RESEARCH LETTER

Adverse outcomes in patients with heart failure admitted for COVID-19 in association with the use of renin-angiotensin-aldosterone system inhibitors

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Introduction The pandemic of COVID-19, caused by SARS-CoV-2, has led to a global health crisis.[1] Patients with cardiovascular disease seem particularly susceptible to severe COVID-19.[2] Among individuals hospitalized for COVID-19, heart failure (HF) has been reported as a factor associated with a potential risk of worse outcomes.[3,4] However, to date, specific data on the clinical profile, course of disease, and prognosis of COVID-19 patients with a history of HF are limited.[4-6]

On the other hand, there has been considerable interest in how the use of renin-angiotensin-aldosterone system inhibitors (RAASi) could potentially affect adverse clinical outcomes in patients with COVID-19. It is known that angiotensin-converting enzyme 2 receptors play a pivotal role in cellular penetration of SARS-CoV-2.[7] In this work, we evaluated the association between in-hospital mortality as well as other adverse outcomes and RAASi treatment during hospitalization.

Methods We selected all patients with a history of HF included in the Spanish Society of Internal Medicine's registry of COVID-19 patients (the SEMI-COVID-19 registry) between March 1 and September 18, 2020. This registry is an ongoing, observational, multicenter, nationwide cohort of adult (≥18 year old) patients admitted for COVID-19 confirmed by a positive real-time reverse transcriptase–polymerase chain reaction test in Spain. Its methodology, collected variables, definitions, data verification procedures, and confidentiality measures have been previously described.[8] In brief, the SEMI-COVID-19 registry retrospectively compiles data on sociodemographic variables, comorbidities, preadmission treatment, clinical presentation, laboratory test results, in-hospital complications, length of hospital stay, and in-hospital death since the first admission for COVID-19. All information contained in the database, the configuration of the information within the database, as well as the database itself, are fully encrypted. Daily backups are performed in order to ensure data integrity.

Only patients who had previously given consent for their data to be used for medical research were included in this study. Patient personal information had been deleted before the database was analyzed so that identification of individual patients in this article or in the database was not possible. The study was conducted pursuant to the Declaration of Helsinki and was approved by the Institutional Research Ethics Committee of Málaga on March 27, 2020 (Ethics Committee code, SEMI-COVID-19 27-03-20).

A diagnosis of HF was established based on a history of HF in medical records, which were manually reviewed by investigators. The degree of functional dependence and the presence of comorbidities were assessed using the Barthel Index and the Charlson Comorbidity Index, respectively.

In-hospital complications included at least one of the following: secondary bacterial pneumonia, acute respiratory distress syndrome, acute decompensated HF (ADHF), arrhythmia, acute coronary syndrome, myocarditis, epileptic seizures, stroke, shock, sepsis, acute kidney failure, disseminated intravascular coagulation, venous thromboembolism, multiple organ dysfunction syndrome, acute

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limb ischemia, admission to the intensive care unit (ICU), or the need for ventilation support, including invasive and noninvasive mechanical ventilation or high-flow oxygen therapy.

The severity of COVID-19 was established according to the patient's clinical condition and classified as mild (symptoms without evidence of pneumonia or hypoxia), moderate (clinical signs of pneumonia but no signs of severe pneumonia, including basal oxygen saturation ≥92%), severe (clinical signs of pneumonia and one of the following: basal oxygen saturation <92%, resting respiratory rate >30 breaths/min, severe respiratory distress), and critical (sepsis or shock with acute respiratory distress syndrome and/or multiple organ dysfunction or failure).

In this study, patients were classified into 3 groups according to RAASi use: in-hospital RAASi continuation (continued to receive RAASi during hospitalization); in-hospital RAASi withdrawal (stopped receiving RAASi during hospitalization); and no RAASi use (did not use RAASi before or during hospitalization). No other patient groups were identified.

The primary outcome was in-hospital mortality according to in-hospital RAASi use. Secondary outcomes were: 1) a composite outcome including the need for ICU admission, invasive and noninvasive mechanical ventilation, or in-hospital mortality; 2) in-hospital complications; and 3) ADHF.

Statistical analysis Statistical analyses were performed using R software, version 3.6.2 (the R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were expressed as absolute values and percentages, whereas continuous variables, as means (SDs) or medians (interquartile ranges), depending on whether they followed a normal or nonnormal distribution. Differences between groups were determined using the Pearson χ^2 test for categorical variables and the 2-sample *t* test or the Mann–Whitney test for continuous variables.

To match a patient in one group with a patient in another group in a 1:1 ratio, propensity scores using nearest neighbour matching with a caliper of 0.1 and a greedy matching algorithm were used. Logistic regression was used to determine the probability of receiving RAASi treatment; it included factors that could have affected outcomes as independent variables (age, sex, comorbidities, preadmission treatment, clinical presentation, laboratory data, and in-hospital treatment). Standardized mean differences were calculated to evaluate the adequacy of propensity matching. To estimate the association between treatment and study outcomes, both conditional logit and mixed effect (matched pairs as random effects) logistic regression models were used.

Results Of the total number of patients included in the SEMI-COVID-19 registry (n = 16 514), 1171 (7.1%) had a history of HF. When grouped according to RAASi use, 333 patients continued RAASi treatment during hospitalization, 288 discontinued RAASi treatment during hospitalization, and 550 did not use RAASi before or during hospitalization. Before propensity matching, several differences between RAASi groups were observed in the comparative analysis with regard to the clinical characteristics, management, and outcomes (Supplementary material, *Table S1*). Following propensity matching of each RAASi group, all patient characteristics were well-balanced and no significant differences were noted. The post-propensity matching characteristics of patients are shown in Supplementary material, *Table S2*.

After propensity matching and logistic regression, patients who continued to receive RAASi during hospitalization had lower rates of in-hospital mortality, the composite adverse outcome, in-hospital complications, and ADHF compared with patients who discontinued the treatment or those who never used RAASi. Patients who discontinued RAASi treatment showed lower rates of in-hospital complications and ADHF compared with individuals who never received RAASi. No differences were observed in terms of in-hospital mortality or the composite adverse outcome between these 2 groups. The associations between in-hospital RAASi continuation, in-hospital RAASi withdrawal, and no RAASi use and the study outcomes after propensity matching are shown in **TABLE 1**.

Discussion Patients with a history of HF have a high rate of comorbidities and are at a high risk of complications during hospitalization for COVID-19. In our study, we found that patients with a history of HF hospitalized for COVID-19 who continued to receive RAASi showed lower rates of in-hospital mortality and other adverse outcomes compared with those in whom the therapy was stopped, and especially compared with nonusers of RAASi. A partial benefit was observed in patients with preadmission RAASi use and in-hospital withdrawal, who showed lower rates of in-hospital complications and ADHF compared with RAASi nonusers.

In patients with COVID-19, HF has been reported as a relevant comorbidity, occurring in up to 10% of cases.[9,10] Furthermore, it is known that HF may negatively impact clinical outcomes in patients with COVID-19.[3,4]

The role of RAASi in patients with COVID-19 has been widely discussed.[7,11] Recent studies indicated that previous treatment could be beneficial.[12,13] There is limited evidence on the effect of RAASi use in patients with HF admitted for COVID-19, and all studies focus on the clinical implications of HF on the course of COVID-19 rather than preadmission treatment.[4,5,11] Although these studies only included a limited number of HF patients, preadmission RAASi use showed a neutral association with adverse events. RAASi are essential medications in patients with HF, particularly in those with reduced ejection fraction,[11] and their withdrawal or nonuse could lead to worse

TABLE 1 Association between in-hospital continuation, in-hospital withdrawal, and nonuse of renin-angiotensin-aldosterone system inhibitors and study outcomes after propensity score matching

Outcomes	Treatment groups			Conditional logit logistic regression		Mixed effect logistic regression	
	In-hospital RAASi continuation (n = 196)	In-hospital RAASi withdrawal (n = 196)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
In-hospital mortality	60 (30.6)	85 (43.4)	0.02	0.79 (0.58–0.91)	0.009	0.79 (0.58–0.92)	0.01
ICU admission, mechanical ventilation, or in-hospital mortality	93 (47.4)	115 (58.7)	0.03	0.83 (0.60–0.94)	0.01	0.83 (0.60–0.92)	0.02
In-hospital complications	126 (64.3)	145 (74.0)	0.04	0.85 (0.61–0.98)	0.04	0.86 (0.60–0.97)	0.04
Acute heart failure decompensation	59 (30.1)	77 (39.3)	0.04	0.85 (0.60–0.95)	0.02	0.86 (0.61–0.95)	0.03
	In-hospital RAASi continuation (n = 236)	No RAASi use (n = 236)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
In-hospital mortality	73 (30.9)	119 (50.4)	0.008	0.67 (0.43–0.89)	0.002	0.67 (0.44–0.89)	0.002
ICU admission, mechanical ventilation, or in-hospital mortality	110 (46.6)	165 (69.9)	0.003	0.65 (0.45–0.91)	0.006	0.65 (0.45–0.92)	0.007
In-hospital complications	149 (63.1)	189 (80.1)	0.01	0.71 (0.46–0.90)	0.01	0.73 (0.47–0.90)	0.01
Acute heart failure decompensation	71 (30.1)	115 (48.7)	0.01	0.69 (0.48–0.91)	0.008	0.69 (0.49–0.91)	0.007
	RAASi withdrawal (n = 178)	No RAASi use (n = 178)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
In-hospital mortality	80 (44.9)	88 (49.4)	0.15	0.90 (0.65–1.27)	0.1	0.91 (0.66–1.27)	0.11
ICU admission, mechanical ventilation, or in-hospital mortality	106 (59.6)	115 (64.6)	0.13	0.89 (0.67–1.30)	0.1	0.90 (0.67–1.31)	0.1
In-hospital complications	125 (70.2)	140 (78.7)	0.04	0.84 (0.68–0.99)	0.041	0.85 (0.67–0.99)	0.04
Acute heart failure decompensation	71 (38.2)	85 (47.8)	0.04	0.84 (0.67–0.99)	0.04	0.83 (0.67–0.98)	0.04

Data are presented as numbers and percentages unless otherwise indicated. A significant imbalance in the group was considered if a standardized mean difference between baseline variables was >10%. Differences were considered statistically significant when $P < 0.05$.

Abbreviations: ICU, intensive care unit; OR, odds ratio; RAASi, renin-angiotensin-aldosterone system inhibitors

clinical outcomes, which is in accordance with our results and with position papers on HF management in patients with COVID-19.[14,15]

Our findings are important because they provide evidence for benefits associated with the continuation of RAASi treatment during hospitalization in patients with HF admitted for COVID-19. In addition, patients treated with RAASi before admission in whom the therapy was discontinued in the hospital also showed some benefits compared with nonusers of RAASi, which shows extended protective effects of the drugs during hospitalization. These findings support previous evidence on the potential beneficial effects of RAASi use in patients with COVID-19.[11,14,15] To the best of our knowledge, this is the first large study which examines the role of RAASi after a robust adjustment for many confounding variables. Nevertheless, several potential limitations of this work must be considered. First, due to the retrospective design of the study and despite the propensity matching analysis, the possibility of leaving out some confounding factors cannot be eliminated. In addition, our findings should be interpreted with caution due to the multiple-comparison analysis between RAASi groups. Second, HF characteristics such as principal etiology of HF, New York Heart Association functional classification, left ventricular ejection fraction, natriuretic peptide levels, and the proportion of patients on β-blockers, mineralocorticoid receptor agonists, or diuretics were not recorded; therefore, the misdiagnosis of HF in certain patients cannot be excluded. Third, no other adverse intermediate outcomes were evaluated because of the low number of instances. Fourth, data on pharmacotherapy before admission did not include information on treatment adherence, duration, or reasons for nonuse. The high proportion of patients who did not receive RAASi before hospitalization could be justified by the initial concerns about the potential association between their use and the risk of COVID-19. Fifth, all in-hospital RAASi users received RAASi before admission; no case of newly-initiated RAASi treatment during hospitalization was identified. Lastly, the withdrawal of RAASi treatment on admission could have been more likely related to

the potential adverse effects attributed to RAASi use at the beginning of the pandemic rather than only to differences in the clinical presentation or actual presence of complications, which could have affected the decision regarding RAASi treatment continuation.

In conclusion, our study found that patients with HF who continued RAASi treatment during hospitalization for COVID-19 had lower rates of in-hospital mortality and other adverse outcomes compared with those in whom the treatment was withdrawn and especially compared with those who never received RAASi treatment. Given the significant impact of HF on COVID-19 and the potential benefits of RAASi, prospective studies are needed to elucidate the relationship between this treatment and patient outcomes.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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