On ED admission, 391 patients (69.1%) were administered with antiviral agents (lopinavir/ritonavir (250 mg/50 mg) or darunavir/cobicistat (800 mg/150 mg), 90.8% with antibacterial agents (mainly ceftriaxone 2 g. once a day or piperacillin/tazobactam), 42.6% with low molecular weight heparin (LMWH), and 72.8% with hydroxychloroquine 200 mg twice a day. In the study cohort, 14.4% of patients were chronically treated with ACE-I, 12.3% with ARBs, 14% with statins and 9.4% with anti-coagulants. Most of patients used ACE-I (84.3%) or ARBs (88.4%) for hypertension. When we stratified for ACE-I and ARBs treatment (Table 1), we found that ACE-I users were older (74.2 vs 63.2 years;  $p < 0.00001$ ) and had more comorbidities (2 vs 1,  $p < 0.00001$ ) compared to non-users, with results replicated in the comparison between ARBs treated and untreated subjects. A difference, albeit not significant, was found in the mortality between ACE-I users and non-users (32.4% vs 24.9%) and between ARBs-users vs non-users (30.9% vs 25.4%). Multivariate analyses showed that the main reason of these findings was due to the age difference between the two groups. Moreover, a longer hospital stay was observed in ARBs-users as compared to non-users (11 vs 9 days;  $p = 0.02$ ).

In hospital mortality was 20.9%, while 55.5% of patients were discharged, 3.8% moved to a long-term care facility and 19.8% still

**Table 2**

Predictors of in-hospital mortality at univariate and multivariate analysis.

Predictors of mortality				
Predictors	Univariate		Multivariate (n = 372)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age: < 60 years	1.0 (Ref.)		1.0 (Ref.)	
60–70 years	3.5 (1.3–9.6)	0.02	3.4 (1.2–9.4)	0.02
70–80 years	27.0 (11–66.2)	<0.0001	25.2 (9.8–64.4)	<0.0001
> 80 years	40.5 (16–102.6)	<0.0001	39.5 (14.7–106.5)	<0.0001
Gender: male vs female	1.3 (0.8–2.1)	$p = 0.2$	1.2 (0.6–2.2)	0.6
Hypertension	2.2 (1.4–3.3)	<0.0001	0.9 (0.5–1.7)	0.7
Cardiovascular diseases	3.8 (2.4–5.9)	<0.0001	1.9 (1.1–3.3)	0.02
Diabetes	2.6 (1.6–4.3)	<0.0001	1.1 (0.5–2.4)	0.7
Respiratory disease	1.9 (1–3.5)	0.04	0.8 (0.3–2.0)	0.7
Malignancy	2 (1.1–3.6)	0.02	1.0 (0.4–2.3)	0.9
Time to ED	0.95 (0.92–0.97)	<0.0001	0.98 (0.92–1.04)	0.5
ACEi	1.4 (0.8–2.5)	0.19	0.5 (0.3–1.0)	0.06
ARB	1.3 (0.7–2.4)	0.38	1.1 (0.5–2.8)	0.8
Therapy: LMWH	0.5 (0.3–0.8)	<0.001	0.4 (0.2–0.6)	<0.0001

Time to ED: time from symptoms onset to ED access. LOS: length of hospitalization. LMWH: low-molecular weight heparin; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker.

hospitalized at time of data analysis. Mean age at time of death was 77.1 years (SD 10.3, range: 38–93).

Univariate and multivariate logistic regression models are represented in Table 2, and related forest plots in Figs. 1 and 2 respectively.

Multivariate logistic regression model was performed to assess the role of ACE-I and ARBs as well as of other parameters on mortality risk. As shown in Table 2 and Fig. 2, the most parsimonious model ( $n = 447$ ,  $R^2 = 0.43$ ) showed that age is a risk factor with OR ranging from 3.4 (95% CI: 1.2–9.4;  $p = 0.02$ ) for patients between 60 and 70 years-old, 25.2 (95% CI: 9.8–64.4;  $p < 0.001$ ) for 70–80 year-old patient group and 39.5 (95% CI: 14.7–106.5;  $p < 0.001$ ) in those >80 years as compared to those <60 years of age. ACE-I use was protective with a border-line significance (OR: 0.5; 95% CI: 0.3–1.0;  $p = 0.06$ ), whereas comorbid cardiovascular condition was a risk factor (OR: 1.9; 95% CI: 1.1–3.3;  $p = 0.02$ ). As of ED admission, a LMWH use in ED was associated with an important reduction in mortality (OR: 0.4; 95% CI: 0.2–0.6;  $p < 0.001$ ).

**Table 1**

Baseline clinical features of patients stratified by anti-hypertensive agents (ACE-I and ARB).

	Total	ACEi		p-value	ARB		p-value
	n = 575	Treated (n = 83)	Not treated (n = 492)		Treated (n = 71)	Not treated n = 504	
Age, mean (SD), min-max	64.8 (14.5) 27–93	74.2 (11.4) 37–93	63.2 (14.4) 27–93	$p < 0.00001$	68.3 (12.0) 37–93	64.4 (14.8) 27–93	$p = 0.03$
Female, n (%)	195 (33.9%)	26 (31.3%)	169 (34.4%)	$p = ns$	23 (32.4%)	172 (34.1%)	$p = ns$
Comorbidities, median (IQR), range	2 (2) 0–1	2 (2) 1–7	1 (2) 0–10	$p < 0.00001$	2 (2) 0–6	1 (2) 0–10	$p < 0.0001$
Antivirals, n (%)	391 (69.1%)	62 (74.7%)	329 (68.1%)	$p = ns$	48 (67.6%)	343 (69.3%)	$p = ns$
Antibiotics, n (%)	515 (90.8%)	81 (97.6%)	434 (89.7%)	$p = 0.02$	66 (93.0%)	449 (90.5%)	$p = ns$
Hydroxychloroquine, n (%)	442 (78.2%)	71 (85.5%)	371 (77.0%)	$p = ns$	56 (78.9%)	386 (78.1%)	$p = ns$
LMWH, n (%)	240 (42.6%)	42 (51.2%)	198 (41.1%)	$p = ns$	34 (47.9%)	206 (41.8%)	$p = ns$
Time to ED (days), median (IQR), min-max	7 (4) 0–351	5 (4) 0–21	7 (7) 0–35	$p = ns$	7 (6) 0–35	7 (7) 0–30	$p = 0.03$
LOS in days, median (IQR), min-max	9 (3) 0–57	11 (8) 0–38	9 (7) 0–57	$p = 0.03$	11 (12) 0–36	9 (9) 0–57	$p = ns$
In-hospital death (n, %)	120 (20.9%)	23 (27.7%)	97 (19.7%)	$p = ns$	17 (23.9%)	103 (20.4%)	$p = ns$

Time to ED: time from symptoms onset to ED access. LOS: length of hospitalization. LMWH: low-molecular weight heparin; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker.

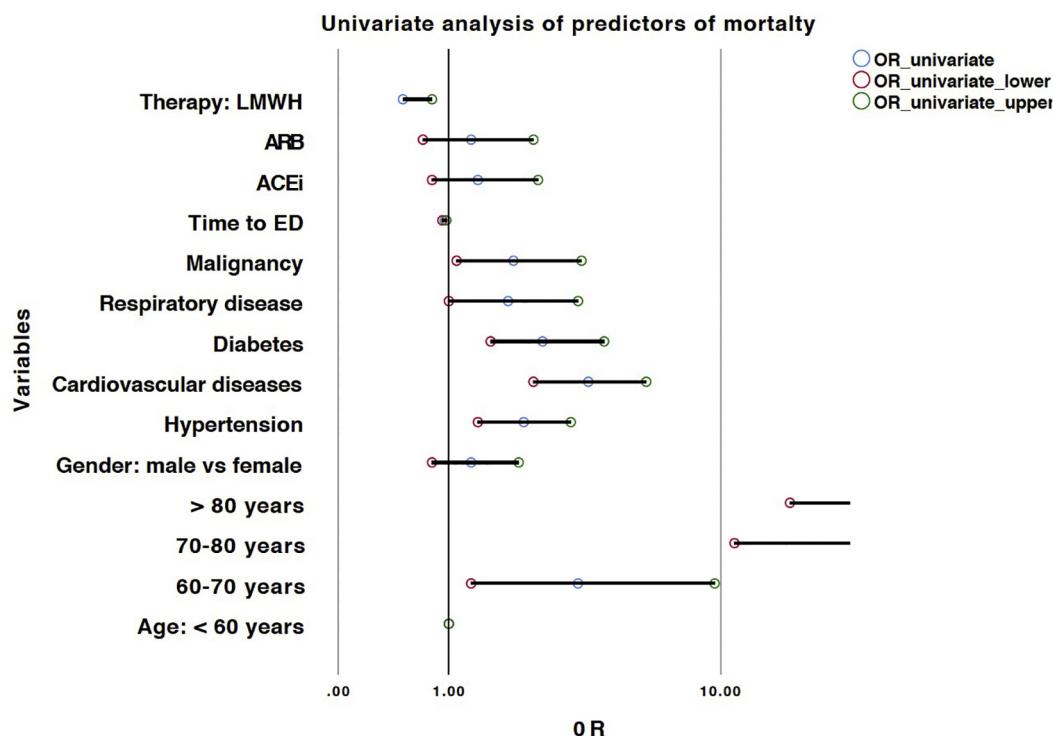


Fig. 1. Forest plot of predictors of in-hospital mortality at univariate logistic regression analysis. X axis was treated in a logarithmic scale.

We used survival analyses to further explore significant findings identified in the logistic regression. Results confirmed that the use of ACE-I was a significant protective factor for COVID-19 in-hospital mortality (Hazard Ratio: 0.61; 95% CI: 0.38–0.98;  $p = 0.04$ ) with a highly significant model ( $p = 9.99\text{E-}22$ ;  $n = 444$ ) (Table 3).

#### 4. Discussion

The study describes predictors of mortality in COVID-19 patients in one of the largest single-center cohort of Italian patients reported so

far, admitted to one of the biggest hospitals in the city of Milan, which is located in the epicenter of the COVID-19 emergency with the highest mortality in Italy.

In order to understand the reasons behind the high mortality rate in this metropolitan area, we performed a multivariate statistical model to assess the role of clinical predictors evaluated at ED admission and of ACE-I and ARBs chronic use. In-hospital mortality was found to be 20.9%.

ACE-I and ARBs act on the RAAS system, and they are widely used to treat primary hypertension [5], heart failure, diabetic nephropathy and secondary prevention of myocardial infarction (MI) [6]. The two drugs

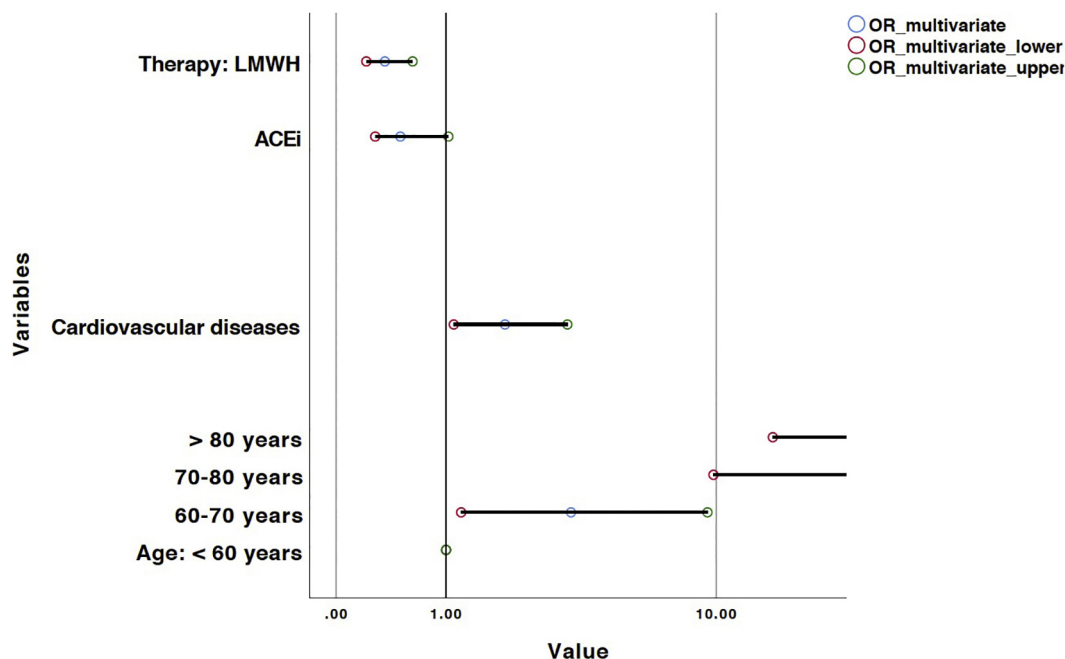


Fig. 2. Forest plot of predictors of in-hospital mortality at multivariate logistic regression analysis. X axis was treated in a logarithmic scale.

**Table 3**  
Predictors of in-hospital mortality using Cox-regression analysis for survival.

Survival analysis (n = 444)		
Predictors	HR (95% CI)	p
Age: <60 years	1.0 (Ref.)	
60–70 years	1.96 (0.73–5.22)	P = 0.18
70–80 years	7.56 (3.19–17.91)	p < 0.001
>80 years	12.51 (5.22–29.96)	p < 0.001
Cardiovascular comorbidity	1.78 (1.21–2.61)	p = 0.003
ACEi	0.61 (0.38–0.99)	p = 0.04
Therapy: LMWH	0.51 (0.34–0.76)	p < 0.001

have indeed a different mechanism of action on the RAAS cascade. While ACE-I inhibits the conversion from angiotensin I to angiotensin II, ARBs antagonize the effects of angiotensin II on its AT<sub>I</sub> and AT<sub>II</sub> receptors [8,9]. There are different hypotheses on the effect of these two drugs on ACE2, which is the protein involved in the host cell entry of the SARS-CoV-2. Whether they are detrimental or protective for disease severity of COVID-19 is still a matter of discussion.

Ferrario and co-workers proved that after a treatment with lisinopril (ACE—I) alone, ACE2 mRNA expression levels were increased without a consensual increase in ACE2 activity [21,22]. In this regard, increased levels of ACE2 may possibly lead to an increase in the number of binding sites for SARS-CoV-2, raising the risk of COVID-19 [21,23]. On the other end, other authors hypothesize that ACE-I and ARBs may interfere with the integrity of the ACE2/angiotensin (1–7)/MAS pathway resulting in a decreased expression of ACE2 and host cell entry of the virus [24].

We found that ACE—I, which acts by inhibiting the conversion from angiotensin I to angiotensin II, showed a trend in protecting from mortality from COVID-19 and was significant in delaying mortality as shown by multivariate Cox regression analysis unlike ARBs, which antagonize the effects of angiotensin II on its receptors [2,3]. The mechanisms underlying this phenomenon are still unclear and further investigations are required in order to shed light on the subject. As demonstrated in a recent paper, another hypothesis is that soluble human ACE2 inhibitors can inhibit SARS-CoV-2 infections, and in this regard it will be useful to investigate whether ACE-I or ARB are able to interfere and increase ACE2 levels [25]. Our data partly confirmed the results of a larger retrospective, multi-centric study performed on 1128 COVID-19 adults from the Hubei province in China, which showed that an inpatient use of either ACE-I or ARBs was associated with a lower risk of all-cause mortality when compared with ACE-I/ARBs non-users [26]. The previous study showed a protective effect given by the use of either drug, with no difference between the two, unlike our cohort in which only ACE-I were found to have a protective role. The reason underlying the difference between the two studies could lie in the different proportion of use of these two drugs [ACE-I (14.4% vs 2.7%) and ARBs (12.3% vs. 13.9%) in the Italian as compared to the Chinese sample].

In addition, an age difference was identified between ACE-I as compared to ARBs users (74.2 vs 68.3) in our sample. A different role of the two drug categories, ACE-I and ARBs has been suggested by a more recent meta-analysis, which showed that the use of ARBs, as opposed to ACE-I, increases the risk of SARS-CoV-2 infection in subjects <60 years [27].

Of note, two recent papers with a large sample size were performed in Lombardy and in the New York State using data from electronic health records, both of which did not confirm the protective role of ACE-I towards disease risk but not towards disease severity [28,29].

Advantages of single-center studies as compared to multicentric studies or to studies using health registries lie on the availability of complete data on patients and on the possibility to follow-up affected individuals despite it is usually associated with a smaller sample size..

As for today we can only say that a daily intake of antihypertensive medications (ACE-I and ARBs) in the setting of COVID-19 should not be discontinued. The replacement of a RAAS inhibitor with an

antihypertensive agent of a different class may require careful monitoring to avoid the rebound effect of blood pressure, as even short periods of blood pressure instability after a therapeutic change have been associated with an increase in cardiovascular risk [30,31].

As of the role of other potential predictors, we confirmed the significant role of age and cardiovascular comorbidities on mortality rate, as shown by other papers, while males were not confirmed to have a higher mortality differently from other studies [32]. On the contrary, the early administration of LMWH in ED was shown to have a protective effect on mortality in the same patients. A prophylactic dose of LMWH was administered at ED admission starting with 0.4 UI/24 h. The dose was adjusted accordingly to renal function and body weight.

Recent best practices have been published to aid health-care professionals to determine the proper anti-coagulant and anti-platelet therapy in COVID-19 patients [33]. Based on our findings, it appears that timely administration of LMWH is of greater importance as compared to initiation of treatment with antivirals, antibiotics and hydroxychloroquine in order to prevent potential thromboembolic events which, according to a previous paper performed in our hospital on a series of COVID-19 patients which partially overlap with ours, occurred in 7.7% of them [34].

The paper underlies the importance of timely treatment in particular among patients with non-modifiable risk factors such as age and cardiovascular comorbidities as it can potentially improve survival rates in these patients. It is worthwhile to consider developing tools for early identification of such patients, to maximize potential outcomes.

Nonetheless, rigorous adherence to state based recommendations are also advisable (e.g. quarantine, social distancing), especially among high-risk patients.

In conclusion, despite the limited nature of the study, identification of predictors of mortality will allow a better management of patients in the face of future disease recurrence.

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## Declaration of Competing Interest

None.

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