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COVID-19 in-hospital mortality and use of renin-angiotensin system blockers in geriatrics

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Brief summary: In very old subjects hospitalized for COVID-19 in geriatric settings, mortality was significantly lower in those treated with ARB or ACEI prior to the onset of infection.

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COVID-19 in-hospital mortality and use of renin-angiotensin system blockers in geriatrics

ABSTRACT

Objective: The role of treatment with renin-angiotensin-aldosterone system blockers at the onset of COVID-19 infection is not known in geriatric population. The aim of this study was to assess the relationship between angiotensin receptor blockers (ARB) and an ACE inhibitor (ACEI) use and in-hospital mortality in geriatric patients hospitalized for COVID-19.

Design: This observational retrospective study was conducted in a French geriatric department. Patients were included between March 17 and April 18, 2020.

Setting and Participants: All consecutive 201 patients hospitalized for COVID-19 (confirmed by RT-PCR methods) were included. All non-deceased patients had 30 days of follow-up and no patient was lost to follow-up.

Methods: Demographic, clinical, biological data and medications were collected. In-hospital mortality of patients treated or not by ACEI/ARB was analyzed using multivariate Cox models.

Results: Mean age of the population was 86.3 (8.0) years old, 62.7% of patients were institutionalized, 88.6% had dementia and 53.5% had severe disability (ADL score < 2). Sixty-three patients were treated with ACEI/ARB and 138 were not. Mean follow-up was 23.4 (10.0) days, 66 (33.8%) patients died after an average of 10.0 days (6.0). Lower mortality rate was observed in patients treated with ACEI/ARB compared with patients not treated with ARB nor ACEI (22.2% (14) vs. 37.7% (52), HR = 0.54 (95% CI = 0.30-0.97), p=0.03). In a multivariate Cox regression model including age, sex, ADL score, Charlson index, renal function, dyspnea, CRP and white blood cells count, use of ACEI/ARB was significantly associated with lower in-hospital mortality (HR = 0.52 (0.27–0.99), p=0.048).
Conclusion and Implications: In very old subjects hospitalized in geriatric settings for COVID-19, mortality was significantly lower in subjects treated with ARB or ACEI prior to the onset of infection. The continuation of ACEI/ARB therapy should be encouraged during periods of coronavirus outbreak in older subjects.
Introduction

Worldwide, as of June 15, 2020, according to John Hopkins University, more than 8 million people have been affected by coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, and more than 400 thousands died of COVID-19 since December 31, 2019. In France according to Santé Publique France, the French health agency, more than 141 thousand people have been contaminated and more than 29 thousands died of COVID-19.

COVID-19 predominantly affects elderly people. Subjects aged 75 years and older accounted for 75% of all deaths related to COVID-19 in France and mortality rate is 31.1% in Italy among people > 80 years old. SARS-CoV-2 virus belongs to the family of orthocoronavirinae, and shares some similarities with the MERS-CoV (75% identical genome sequence) and the SARS-CoV (85% of identical genome sequence respectively) that were responsible for severe pneumonia. Their S protein (of their capsid) are 99% similar and they have the same binding site: the angiotensin 2 conversion enzyme. Angiotensin 2 converting enzyme has a role in the entry of SARS-CoV-2 into target cells and animal experimental data indicate an increase in enzyme expression after administration of renin–angiotensin–aldosterone system blockers (i.e., angiotensin-converting-enzyme inhibitors (ACEI) and receptors blockers (ARB)). Thus the question has arisen as to whether ACEI/ARB treatment could increase severity and mortality of COVID-19.

In observational studies, subjects with cardiovascular diseases and hypertension are often treated with ACEI or ARB, and have an increased risk of in-hospital mortality related to COVID-19. Meanwhile some studies have found no effect or even a beneficial effect of ACEI/ARB on COVID-19 mortality. Older people are frequently treated with ACEI/ARB, however few data are available on their use in geriatric population affected by COVID-19. The aim of this study was to assess the relationship between ACEI/ARB and in-hospital mortality among geriatric patients hospitalized for COVID-19.
Methods

This retrospective study included all symptomatic patients admitted in Acute Geriatric Units dedicated to treating COVID-19, between March 17 and April 18, 2020, in a geriatric department with a positive reverse-transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 on nasal swabs. Patients were followed-up until May 18, 2020. Before admittance in the Acute Geriatric Units, patients with positive RT-PCR for SARS-CoV-2 were first examined in emergency room and had a geriatric evaluation. Only patients who were assessed as not fit enough or had too severe comorbidities for intensive care unit were admitted Acute Geriatric Units and included in the study. As available, four different PCR tests were performed by the hospital’s virology department (Abbott real time SRAS CoV-2, Xpert Xpress SRAS CoV-2, Simplexa COVID 19 direct and Allplex 2019-nCoV Assay).

The study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki. The study protocol was approved by local ethics committee and the study complied with the strengthening the reporting of observational studies in epidemiology statement guidelines. All patients’ data were anonymized prior to analysis. No consent to participate was sought for the participants in accordance with the French law because the study was observational in nature (as part of usual care), and no nominative data were collected.

Data collection

All data were collected as part of usual care. In-hospital mortality was assessed during a follow up of 30 days after RT-PCR confirmation. All patients included in the study were hospitalized at least 30 days in the geriatric department (acute unit and then rehabilitation unit if needed). Thus all non-deceased patients had a full 30-day follow-up.

Ethnicity was not recorded but the sample was overwhelmingly white Caucasian (> 90%). Demographic and clinical characteristics were recorded: sex, age, institutionalization, history of
cancer (localized or metastatic), heart failure, coronary heart disease, atrial fibrillation, hypertension (defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or use of antihypertensive medications or history of hypertension), diabetes mellitus (defined as self-report or use of oral hypoglycemic medication or insulin or a history of diabetes), chronic respiratory disease (chronic obstructive pulmonary disease or asthma), stroke or transient ischemic attacks, dementia (based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition), chronic kidney disease and major depression. Nutritional status was assessed by body mass index (BMI) and serum albumin level and malnutrition was defined as BMI < 21 kg/m² or Albumin < 35 g/l as defined in a Best Practice Guideline by the French health authority. Comorbidity was evaluated with the Charlson Comorbidity Index (CCI). Functional status was assessed with Activities of Daily Living (ADL). ADL was regrouped in 3 classes, no disability to mild disability (ADL ≥ 4 to 6), moderate disability (ADL ≥ 2 to < 4) and severe disability (ADL 0 to < 2).

Symptoms that led to the COVID-19 diagnosis or occurred in the first 72 hours before or after the RT-PCR confirmation, such as fever (defined as T° > 37.8°C), dyspnea, coughing, severe hypotension (SBP < 95 mmHg), digestive disorders (diarrhea and nausea or vomiting) or falls were also collected.

Ongoing treatments defined as treatment taken for at least 1 week before inclusion and taken the day of the inclusion were recorded: ACEI, ARB, diuretics, beta-blockers, calcium channel blockers, antiplatelet therapy, oral anticoagulants, benzodiazepines, neuroleptics, antidepressant therapy and proton pump inhibitors.

Biological data were also collected at admission including hemoglobin level, white blood cell count (WBC), lymphocyte and platelet count, C-reactive protein (CRP), serum creatinine, LDL and albumin. Estimated glomerular filtration (eGFR) rate was calculated with CKD-EPI formula and categorized in 3 classes, eGFR ≥ 50 ml/min, 50 ml/min > eGFR ≥ 30 ml/min and eGFR < 30 ml/min.
**Statistical Analysis**

Baseline characteristics of the participants were analyzed in the whole sample and according to death at 30 days using descriptive statistics: means and standard deviations for continuous variables, and percentages and counts for categorical variables and compare with t-tests and $\chi^2$ respectively.

Variables were also compared with univariate Cox model to take into account the different follow-up durations.

Baseline characteristics of the participants were also analyzed according to the use of ACEI/ARB and compare with t-tests for continuous variables and $\chi^2$ for categorical variables.

A Kaplan Meier curve was drawn for the mortality according to ACEI/ARB use and compared with Log Rank test.

A Cox regression model was built with 30-day in-hospital mortality as dependent variable and use of ACEI/ARB as independent variable adjusted for age, sex and variables associated with 30-day in-hospital mortality in univariate model (i.e., dyspnea, ADL, Charlson Comorbidity Index, eGFR, CRP, WBC in addition with age and sex) and results were presented in a forest plot. CRP, WBC and Charlson Comorbidity Index were standardized in order to obtain HR for an increase of 1 SD of each of those variables. HR for age was calculated for an increase of 10 years.

Another multivariate regression Cox model was built with 30-day in-hospital mortality as dependent variable and use of ARB and ACEI taken separately as independent variable and with the same adjustment as the first Cox regression model.

LDH was not included in this model because it was missing in 50 subjects. Proportional hazard assumption was checked graphically for all covariates and using Schoenfeld residuals.

All analyses were two-sided and a p-value < 0.05 was considered statistically significant. Data analysis was performed using R software version 3.2.3, (R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/).
Results

Among 373 patients hospitalized in a geriatric department from March 17 to April 18, 2020, 201 patients had a positive SARS-CoV-2 RT-PCR and were included in this study. Mean age of the sample was 86.3 (8.0) years old, 126 (62.7 %) patients lived in nursing homes, 178 (88.6%) had dementia and 107 (53.5%) had severe disability. The main symptoms at inclusion were fever (82.1%), dyspnea (28.9%), coughing (32.0%), digestive symptoms (9.95%) and falls (12.4%) (Table 1).

Sixty-six (33.8%) died after an average of 9.9 days in the hospital. All non-deceased patients had a full follow-up of 30 days, thus no participant was lost to follow-up. No patients were managed in intensive care units. Dyspnea (39.4% in non survivors vs. 23.7% in survivors, p=0.01) and poor functional status (ADL score < 2, 67.7% vs. 46.7%, p = 0.02) were significantly associated with in hospital mortality (Table 1). Mean CRP (57.1 vs. 27.6 mg/L, p < 0.0001), creatinine (97.9 vs. 82.7 µmol/L, p=0.007), white blood cells (8.59 vs. 6.03 × 10^9/L, p<0.0001) and LDH (359 vs. 241 UI/L, p = 0.05) were also significantly associated with in hospital mortality (Table 1).

Lower mortality rate was observed in patients treated with ARB or ACEI compared with patients not treated with ARB nor ACEI (22.2% (14) vs. 37.7% (52), HR = 0.54 (95% CI = 0.30-0.97), p=0.03) (Figure 1). Compared with patients not treated with ARB nor ACEI, patients treated with ARB alone had a lower rate of death (HR = 0.36 (0.13-1.00), p=0.05) as well as those with ACEI alone (HR = 0.66 (0.34-1.31), p=0.23) (Table 2).

Among patients with hypertension, 46% (58/125) were treated with ACEI/ARB. Patients receiving ACEI or ARB had more often hypertension and coronary artery disease and less often dementia and lower level of hemoglobin. Overall they had a higher Charlson comorbidity index than
patients not treated with ACEI or ARB. They were more often treated with calcium channel blockers, diuretics, and antiplatelet (table 3).

In a multivariate Cox regression model including age, sex, ADL, CCI, renal function, dyspnea, CRP and WBC, use of ACEI or ARB was significantly associated with lower in-hospital mortality (HR = 0.52 (0.27–0.99), p=0.048) (Figure 2). Severe disability (ADL < 2), (HR = 2.54 (1.13-5.72)), high white blood cells count (HR= 1.45 (1.16-1.81)) and high CRP (HR= 1.37 (1.11-1.69)) were significantly associated with death (Figure 2).

In the multivariate Cox regression model analyzing ARB and ACEI separately, HR was 0.40 (0.14-1.15), p=0.09 for ARB and 0.60 (0.28-1.31), p=0.20 for ACEI (Figure 2).
Discussion

In this cohort of very old patients affected by COVID-19, a high rate of in-hospital mortality was observed. The main factor associated with mortality was severe disability. In-hospital mortality among patients treated with ACEI or ARB was significantly lower compared with patients without ACEI or ARB therapy.

In our study, 33% of the patients died within 30 days of COVID-19 RP PCR confirmation. This mortality is much higher than that of younger population and of other respiratory virus diseases like influenza - and respiratory syncytial virus in elderly people. Older age has already been found a major risk factor for mortality from COVID-19 ranging from 14% to 30 % in patients aged > 80 years old. As of May 28, 2020 among the 59,134 peoples aged > 80 years old affected by COVID-19 in Italy the mortality was 31.1%. The relation of age and COVID-19 mortality is probably related to immunosenescence that has been identified as a major risk factor for respiratory diseases and its related mortality.

As already published, we also found that CRP and leukocytes increase were associated with death. However in our geriatric population, the main factor associated with mortality was severe disability and not factors usually associated with higher mortality in COVID-19 like, cardiovascular diseases, diabetes mellitus, obesity and chronic obstructive pulmonary disease. Disability through ADL is an already known factor of all-cause mortality in the elderly. Interestingly, poor functional status was a most relevant factor associated with mortality than respiratory symptoms like dyspnea that are major prognostic factors in younger population. Conversely to other studies, age was not associated with in-hospital mortality in our study probably because of the specificity of our population that was very old with a somewhat narrow age range. Therefore our results suggest that in older geriatric patients affected by COVID-19, functional status is the most important prognostic factor of mortality.
Studies on use of ACEI or ARB in COVID-19 patients have yielded conflicting results. Hypertension had been associated with mortality in hospitalized COVID-19 patients, and hypertensive patients are frequently treated with ACEI/ARB. Because ARB or ACEI therapeutics interact with ACE2 that is a required receptor for SARS-CoV-2 entry and propagation in host cells, ARB or ACEI could promote SARS-CoV-2 susceptibility and COVID-19 severity through increase of ACE2 expression. Some studies did not show any increased mortality associated with use of ACEI or ARB in populations aged on average 45, 55.5, 58 and 68 years old. However few data were available in very old geriatric patient at high risk of mortality from COVID-19 treated with ACEI/ARB.

In our study, mortality among patients treated with ACEI or ARB was significantly lower compared with patients without ACEI or ARB therapy, after adjustment for confounding variables. This result is consistent with a study from 9 hospitals in China including 1128 in-patients with hypertension and COVID-19 that demonstrated lower risk of mortality among patients treated with ACEI/ARB (HR = 0.42, 95% CI = 0.15-0.89, mean age 64 years old). Another collaborative study analyzing data from 169 hospitals in Asia, Europe and North America showed that in-hospital mortality was lower in ACEI-treated subjects (OR = 0.33, 95% CI = 0.20 to 0.54, mean age 49 years old, 16.5% > 65 years old). Lastly, an analysis of the data from 7 Madrid’s hospitals found a lower risk of COVID-19 requiring hospitalization in diabetic patients treated with ACEI/ARB (OR = 0.53, 95% CI = 0.34-0.80, mean age 69.1 years old).

It has been shown that SARS-CoV-2 cell entry leads to down-regulation of ACE2 contributing to an increase in harmful Angiotensin II and a decrease in protective Angiotensin 1-7. This increase in Angiotensin II might worsen lung injury from COVID-19 through excessive inflammatory response and cytokine storm, stimulating vascular leakage and pulmonary fibrosis. Treatment with ARB may protect against lung injury by Angiotensin I Type 1 receptor blockade and ACEI may protect by reducing Angiotensin II levels due to inhibition of Angiotensin I to Angiotensin II conversion.
ACEI/ARB could also be beneficial to patients with COVID-19 because they modulate inflammation, endothelial damage and fibrosis and may be involved in coagulation cascade.\textsuperscript{37} In our geriatric population no patient were managed in intensive care unit because of high level of comorbidity, dementia and low physiologic reserves that make prolonged intensive care unreasonable. Indeed, among critically ill elderly geriatric patients, ICU admission do not reduce 6-month mortality.\textsuperscript{38} In this frail population at high risk of mortality, the need of effective treatment before critical stage of COVID-19 is of paramount importance.

The high prevalence of dementia could be explained by the fact that only patients who were assessed too debilitated or had too severe comorbidities for intensive care unit after a geriatric evaluation were transferred in the Acute Geriatric Units and because 60% of our patients came from nursing homes.

This study has several strengths. Very few data existed on geriatric population affected by COVID-19, characterized by high risk of mortality and no access to intensive care unit.\textsuperscript{39} Prevalence of dementia was very high (89%) and few data exist on such population. There was no loss to follow-up and all non-deceased patients were followed-up for 30 days enabling the estimate of the actual 30-day mortality. Our results were adjusted on confounding factors including symptoms, comorbidity, disability and biological factors and suggest that in this population the ACEI/ARB therapy could be associated with better prognosis and ought to be confirm in other geriatric populations. Randomized controlled trials are much needed to assess the benefit on mortality associated with ACEI/ARB treatment in elderly patients with COVID-19.

This study has also some limitations, this cohort was monocentric and retrospective, so causality between ACEI or ARB use and mortality cannot be ascertained. Moreover dosing, indication and duration of ARB and ACEI prescriptions were not recorded as well as their continuations during COVID-19 course. However, only 2 patients had a severe renal insufficiency and 2 had severe hypotension (SBP < 95 mm Hg) at baseline in the ACEI/ARB group, conditions that would require
stopping ACEI/ARB. There was no sufficient power to analyze ARB and ACEI separately. Finally
duration of the infection before hospitalization was unknown. Statin use was not recorded even
though it has been recently shown to reduce mortality and severity in elderly patients with COVID-
19. Some blood measurement like D-Dimer, Fibrinogen, BNP, Troponin and IL-6 were not
performed and others like LDH were only measured in portion of the sample, precluding their use in
multivariate models. The precise causes of death were not recorded and death within 30 days of
positive COVID-19 RP-PRC was assumed to be COVID-19 related. Lastly, diagnosis was only based on
RP-PRC and not on pulmonary CT-scan because it was difficult to move very frail patients with pulmonary
symptoms to another hospital to get the CT-scan. Therefore we might have missed some patients with
false negative COVID-19 RP-PRC.

Conclusions and Implications

In very old subjects hospitalized in geriatric settings for COVID-19, mortality was lower in subjects
treated with ARB or ACEI prior to the onset of infection. The continuation of ACEI/ARB therapy
should be encouraged during periods of coronavirus outbreak in older subjects.
References

1. John Hopkins University. URL: https://coronavirus.jhu.edu/. Accessed on June 15, 2020.

2. Santé Publique France. URL: https://www.santepubliquefrance.fr/maladies-etravaux-traumatismes/maladies-eti-infections-respiratoires/infection-a-coronavirus/articles/infection-au-nouveau-coronavirus-sars-cov-2-covid-19-france-et-monde. Accessed on June 15, 2020.

3. Instituto Superiore di Sanità. EPIDEMIA COVID-19. Aggiornamento nazionale. 2020. https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19_26-maggio-2020.pdf. Accessed on June 15, 2020.

4. Wan Y, Shang J, Graham R, Baric RS et al. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. J Virol 2020;94:. doi: 10.1128/JVI.00127-20.

5. Mehra MR, Desai SS, Kuy S, Henry TD et al. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. N Engl J Med 2020;:. doi: 10.1056/NEJMoa2007621.

6. Kreutz R, Algharably EAE, Azizi M, Dobrowolski P et al. Hypertension, the renin-angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19. Cardiovasc Res 2020;:. doi: 10.1093/cvr/cvaa097.

7. Mancia G, Rea F, Ludergnani M, Apolone G et al. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. N Engl J Med 2020;:. doi: 10.1056/NEJMoa2006923.

8. Li J, Wang X, Chen J, Zhang H et al. Association of Renin-Angiotensin System Inhibitors With Severity or Risk of Death in Patients With Hypertension Hospitalized for Coronavirus Disease 2019 (COVID-19) Infection in Wuhan, China. JAMA Cardiol 2020;:. doi: 10.1001/jamacardio.2020.1624.

9. Fosbøl EL, Butt JH, Østergaard L, Andersson C et al. Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With COVID-19 Diagnosis and Mortality. JAMA 2020;:. doi: 10.1001/jama.2020.11301.

10. Zhang P, Zhu L, Cai J, Lei F et al. Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Mortality Among Patients With Hypertension Hospitalized With COVID-19. Circ Res 2020;126:1671-1681. doi: 10.1161/CIRCRESAHA.120.317134.

11. Yang G, Tan Z, Zhou L, Yang M et al. Effects of Angiotensin II Receptor Blockers and ACE (Angiotensin-Converting Enzyme) Inhibitors on Virus Infection, Inflammatory Status, and Clinical...
12. De Spiegeleer A, Bronselaer A, Teo JT, Byttebier G et al. The Effects of ARBs, ACEis, and Statins on Clinical Outcomes of COVID-19 Infection Among Nursing Home Residents. J Am Med Dir Assoc 2020;21:909-914.e2. doi: 10.1016/j.jamda.2020.06.018.

13. von Elm E, Altman DG, Egger M, Pocock SJ et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med 2007;4:e296. doi: 10.1371/journal.pmed.0040296.

14. Code de la Santé Publique. Article L1121-1. 2016. https://www.legifrance.gouv.fr/affichCodeArticle.do;jsessionid=9FB1F2500936F09468CC5367943F7FAF.tplgfr23s_1?idArticle=LEGIARTI000032722870&cidTexte=LEGITEXT000006072665&categorieLien=id&dateTexte=. Accessed on June 15, 2020.

15. American psychiatric association. DSM-5: diagnostic and statistical manual of mental disorders-5th ed. Washington, DC: American Psychiatric Association; 2013.

16. Haute Autorité de Santé. Stratégie de prise en charge en cas de dénutrition protéino-énergétique chez la personne âgée. 2007. https://www.has-sante.fr/upload/docs/application/pdf/synthese_denutrition_personnes_agees.pdf. Accessed on July 30, 2020.

17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-383. doi: 10.1016/0021-9681(87)90171-8.

18. Katz S, Ford AB, Moskowitz RW, Jackson BA et al. Studies of Illness in the Aged. The Index of ADL: A Standardized Measure of Biological and Psychosocial Function. JAMA 1963;185:914-919. doi: .

19. Levey AS, Stevens LA, Schmid CH, Zhang YL et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-612. doi: 10.7326/0003-4819-150-9-200905050-00006.

20. Falsey AR, Hennessey PA, Formica MA, Cox C et al. Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med 2005;352:1749-1759. doi: 10.1056/NEJMoa043951.

21. Ferrari R, Maggioni AP, Tavazzi L, Rapezzi C. The battle against COVID-19: mortality in Italy. Eur Heart J 2020;41:2050-2052. doi: 10.1093/eurheartj/ehaa326.
22. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72,314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020;323(8):e200134. doi: 10.1001/jama.2020.2648.

23. Marrie TJ. Community-acquired pneumonia in the elderly. Clin Infect Dis 2000;31:1066-1078. doi: 10.1086/318124.

24. Qin C, Zhou L, Hu Z, Zhang S et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020;71(12):1821-1829. doi: 10.1093/cid/ciaa248.

25. Chen J, Qi T, Liu L, Ling Y et al. Clinical progression of patients with COVID-19 in Shanghai, China. J Infect 2020;80:e1-e6. doi: 10.1016/j.jinf.2020.03.004.

26. Inciardi RM, Adamo M, Lupi L, Cani DS et al. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. Eur Heart J 2020;41:1821-1829. doi: 10.1093/eurheartj/ehaa388.

27. Buscemi S, Buscemi C, Batsis JA. There is a relationship between obesity and COVID-19 but more information is needed. Obesity (Silver Spring) 2020;8:299-301. doi: 10.1002/oby.22883.

28. Zhou F, Yu T, Du R, Fan G et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-1062. doi: 10.1016/S0140-6736(20)30566-3.

29. Conde-Sala JL, Garre-Olmo J, Calvó-Perxas L, Turró-Garriga O et al. CAUSES, mortality rates and risk factors of death in community-dwelling Europeans aged 50 years and over: Results from the Survey of Health, Ageing and Retirement in Europe 2013-2015. Arch Gerontol Geriatr 2020;89:104035. doi: 10.1016/j.archger.2020.104035.

30. Courtright KR, Jordan L, Murtaugh CM, Barrón Y et al. Risk Factors for Long-term Mortality and Patterns of End-of-Life Care Among Medicare Sepsis Survivors Discharged to Home Health Care. JAMA Netw Open 2020;3:e200038. doi: 10.1001/jamanetworkopen.2020.0038.

31. Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. J Infect 2020;80:e14-e18. doi: 10.1016/j.jinf.2020.03.005.

32. Zhang G, Hu C, Luo L, Fang F et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. J Clin Virol 2020;127:104364. doi: 10.1016/j.jcv.2020.104364.

33. Chen G, Wu D, Guo W, Cao Y et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020;130:2620-2629. doi: 10.1172/JCI137244.
34. Jung S, Choi JC, You S, Kim W. Association of renin-angiotensin-aldosterone system inhibitors with COVID-19-related outcomes in Korea: a nationwide population-based cohort study. Clin Infect Dis 2020; doi: 10.1093/cid/ciaa624.

35. Gao C, Cai Y, Zhang K, Zhou L et al. Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. Eur Heart J 2020;41:2058-2066. doi: 10.1093/eurheartj/ehaa433.

36. de Abajo FJ, Rodríguez-Martín S, Lerma V, Mejía-Abril G et al. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. Lancet 2020;395:1705-1714. doi: 10.1016/S0140-6736(20)31030-8.

37. Saavedra JM. Angiotensin receptor blockers and COVID-19. Pharmacol Res 2020;156:104832. doi: 10.1016/j.phrs.2020.104832.

38. Guidet B, Leblanc G, Simon T, Woimant M et al. Effect of Systematic Intensive Care Unit Triage on Long-term Mortality Among Critically Ill Elderly Patients in France: A Randomized Clinical Trial. JAMA 2017;318:1450-1459. doi: 10.1001/jama.2017.13889.

39. Zhang X, Qin J, Cheng X, Shen L et al. In-Hospital Use of Statins Is Associated with a Reduced Risk of Mortality among Individuals with COVID-19. Cell Metab 2020; doi: 10.1016/j.cmet.2020.06.015.
### Table 1, General characteristics in the whole sample and according to 30-day in-hospital mortality

| Characteristics, % (N) | Whole sample | Survivors | Non-survivors | p* |
|------------------------|--------------|-----------|---------------|----|
| **N=201**              | N=135        | N=66      |               |    |
| Age (years), M (SD)    | 86.3 (8.0)   | 86.2 (8.2)| 86.4 (7.6)  | 0.87|
| Women                  | 67.2 (135)   | 68.9 (93) | 63.6 (42)   | 0.40|
| Nursing home           | 62.7 (126)   | 60.7 (82) | 66.7 (44)   | 0.36|
| Activities of daily living score |          |           |               | 0.02†|
| [0-2]                  | 53.5 (107)   | 46.7 (63) | 67.7 (44)   |    |
| [2-4]                  | 25.5 (51)    | 28.1 (38) | 20.0 (13)   |    |
| [4-6]                  | 21.0 (42)    | 25.2 (34) | 12.3 (8)    |    |
| BMI (kg/m²), M (SD)    | 24.1 (6.0)   | 23.9 (5.8)| 24.4 (6.4)  | 0.53|

#### Comorbidity

| Comorbidity                          | Whole sample | Survivors | Non-survivors | p* |
|--------------------------------------|--------------|-----------|---------------|----|
| Charlson comorbidity index           | 3.17 (2.22)  | 3.03 (2.21)| 3.46 (2.24)  | 0.17|
| Dementia                             | 88.6 (178)   | 86.7 (117)| 92.4 (61)    | 0.2 |
| Cancer                               | 18.0 (36)    | 15.7 (21) | 22.7 (15)    | 0.18|
| Stroke or TIA                        | 23.9 (48)    | 20.7 (28) | 30.3 (20)    | 0.20|
| Chronic heart failure                | 34.8 (70)    | 34.1 (46) | 36.4 (24)    | 0.67|
| Hypertension                         | 62.2 (125)   | 63.0 (85)| 60.6 (40)    | 0.73|
| Atrial fibrillation                  | 34.3 (69)    | 34.1 (46)| 34.8 (23)    | 0.77|
| Coronary artery disease              | 23.4 (47)    | 25.2 (34)| 19.7 (13)    | 0.34|
| COPD                                 | 15.4 (31)    | 15.6 (21)| 15.2 (10)    | 0.99|
| Diabetes mellitus                    | 19.4 (39)    | 16.3 (22)| 25.8 (17)    | 0.12|
| Depression                           | 46.3 (93)    | 46.7 (63)| 45.5 (30)    | 0.79|
| Anemia†                              | 45.5 (90)    | 46.3 (62)| 43.8 (28)    | 0.88|
| Malnutrition                         | 74.4 (134)   | 73.6 (92)| 76.4 (42)    | 0.66|

#### Symptoms

| Symptoms                              | Whole sample | Survivors | Non-survivors | p* |
|---------------------------------------|--------------|-----------|---------------|----|
| Fever (> 37.8°C)                      | 82.1 (165)   | 80.0 (108)| 86.4 (57)    | 0.26|
| Dyspnea                               | 28.9 (58)    | 23.7 (32)| 39.4 (26)    | 0.01|
| Coughing                              | 32.0 (64)    | 34.1 (46)| 27.7 (18)    | 0.32|
| SpO₂ < 90%                            | 4.19 (8)     | 3.03 (4) | 6.78 (4)     | 0.22|
| Digestive symptoms                    | 9.95 (20)    | 9.63 (13)| 10.6 (7)     | 0.69|
| Fall                                  | 12.4 (25)    | 10.4 (14)| 16.7 (11)    | 0.17|
| Severe hypotension (SBP < 95 mm Hg)   | 2.2 (4)      | 2.4 (3)  | 1.7 (1)      | 0.78|

#### Biological characteristics, M (SD)

| Biological characteristics, M (SD)   | Whole sample | Survivors | Non-survivors | p* |
|--------------------------------------|--------------|-----------|---------------|----|
| Hemoglobin (g/dL)                    | 12.4 (1.7)   | 12.4 (1.7)| 12.5 (1.7)   | 0.86|
| WBC (× 10⁹/L)                        | 6.86 (3.83)  | 6.03 (2.49)| 8.59 (5.32) | <.0001|
| Lymphocytes (× 10⁹/L)                | 1.31 (0.81)  | 1.30 (0.75)| 1.34 (0.93) | 0.64|
| Platelets (× 10⁹/L)                  | 215 (89)     | 220 (84)  | 207 (98)     | 0.37|
| Creatinine (µmol/L)                  | 87.5 (37.8)  | 82.7 (35.6)| 97.9 (40.5) | 0.007|
| eGFR (CPK EPI formula)               |              |           |               | 0.04|
| ≥ 50 mL/min/1.73 m²                  | 71.1 (140)   | 75.4 (101)| 61.9 (39)    |    |
| 30-50 mL/min/1.73 m²                 | 21.8 (43)    | 20.1 (27) | 25.4 (16)    |    |
| < 30 mL/min/1.73 m²                  | 7.11 (14)    | 4.48 (6)  | 12.7 (8)     |    |
| Albumin (g/L)                        | 35.2 (10.1)  | 35.8 (11.8)| 34.0 (4.0)  | 0.11|
| Albumin < 35 g/L                     | 53.9 (89)    | 51.3 (59) | 60.0 (30)    | 0.31|
| LDH (mg/L)                           | 264 (136)    | 241 (77)  | 359 (251)    | 0.05|
| CRP (mg/L)                           | 37.0 (49.0)  | 27.6 (42.5)| 57.1 (56.0)| ≤.0001|

% (N), percentage (count); M (SD), mean (standard deviation); BMI, body mass index; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; SpO₂, peripheral oxygen saturation; WBC, white blood cells; eGFR, glomerular filtration rate estimated with CPK-EPI formula; CRP, C-reactive protein.

* p values from univariate Cox regression model; † Anemia according to World Health Organization definition: hemoglobin < 130 g/L in men and < 120 g/L in women.
Table 2, Medication in the whole sample and according to 30-day in-hospital mortality.

| Medications, % (N)                      | Whole sample | Survivors | Non-survivors | p*  |
|----------------------------------------|--------------|-----------|---------------|-----|
|                                        | N=201        | N=135     | N=66          |     |
| Renin-angiotensin system inhibitors    |              |           |               |     |
| ARB or ACEI                            | 31.3 (63)    | 36.3 (49) | 21.2 (14)     | 0.03|
| Renin-angiotensin system inhibitors †  |              |           |               |     |
| No ARB nor ACEI                        | 68.7 (138)   | 63.7 (86) | 78.8 (52)     | Ref |
| ACEI                                   | 18.9 (38)    | 20.7 (28) | 15.2 (10)     | 0.23|
| ARB                                    | 12.4 (25)    | 15.6 (21) | 6.06 (4)      | 0.05|
| Calcium channel blockers               | 16.4 (33)    | 18.5 (25) | 12.1 (8)      | 0.21|
| Diuretics                              | 27.6 (55)    | 26.1 (35) | 30.8 (20)     | 0.46|
| Beta-blockers                          | 43.5 (87)    | 42.5 (57) | 45.5 (30)     | 0.72|
| Anticoagulants                         | 25.5 (51)    | 24.6 (33) | 27.3 (18)     | 0.55|
| Anti-platelets                         | 25.0 (50)    | 24.6 (33) | 25.8 (17)     | 0.94|
| PPI                                    | 41.0 (82)    | 41.8 (56) | 39.4 (26)     | 0.79|
| Antidepressants                        | 54.0 (108)   | 56.7 (76) | 48.5 (32)     | 0.22|
| Neuroleptics                           | 23.5 (47)    | 21.6 (29) | 27.3 (18)     | 0.49|
| Benzodiazepines                        | 55.0 (110)   | 53.7 (72) | 57.6 (38)     | 0.63|

% (N), percentage (count); ARB, angiotensin II receptor blocker; ACEI, angiotensin-converting-enzyme inhibitors; PPI, proton-pump inhibitor.

*p values from univariate Cox regression model;

† Overall difference between no ACEI nor ARB, ACEI, ARB in Cox regression model, p=0.06.
Table 3, Cohort characteristics according to ACEI/ARB use.

| Variables, M (SD)          | No ARB nor ACE inhibitors | ARB or ACE inhibitors | p*  |
|---------------------------|----------------------------|-----------------------|-----|
| Age (years)               | 86.0 (8.6)                 | 86.9 (6.3)            | 0.46|
| Women, % (N)              | 65.2 (90)                  | 71.4 (45)             | 0.48|
| Nursing home living, % (N)| 67.4 (93)                  | 52.4 (33)             | 0.06|
| Activities of daily living, % (N) |                        |                       |     |
| [0-2]                     | 58.4 (80)                  | 42.9 (27)             |     |
| [2-4]                     | 24.8 (34)                  | 27.0 (17)             | 0.06|
| [4-6]                     | 16.8 (23)                  | 30.2 (19)             |     |
| BMI (kg/m^2)              | 23.9 (6.2)                 | 24.5 (5.6)            | 0.47|
| Comorbidity, % (N)        |                            |                       |     |
| Charlson comorbidity index| 2.98 (2.18)                | 3.59 (2.29)           | 0.07|
| Dementia                  | 93.5 (129)                 | 77.8 (49)             | 0.003|
| Cancer                    | 17.5 (24)                  | 19.0 (12)             | 0.95|
| Stroke or TIA             | 20.3 (28)                  | 31.7 (20)             | 0.11|
| Chronic heart Failure     | 31.2 (43)                  | 42.9 (27)             | 0.15|
| Hypertension              | 48.6 (67)                  | 92.1 (58)             | <0.001|
| Atrial fibrillation       | 34.1 (47)                  | 34.9 (22)             | 0.99|
| Coronary artery disease   | 18.8 (26)                  | 33.3 (21)             | 0.04|
| COPD                      | 14.5 (20)                  | 17.5 (11)             | 0.74|
| Diabetes mellitus         | 17.4 (24)                  | 23.8 (15)             | 0.38|
| Depression                | 44.2 (61)                  | 50.8 (32)             | 0.47|
| Anemia†                   | 41.9 (57)                  | 53.2 (33)             | 0.18|
| Malnutrition              | 76.2 (93)                  | 70.7 (41)             | 0.54|
| Medication, % (N)         |                            |                       |     |
| Calcium blockers          | 12.3 (17)                  | 28.6 (18)             | 0.009|
| Diuretics                 | 22.6 (31)                  | 38.7 (24)             | 0.03|
| Beta-blockers             | 39.9 (55)                  | 51.6 (32)             | 0.16|
| DOACs                     | 25.4 (35)                  | 25.8 (16)             | 0.99|
| Anti-platelet             | 20.3 (28)                  | 35.5 (22)             | 0.03|
| Antidepressant            | 52.2 (72)                  | 58.1 (36)             | 0.54|
| Neuroleptics              | 24.6 (34)                  | 21.0 (13)             | 0.70|
| Benzodiazepine            | 55.8 (77)                  | 53.2 (33)             | 0.85|
| PPI                       | 39.1 (54)                  | 45.2 (28)             | 0.52|
| Symptoms, % (N)           |                            |                       |     |
| Fever (>37.8°C)           | 83.3 (115)                 | 79.4 (50)             | 0.63|
| Dyspnea                   | 27.5 (38)                  | 31.7 (20)             | 0.66|
| Coughing                  | 31.4 (43)                  | 33.3 (21)             | 0.91|
| SpO₂ < 90%                | 4.62 (6)                   | 3.28 (2)              | 0.97|
| Digestive symptoms        | 10.9 (15)                  | 7.94 (5)              | 0.70|
| Falls                     | 13.8 (19)                  | 9.52 (6)              | 0.54|
| Severe hypotension (SBP < 95 mm Hg) | 1.5 (2)               | 4.1 (2)               | 0.30‡|
| Biological characteristics |                            |                       |     |
| Hemoglobin (g/dL)         | 12.6 (1.8)                 | 12.1 (1.5)            | 0.05|
| WBC (×10^9/L)             | 6.69 (3.40)                | 7.23 (4.65)           | 0.35|
| Lymphocytes (×10^9/L)     | 1.25 (0.76)                | 1.44 (0.91)           | 0.13|
| Platelets (×10^9/L)       | 212 (73)                   | 222 (116)             | 0.50|
| Creatinine (µmol/L)       | 88.4 (39.4)                | 85.6 (34.4)           | 0.64|
| eGFR (CPK EPI formula)    |                            |                       |     |
| ≥ 50 mL/min/1.73 m²       | 72.0 (95)                  | 64.0 (32)             | 0.11|
| 30-50 mL/min/1.73 m²      | 19.0 (25)                  | 32.0 (16)             | 0.12|
| < 30 mL/min/1.73 m²       | 9.1 (12)                   | 4.0 (2)               |     |
| Albumin (g/L)             | 34.4 (3.9)                 | 37.0 (16.7)           | 0.11|
| Albumin < 35 mg/mL        | 53.8 (63)                  | 54.2 (26)             | 0.99|
| LDH (UI/L)                | 247 (78)                   | 292 (201)             | 0.11|
| CRP (mg/L)                | 36.6 (45.3)                | 37.9 (56.7)           | 0.86|
% (N), percentage (count); M (SD), mean (standard deviation); ARB, angiotensin II receptor blocker; ACEI, angiotensin-converting-enzyme inhibitors; BMI, body mass index; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; PPI, proton-pump inhibitor; WBC, white blood cells; eGFR, glomerular filtration rate estimated with CPK-EPI formula; CRP, C-reactive protein.

* p values from T-test or \( \chi^2 \); † Anemia according to World Health Organization definition: hemoglobin < 130 g/L in men and < 120 g/L in women; ‡ Fisher exact test.
Figure 1, 30-day in-hospital mortality according to ACEI or ARB use.
Figure 2, Factors associated with 30-day in-hospital mortality in a multivariate Cox regression model. 

SD, standard deviation; ADL, Activities of daily living; eGFR, glomerular filtration rate estimated with CPK-EPI formula; CRP, C-reactive protein; WBC, white blood cells; ARB, angiotensin II receptor blockers; ACEI, angiotensin-converting-enzyme inhibitors. 

1 SD for age = 8.0 years, 1 SD for Charlson index = 2.2 points, 1 SD for CRP = 49 mg/mL, 1 SD for WBC = 3.9 x 10^9/L.

* p < 0.05; ** p < 0.01.
HR = 0.54 (95% CI, 0.30–0.97), p=0.03

No ACEI/ARB

ACEI/ARB

| Days Since RT–PCR Confirmation | No ACEI/ARB | ACEI/ARB |
|-------------------------------|-------------|----------|
| 0                             | 138         | 63       |
| 5                             | 128         | 59       |
| 10                            | 107         | 56       |
| 15                            | 97          | 51       |
| 20                            | 90          | 50       |
| 25                            | 87          | 49       |
| 30                            | 86          | 49       |
| Factor                        | Hazard Ratio and 95% Confidence Interval |
|------------------------------|-----------------------------------------|
| Age (for 1 SD-increase)      | 0.94 (0.71–1.25)                        |
| Women                        | 0.98 (0.57–1.71)                        |
| ADL score ([4–6] as reference)| * 2.54 (1.13–5.72)                      |
|                              | [2–4] 1.87 (0.74–4.73)                  |
| Charlson index (for 1 SD-increase) | 1.24 (0.95–1.61)                         |
| Renal function (eGFR > 50 ml/min/1.73 m2 as reference) | |
| eGFR 30–50                   | 1.25 (0.66–2.38)                        |
| eGFR < 30                    | 1.63 (0.68–3.86)                        |
| Dyspnea                      | 1.55 (0.89–2.70)                        |
| CRP (for 1 SD-increase)      | 1.37 (1.11–1.69)**                      |
| WBC (for 1 SD-increase)      | 1.45 (1.16–1.81)**                      |
| ARB or ACEI                  | 0.52 (0.27–0.99)*                       |
| ACEI alone                   | 0.60 (0.28–1.31)                        |
| ARB alone                    | 0.40 (0.14–1.15)                        |